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REVIEW

Nutrition in acute pancreatitis: a critical review

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ABSTRACT

Severe acute pancreatitis poses unique nutritional challenges. The optimal nutritional support in patients with severe acute pancreatitis has been a subject of debate for decades. This review provides a critical review of the available literature.

According to current literature, enteral nutrition is superior to parenteral nutrition, although several limitations should be taken into account. The optimal route of enteral nutrition remains unclear, but normal or nasogastric tube feeding seems safe when tolerated. In patients with predicted severe acute pancreatitis an on-demand feeding strategy is advised and when patients do not tolerate an oral diet after 72 hours, enteral nutrition can be started. The use of supplements, both parenteral as enteral, are not recommended. Optimal nutritional support in severe cases often requires a tailor-made approach with day-to-day evaluation of its effectiveness.

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Introduction

Acute pancreatitis is the most common gastrointestinal reason for acute hospital admission in the United States [1] with an increasing incidence worldwide [2,3]. In the majority of patients, acute pancreatitis runs a mild clinical course. However, in patients who develop necrotizing pancreatitis, mortality is approximately 15% [4]. In case of infection of pancreatic necrosis, persistent organ failure, or both, mortality rises up to 30% [5].

Acute pancreatitis is associated with systemic and metabolic derangements due to the release of hydrolytic enzymes, toxins, and cytokines, and may result in failure of several organ systems. It may promote hypermetabolism and negative nitrogen balance with negative energy balance [6–9]. Additionally, severe pancreatitis may be associated with hyperglycemia and may cause diabetes [10,11]. Interventions (i.e. surgical, endoscopic, and radiological) are needed in a proportion of patients [12], and in these patients nutritional support may be challenging.

Optimal nutritional support in acute pancreatitis has been a subject of debate for decades. Initially, the concept of pancreatic rest by fasting was thought to improve outcome because enteral nutrition was believed to aggravate inflammation through pancreatic stimulation [13]. Subsequently, parenteral nutritional support was believed to avoid pancreatic stimulation and provided the needed nutritional components. From the mid-1990s, many trials on enteral nutrition were performed showing a benefit of enteral nutrition [14]. In daily practice, however, it remains challenging to predict whether enteral nutrition will be tolerated in patients with acute pancreatitis.

In this review, we provide a critical appraisal of the available evidence on nutritional support in patients with severe pancreatitis. The route, timing, and type of nutritional support in acute pancreatitis are discussed including the quality of the available evidence. Finally, new strategies are reviewed including the role of nutritional supplements.

Methods

We divided this review into different topics. Enteral versus parenteral nutrition, nasogastric or nasojejunal nutrition, timing of nutrition, and use of supplements. For each topic, a different search strategy was followed. In the PubMed database, we selected full-text articles in English from the past 10 years. Exceptions were made for older highly cited papers and important articles concerning critically ill patients and nutrition. We describe results of randomized controlled trials. In addition, reference lists of articles were manually searched.

For parenteral versus enteral nutrition, we used the terms 'acute pancreatitis' combined with 'mortality', 'infection', 'necrosis', 'parenteral', 'enteral', and 'nutrition'. For nasogastric versus nasojejunal nutrition, we used the terms 'acute pancreatitis' combined with 'enteral', 'nasogastric', 'nasojejunal', 'nutrition', 'mortality', 'necrosis', and 'infection'. In timing we used the terms 'acute pancreatitis', 'oral', 'soft diet', 'liquid diet', 'timing', 'enteral', 'mortality', 'infection', and 'necrosis'. Finally for supplements, we used the terms 'acute pancreatitis' combined with 'glutamine', 'probiotics', 'enteral', 'parenteral', 'lactobacillus', 'omega-3 fatty acids', 'elemental', 'polymeric', 'vitamins', 'anti-oxidants', 'mortality', 'necrosis', and 'infection'.

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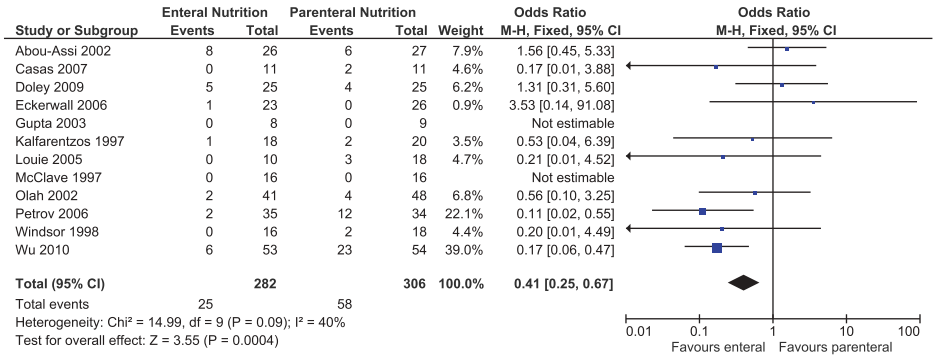

Figure 1. Abou-Assi 2002 = [8]; Casas 2007 = [26]; Doley 2009 = [34]; Eckerwall 2006 = [24]; Gupta 2003 = [27]; Kalfarentzos 1997 = [28]; Louie 2005 = [29]; McClave 1997 = [30]; Olah 2002 = [31]; Petrov 2006 = [32]; Windsor 1998 = [35]; Wu 2010 = [33].

Enteral versus parenteral nutrition

Parenteral nutrition was administered routinely in acute pancreatitis with the aim to prevent pancreatic stimulation. It was long thought that nutrition administered proximal of Treitz' ligament would stimulate the pancreas and thereby aggravate the severity of acute pancreatitis [15,16]. For this reason, parenteral nutrition seemed ideal for adequate nutritional support without pancreatic stimulation. For acute pancreatitis, there are no randomized trials comparing parenteral nutrition to intravenous fluids alone. However, parenteral nutrition is associated with multiple complications, such as central venous catheter-related infections and metabolic complications [17,18].

Gut barrier dysfunction is present in around 60% of patients with acute pancreatitis [19]. Enteral feeding has immunomodulating effects, such as preserving the integrity of the gut mucosa, stimulating intestinal motility – thus reducing bacterial overgrowth – and may increase splanchnic blood flow [20,21]. As a result, bacterial translocation from the gut may be prevented [22]. Therefore, it is thought that enteral nutrition may reduce the risk of infected pancreatic necrosis and mortality [23] although no randomized trial has been published to confirm this hypothesis.

Since 1996, 12 randomized controlled trials [24–35] including 555 patients with acute pancreatitis have compared enteral with parenteral nutrition (Figure 1). The methodological quality of the studies as scored with the Jadad composite scale [36] is shown in Table 1. With these 12 trials, 8 meta-analyses have been performed. The three most recent meta-analyses concluded that enteral nutrition significantly reduces infections, organ failure, and mortality in patients with acute pancreatitis compared with parenteral nutrition [37–39]. Therefore, guidelines recommend enteral nutrition over parenteral nutrition [40–43]. However, these randomized trials have several limitations, which should be taken into account.

First, inclusion criteria varied widely between trials. Different predictive scoring systems have been used with different cutoff values. Some trials included patients with mild acute pancreatitis who do not need nutritional support. Despite extensive research, scoring systems only reach modest accuracy in predicting complications in acute pancreatitis [44]. This results in inclusion of patient identified as predicted severe, but who finally develop mild pancreatitis. This is a well-known limitation of intervention trials early in the disease course of acute pancreatitis. Unfortunately, to date more accurate tools than existing scoring systems are not available. Several trials also used other inclusion criteria than predictive scoring systems, such as the inability to have oral intake after 48 h [25] or after 96 h [29], or contrast-enhanced computed tomography evidence of pancreatic necrosis [28] or a computed tomography severity index >6 [34]. These different inclusion criteria resulted in a heterogeneous inclusion of patients with acute pancreatitis. This is also reflected in the variation of complication rates between trials. The highest mortality rate was 43% [33] compared with 0% [27]. The rate of organ failure varied from 81% [33] to 8% [24]. When interpreting the results of meta-analyses with inclusion of relatively mild and severe patients, these differences should be taken into account: trials with high complication rates strongly influence the outcome of a meta-analysis.

Second, most trials were aimed at preventing complications such as infections. Complications and infections may develop early in the disease course. Therefore, recruiting patients early in their disease course, before complications have developed, is crucial [12,45]. This time window is small, and clinical deteriora-

Table 1. Enteral versus parenteral nutrition: summary of methodological quality.

Study	Randomization method	Blinding	An account of all patients	Jadad score
Abou-Assi [8]	Randomly assigned	None	Yes	2
Casas [26]	Computerized random number generation	None	Yes	3
Doley [34]	Odd/even numbers	None	Yes	1
Eckerwall [24]	Sealed, numbered envelopes	None	Yes	3
Gupta [27]	Sealed envelopes	None	Yes	3
Kalfarentzos [28]	Numbered envelopes	None	Yes	3
Louie [29]	Computer-generated assignment placed in sealed envelopes	None	Yes	3
McClave [30]	Not stated	None	Yes	2
Olah [31]	Birth dates	None	Yes	1
Petrov [32]	Computerized number generation	None	Yes	3
Windsor [35]	Odd or even hospital number	None	Yes	1
Wu [33]	Not stated	None	Yes	2

tion may occur unexpectedly. For effective early prevention of complications, patients theoretically need to be identified on admission or during the first 24–48 h after admission. The time to inclusion, randomization, and start of intervention varied between trials from immediately on admission [26] to 96 h after admission [29]. It is very likely that 96 h after admission, prophylactic interventions will not be effective anymore.

Third, there was a large variation in sample size between trials (Figure 1). It has often been suggested that small trials tend to report larger treatment benefits than larger trials [46]. This may be the result of a combination of lower methodological quality, publication, and other reporting biases, but could also reflect clinical heterogeneity if small trials were more careful in selecting patients and implementing the experimental intervention [46]. However, when these small trials are pooled in meta-analyses, significant differences may be found. The validity of these significant results is questioned.

Fourth, many trials were done before hyperglycemia was recognized as a risk factor for infections. The prevalence of hyperglycemia in patients receiving a specialized nutritional support is higher and reported in up to 30% of patients receiving enteral nutrition and more than half of patients receiving parenteral nutrition [47,48]. In turn, hyperglycemia increases the risk of infectious complications and mortality in parenteral nutrition [18,49,50]. Glycemic control improves clinical outcome and may reduce and improve the outcome of complications [51,52].

Finally, in some trials caloric goals were not always met. This may result in a poorer clinical outcome. Only two trials on enteral nutrition did not meet the caloric goals [25,35]. They demonstrated a significant lower protein quantity and caloric intake. In several trials, protein quantity or caloric intake were similar between groups [24–28,31–35] and in one trial caloric intake was not reported [30]. Although it is thought that outcome is worse when caloric goals are not achieved, a recent randomized controlled trial in critically ill patients demonstrated that mortality was similar with permissive underfeeding compared with standard enteral feeding [53].

The first trial that showed a significant reduction in mortality with the use of enteral nutrition compared with parenteral nutrition was a randomized controlled trial of 69 patients with predicted severe acute pancreatitis [32]. A reduction in pancreatic infectious complications (20% vs. 47%, $p < 0.05$), multiple organ failure (20% vs. 50%, $p < 0.05$), as well as mortality (6% vs. 35%, $p < 0.01$) in favor of enteral nutrition was demonstrated. A mortality rate of 35% was found in the parenteral nutrition group. Previous studies with similar numbers of patients with predicted severe acute pancreatitis did not find a significant reduction in mortality [25,27–31]. Additionally, the mortality rates were lower, ranging from 0% to 26% [25,27–31]. Unfortunately, several important patient characteristics that may influence outcome such as comorbidity, extent of pancreatic necrosis, timing and type of interventions to treat infected necrosis were not described.

The most recent trial [33] also showed a significant reduction in mortality in favor of enteral nutrition. This study included 107 patients admitted to the intensive care unit (ICU) with pancreatic necrosis on computed tomography scan and a C-reactive protein >195 mg/L. All patients received antibiotic prophylaxis. Parenteral or enteral nutrition was given in the first seven days of admission to the intensive care. Unfortunately, time from start of symptoms to start of nutrition was not mentioned. Differences in organ failure (81% with parenteral nutrition vs. 21% with enteral nutrition, $p < 0.05$), infected necrosis (72% with parenteral nutrition vs. 21% with enteral nutrition, $p < 0.05$), and mortality (43% with parenteral nutrition and 11% with enteral nutrition, $p < 0.05$) were found.

Despite the addressed limitations, enteral nutrition is recommended over parenteral nutrition in patients with acute pancreatitis who need nutritional support (Figure 1). Parenteral nutrition is only indicated when enteral nutrition is not tolerated and nutritional support is needed [54,55].

Nasojejunal or nasogastric feeding?

Trials on enteral nutrition in acute pancreatitis have mainly focused on nasojejunal tube feeding for optimal nutritional delivery [37]. Nasojejunal feeding tubes have certain advantages over nasogastric tubes. For example, when placed beyond Treitz' ligament it is suggested that the risk of tube migration to the stomach is reduced and reflux of enteral feeding into the stomach is prevented [16,56]. Studies demonstrated that jejunal feeding (even with elemental nutrition) still stimulates the pancreas by hormonal pathways through the blood and cholinergic enteropancreatic reflexes [16,56,57]. Only when enteral nutrition is given in the mid-distal jejunum is pancreatic stimulation absent [16,58].

Nasogastric tube feeding is an alternative that may eventually cause similar pancreatic stimulation, but it is a simple procedure. Three trials compared nasojejunal with nasogastric nutrition in patients with severe acute pancreatitis [59–61]. Additionally, one randomized controlled trial compared enteral nutrition through a nasogastric tube with parenteral nutrition [24]. With these trials, three meta-analyses have been performed [62–64]. One of these meta-analyses also included nonrandomized controlled trials [62]. No significant differences in end points were observed within the individual trials (Table 2). In line with these results, a meta-analysis [64] (Table 2) including the three randomized trials on nasogastric versus nasojejunal tube feeding showed no differences in mortality (risk ratio (RR) = 0.69, 95% CI 0.37 to 1.29, $p = 0.25$), tracheal aspiration (RR = 0.46, 95% CI 0.14 to 1.53, $p = 0.20$), and reaching energy balance (RR = 1.00, 95% CI 0.92 to 1.09, $p = 0.97$) between the two groups. The following limitations of the individual trials should be taken into account.

First, the sample sizes of these studies were small, varying between 31 [61] and 78 patients [60]. Therefore, one may argue whether the individual trials had sufficient power to detect small but clinically relevant differences in outcome.

Second, as has been mentioned earlier, the inclusion criteria of patients with acute pancreatitis varied between trials. Different predictive scoring systems were used. Additionally, in one single-center trial [61] patients received numerous weeks of nutritional treatment in other centers prior to referral. As a result, patient characteristics may differ between trials.

Finally, a retrospective study in pancreatic surgery patients has shown that a third of the nasojejunal tubes dislodges [65].

Table 2. Nasogastric versus nasojejunal nutrition: summary of studies and end points.

Author	Number of included patients	Intervention (number of patients)	Control group (number of patients)	(Primary) end point (s)	*p*-Value of end point or achieved end point
Eatock [59], RCT	50	Nasogastric (27)	Nasojejunal (23)	APACHE-II scores daily[a,b]	NS
				CRP measurements daily[a]	NS
				Pain patterns through visual analog scale daily[a]	NS
Kumar [61], RCT	31	Nasogastric (15)	Nasojejunal (16)	Recurrence of pain	1.00
				Tolerance of feeding	0.71
Singh [60], RCT	78	Nasogastric (39)	Nasojejunal (39)	Infectious complications[c]	0.64
				Length of hospital stay	0.44
				Pain in refeeding	0.60
Chang [64], MA	157	Nasogastric (82)	Nasojejunal (75)	Mortality	0.25
				Multiorgan failure	0.28
				Infected pancreatic necrosis	0.11
Petrov [63], SR	131	Nasogastric (93)	Nasojejunal (38) Parenteral (26)	Mortality	0.45
				Hospital stay	0.43
				Complication rate or infection	0.41
Nally [62], MA	258	Nasogastric (147)	Nasojejunal (85) Parenteral (26)	Nasogastric nutrition without any other modality	Achieved in 90.5%

[a]Mean daily measurements compared with each group (daily) on each end point.
[b]Pain patterns as measured by visual analog scores and analgesic requirements.
[c]Infectious complications (i.e. cultures) individual were not significant, though when accumulated a significant difference was found in favor of nasogastric nutrition.
APACHE II: Acute Physiology and Chronic Health Evaluation II; CRP: C-reactive protein; MA: meta-analysis; NS: no significant difference on each daily measurement for the first five days after initiation of nutrition; RCT: randomized controlled trial.

Another study [66] demonstrated that 40% (which occurred in 15 of the 25 patients) of the nasogastric tubes spontaneously migrated to the jejunum (beyond Treitz' ligament). Either way, a limitation of the randomized controlled trials comparing nasogastric with nasojejunal feeding is that they did not control the location of the tube after several days. As a result, one may question whether patients were actually treated with nasogastric or nasojejunal tube feeding.

Regarding pulmonary complications, a large meta-analysis in patients without pancreatitis [67] compared nasojejunal with nasogastric tube feeding and showed a reduction of pneumonia ($p = 0.004$, 15.8% vs. 22.8%) and ventilator-associated pneumonia ($p = 0.005$, 16.9% vs. 25%) with the use of nasojejunal feeding. This meta-analysis included 1394 patients on the ICU of whom 1117 (80%) were mechanically ventilated. Other meta-analyses, however, did not find significant differences in incidence of pneumonia between nasogastric and nasojejunal feeding [68,69].

In conclusion, considering the limited quality of evidence, when tolerated, nasogastric nutrition appears to be safe. When nasogastric nutrition is not tolerated, or when the caloric need is not reached, nasojejunal feeding tube located beyond Treitz' ligament is recommended. A large high-quality randomized trial is still required to determine whether nasogastric or nasojejunal tube feeding should be the optimal initial treatment strategy. It is possible that in the near future a new method of bedside placement of nasojejunal feeding tubes using electromagnetic guidance can improve the logistics involved with placement of feeding tubes [70–73].

Timing of enteral nutrition

Timing of (oral) nutrition and type of nutrition in (mild) pancreatitis

It has long been believed that oral feeding exacerbates an attack of acute pancreatitis or causes a relapse of pain [21]. Pain relapse after oral intake is associated with prolonged hospital admission and increased costs [74,75].

However, a systematic review [76] showed that only around 20% of patients experience pain relapse during the course of mild acute pancreatitis. In 80% of these patients, pain relapse occurred in the first 48 h after initiation of oral feeding [76]. Another randomized trial including 60 patients with predicted mild acute pancreatitis randomized between nil per mouth until abdominal pain was resolved and immediate start of oral feeding. Hospital stay was shorter when oral feeding was initiated immediately ($p = 0.047$). There was no difference in pain relapse and serum amylase levels [77]. Also, no significant differences were found in a trial comparing oral nutrition based on patient preference versus start of oral nutrition after normalization of serum lipase level [78].

A randomized trial in patients with predicted mild pancreatitis comparing enteral nutrition started on admission with a nil-per-mouth regimen found a significant reduction in pain, need for opiates, and risk of oral food intolerance in favor of the early enteral nutrition group [79]. Unfortunately, these differences did not lead to a reduction in hospital stay. In contrast, patient discomfort caused by tube feeding was not mentioned. A randomized study of 28 patients with predicted mild pancreatitis [75], comparing initiation of oral or jejunal tube nutrition after 48 h, did not find a difference in pain relapse.

Multiple trials have compared different types of initial nutrition (i.e. soft diet, liquid diet, solid diet) in patients with mild acute pancreatitis [80–83]. None of the trials showed a greater recurrence of pain after a specific diet. A meta-analysis showed a reduction in length of hospital stay when a non-liquid diet was given [84].

Recent trials actually showed that refeeding with a full caloric low-fat diet is safe and well tolerated when bowel sounds are present in all patients with (mild or severe) acute pancreatitis [85]. Two recent trials showed that in patients with acute pancreatitis (mild or severe), a strategy with oral feeding with a liquid to low-fat diet and started once they subjectively felt hungry when compared with a strategy of routine oral refeeding (absence of abdominal comfort,

decrease of serum amylase or lipase levels, normal bowel sounds) was safe, feasible, and significantly reduced length of hospital stay [86,87].

Given these results, in patients with pancreatitis it is advised to start oral nutrition with a nonliquid diet when they experience decrease in abdominal pain, are hemodynamically stable, do not require ventilator support, and request oral food.

Timing of nutrition in severe pancreatitis

In acute pancreatitis, reduced contractility of the small bowel promotes bacterial overgrowth and reduced splanchnic blood flow increases intestinal permeability [88]. These pathological processes may enhance the systemic inflammatory response. Current evidence suggests that a very early start of enteral nutrition has a trophic effect on gut wall integrity and may reduce the inflammatory response [88,89]. This hypothesis was confirmed by multiple studies [90,91] including several conventional meta-analyses [92–94] and a recent individual patient data meta-analysis [95]. However, none of these randomized studies primarily focused on timing of enteral feeding.

Recently, the first multicenter randomized trial specifically investigating timing of enteral nutrition in patients with predicted severe acute pancreatitis (PYTHON trial) was published [96]. Patients with predicted severe acute pancreatitis were randomized to receive either early enteral nutrition through a nasojejunal feeding tube (within 24 h after presentation to the emergency department) or a nil-per-mouth regimen for 72 h followed by an oral diet. If oral intake was insufficient, a feeding tube was given and enteral nutrition started (on-demand strategy). In total, 208 patients with predicted severe acute pancreatitis were included. The primary end point consisted of major infection or death within 6 months after randomization. The primary composite end point occurred in 30% in the early group as compared with 27% in the on-demand group ($p = 0.76$). Major infection occurred in 25% in the early group compared with 26% in the delayed group ($p = 0.87$). Mortality was 11% in the early group and 7% in the on-demand group ($p = 0.33$). With the oral diet and on-demand tube feeding strategy, only approximately one-third of patients required a nasojejunal feeding tube.

This trial did not show the hypothesized benefit of early nasoenteric tube feeding in patients with acute pancreatitis who were at high risk for complications. The observation that the clinical outcomes of early tube feeding were similar to those of a diet initiated at 72 h, with tube feeding only if required, challenges the concept of the gut mucosa-preserving effect of early enteral feeding during acute pancreatitis. If tube feeding is restricted to patients who do not tolerate or have insufficient intake with an oral diet, this may result in substantial avoidance of discomfort and costs [97,98].

Achieving caloric targets with enteral nutrition may be challenging in the critically ill patients. Often, caloric targets are not achieved by enteral nutrition alone [99]. In addition, underfeeding is associated with infection [100], an increased duration of mechanical ventilation [101,102], and death [103]. It seems logical to start early initiation of parenteral nutrition to supplement insufficient enteral nutrition during the first week after ICU admission in severely ill patients at risk for malnutrition. In contrast to this hypothesis, a randomized trial [55] and a meta-analysis [54] showed that early parenteral nutrition was inferior to the strategy withholding parenteral nutrition until day 8. Late parenteral nutrition was associated with statistically significant fewer infections, enhanced recovery, and lower health-care costs. Given these results, parenteral nutrition should be withheld till day 7 if caloric goals are not met. Future research needs to establish the optimal timing for initiation of parenteral nutrition in patients with acute pancreatitis.

Use of supplements

Various supplements, such as probiotics, glutamine, omega-3 fatty acids, and different formulations of enteral and parenteral nutrition, are suggested to reduce inflammation and improve outcome in acute pancreatitis [88], although, as discussed below, the results of trials with supplements are disappointing.

Probiotics

Probiotics are considered 'healthy bacteria' as they are thought to play an important role in preventing colonization by potentially pathogenic gastrointestinal microorganisms [104]. A randomized trial with probiotics in 45 patients with acute pancreatitis showed a reduction of infectious complications [105]. Despite these promising results, probiotics were not implemented as a preventive measure in acute pancreatitis because of the small size of the trial and the absence of an intention-to-treat analysis.

A randomized trial [106] with 62 patients receiving nasojejunal nutrition studied the effect of *Lactobacillus* (probiotics) in addition to prebiotics. No significant differences were found in mortality, septic complications, or multiorgan failure. However, the incidence of multiorgan failure and systemic inflammatory response syndrome were significantly lower in the lactobacilli group.

Subsequently, a randomized trial [107] comparing probiotic prophylaxis with placebo in 298 patients with predicted severe acute pancreatitis showed no reduction in infectious complications. Surprisingly, a significant increase in mortality (16% vs. 6%, $p = 0.01$) was seen. Nonocclusive mesenteric ischemia was diagnosed in the probiotics group but not in the placebo group (6% vs. 0%, $p = 0.004$). Subgroup analysis of the patients who had received probiotics demonstrated that bowel ischemia and mortality had only occurred in patients with coexisting multiorgan failure [108]. A retrospective study from Prague [109], where the same mixture of probiotics had been used, supported the hypothesis that the negative effects of probiotics may only be present in patients with organ failure: no effect of probiotic treatment on outcome was demonstrated in 99 patients with pancreatitis without organ failure.

Because of the lack of effect and the possible risk, we recommend against the use of probiotics in acute pancreatitis [40].

Glutamine

Glutamine accounts for 30–35% of all amino acid nitrogen that is transported in plasma and has a protective role against toxic effects of circulating ammonia. Additionally, glutamine is important for the transfer of nitrogen between tissues and is a precursor for many biologically active molecules (i.e. liver, lymphocytes, gut, kidney) [110,111].

In patients with acute pancreatitis, a meta-analysis including 12 randomized trials with in total 505 patients [112] showed a significant reduction in mortality in patients treated with total parenteral nutrition when they received glutamine supplementation (RR = 0.30, 95% CI, 0.15 to 0.60, $p < 0.001$). Unfortunately, no similar beneficial effect was observed in patients receiving glutamine-enriched enteral nutrition.

In critically ill, mechanically ventilated patients, a large, blinded 2-by-2 factorial trial glutamine, provided both intravenously and enterally, did not improve clinical course but increased mortality [113]. Based on these results, glutamine supplements are not recommended in patients with acute pancreatitis. Future studies should focus on enteral glutamine supplementation.

Omega-3 fatty acids

Long-chain polyunsaturated fatty acid derivatives, notably lipoxins, resolvins, and protectins, may have beneficial effects on the inflammatory processes [114]. A randomized controlled trial (Wang 2008) in 40 patients with predicted severe acute pancreatitis, comparing parenteral nutrition with or without omega-3 fatty acids, only found a significant lower C-reactive protein at day 6 without differences in acute respiratory distress syndrome, renal replacement therapy, systemic inflammatory response syndrome, or infectious complications. In other randomized trials including patients with pancreatitis, fatty acid supplementation was associated with a significant decrease in hospital stay [115], significant increase in C-reactive protein [116], or significantly lower APACHE II scores [117]. To date, no adequately powered, randomized trial, with clinical relevant outcomes in patients with acute pancreatitis receiving enteral nutrition with or without omega-3 fatty acid supplements has been performed. Based on the results in these trials, omega-3 fatty acid supplements are not recommended.

(Semi)-elemental versus polymeric formulations

Multiple formulations of enteral nutrition exist, which can be classified in two categories: polymeric and (semi)-elemental [118]. (Semi)-elemental formulations are proposed to have improved absorption rates from the intestine, cause less stimulation of the pancreas, and may be associated with improved tolerance [119]. In contrast, (semi)-elemental nutrition is more expensive and has increased osmolality opposed to polymeric nutrition formulas [120]. One randomized study compared (semi)elemental with a polymeric formulation in 30 patients with acute pancreatitis [119]. In 30 patients, both semi-elemental and polymeric nutrition were well tolerated but length of hospital stay was shorter in the semi-elemental group (23 ± 2 days vs. 27 ± 1 days, $p = 0.006$).

In 2009, a meta-analysis [121] including 20 randomized controlled trials – with 1070 patients with acute pancreatitis – compared the effect of different formulations on outcome. Although the individual trials compared enteral nutrition with parenteral nutrition instead of comparing different formulations, the meta-analysis by means of secondary analysis concluded that polymeric formulations and (semi)-elemental formulations were similar in terms of intolerance and their effect in reducing infections and mortality. These results were similar in a recent Cochrane meta-analysis [122]. Given this, with respect to tolerance and costs, we recommend a polymeric formula.

Vitamins and antioxidants

Patients with severe pancreatitis are suggested to have lower serum levels of antioxidant vitamins and may benefit from supplementation [123]. One trial in patients with predicted severe acute pancreatitis, comparing administration of vitamin C, *n*-acetylcysteine, and selenium with no supplementation, showed no benefit [124]. Antioxidant vitamins could play an additional role in reducing inflammation, but to date this effect has not been confirmed in clinical studies [125].

Expert commentary

In most patients with acute pancreatitis, an oral diet can lead to satisfactory outcomes. Based on patient preference, this can either be a soft or solid diet. Liquid diets are not recommended as these diets may increase the time to tolerance of a full oral diet. When oral feeding is not tolerated for several days after admission or when organ failure develops, enteral feeding should be provided through a nasogastric or nasojejunal feeding tube. Routine early initiation of enteral tube feeding in all patients does not further improve outcome. Only if nasojejunal tube feeding is not tolerated or not feasible after several days is parenteral nutrition advised. Nutritional supplements do not improve outcome (Figure 2).

Five-year view

Nutritional support will continue to play an important role in the management of patients with severe acute pancreatitis. The question whether nasogastric feeding is as safe and effective as nasojejunal feeding in patients with severe acute pancreatitis still needs to be answered.

Perhaps in the future, new compositions of nutritional supplements will become important and new enteral formulas with improved intestinal tolerance will be tested. Although enteral nutrition started within 24 h after admission does not improve outcome, the optimal timing of nutritional support remains unknown.

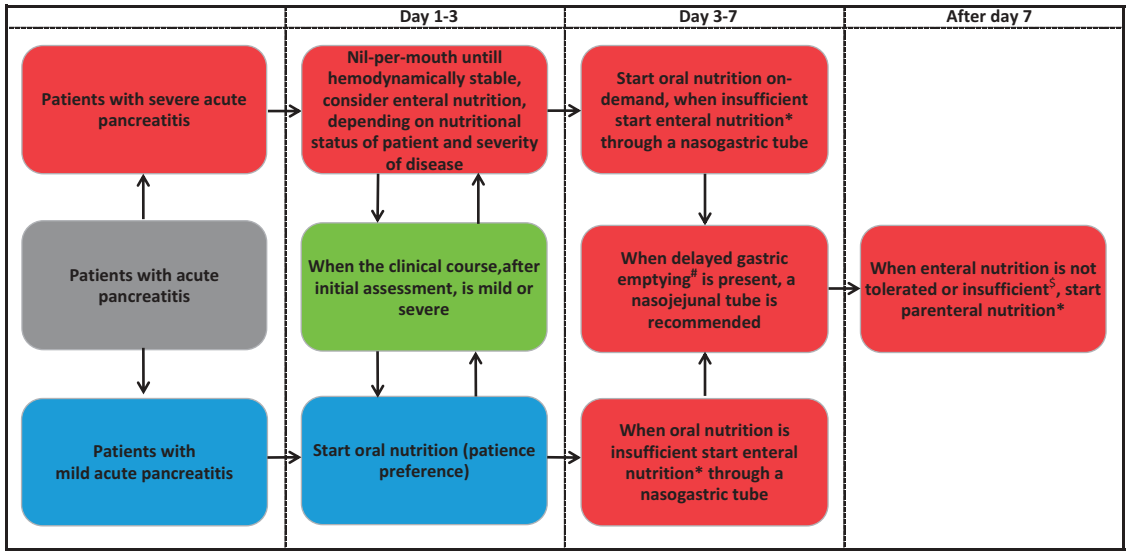

Figure 2. is based on current literature; references Day 1–3 Nil per mouth PYTHON [96]; Oral nutrition in day 1–3 Patient Preference [85–87]; Start Nasogastric tube day 3–7 [59–61]; Start Parenteral Nutrition after day 7 [24–35,54,55].

Finally, accurately predicting the clinical course and nutritional tolerance of patients with acute pancreatitis on admission remains challenging. A more accurate scoring system predicting the need for enteral nutritions needed.

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Key issues

- Oral feeding can be initiated in both predicted mild and predicted severe pancreatitis on patient preference providing that patients are hemodynamically stable and do not require ventilator support [85–87].
- Enteral tube feeding needs to be initiated when oral intake is insufficient after 3–4 days [96].
- Parenteral nutrition should only be used when nasojejunal tube feeding is not tolerated and nutritional support is required [24–43,54,55].
- Enteral nutrition can be administered by either the nasogastric or nasojejunal route, depending on the presence of gastric emptying and the risk of aspiration/pneumonia [59–64].
- Both elemental or polymeric enteral nutrition formulations can be used in patients with acute pancreatitis [121,122].
- There is no evidence base for the use of probiotics, glutamine, vitamins, or antioxidants [105–117].
- Delayed gastric emptying is determined by nausea and/or vomiting and can be measured by gastric retention after 4 h [126].

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