

# Timing and Route of Nutritional Therapy for Severe Acute Pancreatitis: From Bench to Bedside

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ABSTRACT

Nutritional support is one of the core issues in the treatment of severe acute pancreatitis (SAP). With the continuous progression of research on nutritional therapy, a large volume of evidence has emerged on the strategies and approaches of nutritional support for SAP patients. At the same time, the pathogenesis of SAP and the metabolic characteristics have been intensified in the acute phase of critically ill patients, which helps better understand the nutritional treatment strategy of SAP in terms of pathophysiology and pathogenesis. In this article, by searching electronic databases (PubMed, EMBASE, and Web of Science) from the earliest achievable date of each database to November 13, 2021, we discuss and analyze recent hot spots of SAP nutritional support to help individualize the implementation of nutritional strategies.

**KEYWORDS:** Enteral nutrition, nutritional support, severe acute pancreatitis

## INTRODUCTION

The incidence of acute pancreatitis (AP) is increasing annually,<sup>[1,2]</sup> with severe acute pancreatitis (SAP) accounting for approximately 20% of the incidence of AP. According to the revised Atlanta classification (2012),<sup>[3]</sup> SAP was defined as patients with AP who develop persistent organ failure (>48 h). SAP is often accompanied by pancreatic and peripancreatic necrosis and organ failure, with a mortality rate of 20%–40%.<sup>[4,5]</sup> Animal experiments and *in vitro* studies have described pathophysiological processes at the onset of AP,<sup>[6–8]</sup> with severe damage to glandular alveolar cells and an enhanced inflammatory response, leading to systemic inflammatory response syndrome (SIRS) and multiple organ dysfunction syndrome (MODS), resulting in increased AP mortality.<sup>[9]</sup> The treatment of SAP includes early resuscitation, pain management, local treatment of infected necrosis (endoscopic or surgical interventions), and nutritional support.<sup>[10]</sup> SAP is often accompanied by significant catabolism, and nutritional support is therefore an important part of the treatment strategy.<sup>[11,12]</sup> This article combines the latest advances and reviews the controversies that remain in the nutritional treatment of SAP, focusing on the approaches and timing of initiation.

## DATA SOURCES AND SEARCHES

We searched the electronic databases of PubMed, EMBASE and Web of Science. The search terms and MeSH heading were as follows: “acute pancreatitis,” or “severe acute pancreatitis,” or “acute necrotizing pancreatitis” and “nutrition” or “nutritional therapy” or “nutritional support” or “nutritional intervention” or “enteral nutrition” or “parenteral nutrition” or “nasogastric feeding” or “nasojejunal feeding” or “total parenteral nutrition” or “supplementary parenteral nutrition.” The search included literature published from the earliest achievable date of each database to November 13, 2021. The selected articles were discussed.

## ETIOLOGY AND PATHOPHYSIOLOGY OF SEVERE ACUTE PANCREATITIS

AP is more common in patients with gallstones and alcoholism, and other causative factors include drugs,


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endoscopic retrograde cholangiopancreatography, hypercalcemia, hypertriglyceridemia, surgery, and trauma.<sup>[13,14]</sup> The pathogenesis of SAP includes the classic theory of pancreas autodigestion<sup>[15]</sup> and the leukocyte overactivation–inflammatory cytokines cascade,<sup>[16]</sup> calcium overload in pancreatic acinar,<sup>[17]</sup> and apoptosis.<sup>[6]</sup> Among them, premature trypsinogen activation plays a leading role in the pathogenesis of pancreatitis. Alcohol and other pancreatic toxins impair the function of microtubules and thus impair exocytosis at the top of zymogen granules in acinar cells, resulting in the accumulation of zymogen granules in the cells, and the synthesis of lysosomes and digestive enzymes. After the fusion of lysosomes and zymogen particles, cathepsin B in lysosomes activates trypsinogen into trypsin,<sup>[18]</sup> the latter activates a series of digestive enzymes, which are released into the cytoplasm, resulting in membrane damage and cell necrosis.<sup>[10,19]</sup>

Recent studies on the mechanism of SAP have shown that in the early stage of pancreatitis, in addition to the activation pathway of trypsinogen in the acinar cells, the Nuclear Factor Kappa-B (NF- $\kappa$ B) pathway might also play an important role. The NF- $\kappa$ B activation and zymogen activation pathways parallel each other; approximately 50% of acinar cells are damaged by early trypsinogen activation, while NF- $\kappa$ B activation leads to a severe local inflammatory response, accounting for the other half.<sup>[15,20]</sup> The progression of early AP is caused by inflammatory factors produced by acinar cells and their proinflammatory response, leading to the spread of systemic inflammation. In fact, the early activation of NF- $\kappa$ B in AP does not depend on trypsin. NF- $\kappa$ B activates inflammatory factors/immune cells, leading to late acinar cell necrosis and SIRS, which is another important pathway of AP.<sup>[15,20]</sup>

Furthermore, recent studies have shown that pancreatic duct secretions can reduce pancreatic injury.<sup>[21]</sup> Pancreatitis still occurs and progresses in animal models lacking trypsinogen activation,<sup>[22]</sup> while cytokines play an increasingly important role in predicting the occurrence of AP. The activation of inflammatory signal transduction in the acinar cells may lead to autophagy and dysfunction of lysosomes and mitochondria. Reactive oxygen species, calcium signaling pathways, and changes in cystic fibrosis transmembrane regulatory factor are also important mechanisms in the pathogenesis of AP.<sup>[10,15]</sup> Alcohol, nicotine, and bile acids can also damage acini and activate the above mechanisms.<sup>[10]</sup>

## CONTROVERSIES IN THE NUTRITION SUPPORT OF SEVERE ACUTE PANCREATITIS

In SAP, inflammation caused by necrosis or secondary infection will lead to increased calorie demand, loss of a large amount of protein, as well as abdominal pain,

abdominal distension,<sup>[23]</sup> and nausea and vomiting, which will lead to reduced food intake and decreased pancreatic exocrine function. Coupled with some complications, these events will lead to nutritional deterioration and negative nitrogen balance, and finally damage to the function and structure of vital organs.<sup>[24]</sup>

In the early years, many nutritional treatment concepts for severe pancreatitis were put forward based on the classical theory of pancreatic self-digestion, the main purpose of which was to reduce/inhibit self-digestion, including intestinal rest<sup>[25-28]</sup> (nothing by mouth, gastrointestinal decompression, and early total parenteral nutrition [TPN]), to reduce pancreatic exocrine secretion,<sup>[29]</sup> and to reduce the activation of trypsin by gastric fluid stimulation (gastrin) and small intestinal fluid stimulation (cholecystokinin).<sup>[30,31]</sup> Somatostatin and its analogs were also used to inhibit the secretion of pancreatic exocrine enzymes, which was thought to decrease the severity of pancreatitis.<sup>[32]</sup> Early studies implied that the decrease in pancreatic exocrine secretion and trypsin during TPN treatment can reduce the inflammatory response induced by trypsin, which is theoretically beneficial to the recovery of pancreatic function.<sup>[28,33]</sup> In addition, TPN can partially meet the energy needs of the body and reduce metabolic-related complications. However, a recent meta-analysis suggested that enteral nutrition (EN) is recommended as the initial treatment option for patients with SAP compared with TPN.<sup>[34,35]</sup> At present, there is increasing evidence that intestinal rest is related to the increase in infectious complications caused by intestinal mucosal atrophy and bacterial translocation.<sup>[36]</sup> Therefore, to maintain intestinal barrier function, EN has received increasing attention in the nutritional treatment of SAP.<sup>[37-39]</sup>

## ROUTE OF NUTRITION

### Route of nutrition: Enteral or parenteral?

A recent meta-analysis showed that<sup>[40,41]</sup> early EN can greatly reduce the incidence of infectious complications, while there was no significant difference in mortality compared with early parenteral nutrition (PN) in critically ill patients. Similarly, studies on severe pancreatitis have shown that compared with PN, EN can significantly reduce the incidence of infective peripancreatic necrosis and single organ failure/multiple organ failure.<sup>[42-44]</sup>

In fact, the intestinal epithelium is damaged in patients with severe pancreatitis who lack EN.<sup>[45]</sup> In the absence of food stimulation, the contractility of the small intestine decreases, which promotes the excessive growth of bacteria in the intestinal cavity and attaches to the intestinal epithelial cells, resulting in programmed apoptosis and intestinal barrier dysfunction.<sup>[46,47]</sup> Second, the decrease in visceral blood flow leads to ischemia–reperfusion injury,<sup>[48]</sup>

which increases intestinal vascular permeability and enables bacteria to activate macrophages in the blood vessels.<sup>[49-51]</sup> Once macrophages are activated, circulating neutrophils are activated and spread far away (such as to the lungs, liver, and kidneys), further promoting oxidative stress. These pathological processes may enhance the systemic inflammatory response.<sup>[52]</sup>

Therefore, EN and PN are different not only in nutritional approaches. EN therapy has many theoretical and laboratory advantages, including protection of gastrointestinal barrier function (such as tight junctions),<sup>[53,54]</sup> preservation of intestinal B cells/lymphoid tissue, regulation of intestinal microecology to maintain the normal growth of intestinal flora,<sup>[43]</sup> stimulation of intestinal blood flow<sup>[55]</sup> to promote the release of endogenous factors, and protection of intestinal immune function.<sup>[56-58]</sup> At the same time, it may help prevent stress ulcers and protect distal organs through the enteropulmonary axis.<sup>[59]</sup>

At present, most studies have found that EN can reduce infectious complications, even reduce the length of hospitalization and mechanical ventilation, and improve the prognosis<sup>[60,61]</sup> and is more economic.<sup>[62,63]</sup> However, critically ill patients often develop gastrointestinal dysfunction that leads to underfeeding, which increases nutritional risk, infection, and intensive care unit (ICU) hospitalization.<sup>[63]</sup> PN can easily reach the feeding target and avoid the risk of malnutrition. There is also a theoretical possibility for avoiding stimulated gastrointestinal pancreatic exocrine secretion; however, PN was found to increase the risk of infection (controversial), to be prone to overfeeding and metabolic complications, and to increase costs.<sup>[63]</sup> In summary, many current guidelines and consensus believe that critically ill patients, including SAP, prefer EN treatment to PN.<sup>[11,63,64]</sup> Summary of articles regarding comparison of EN and PN in SAP is presented in Table 1.

#### **Route of enteral nutrition: Nasojejunal or nasogastric?**

Nasojejunal feeding has been believed to decrease pancreatic secretion, which helps restore gut mucosal integrity, whereas gastric or duodenal feeding has been believed to stimulate pancreatic secretion, causing an exacerbation of the inflammatory process in the pancreas.<sup>[35,69]</sup> However, recent randomized controlled trials (RCTs) on pancreatitis have not found a significant advantage of nasojejunal feeding over gastrointestinal feeding in terms of mortality, infectious complications, gastrointestinal complications, energy balance, or length of hospital stay.<sup>[42,70-72]</sup> Feeding intolerance, risk of aspiration,<sup>[40]</sup> and risk of pneumonia were the main factors that need to be considered for critically ill patients when choosing the nasojejunal or nasogastric route.<sup>[63]</sup> The incidence of pneumonia by jejunal feeding was relatively

low while preserving a high nutritional efficiency compared with gastric feeding, but there was no difference in mortality or ICU admission.<sup>[1,73,74]</sup> If the nasojejunal feeding approach cannot be conducted in a short time, it is recommended not to wait and to choose nasogastric feeding.<sup>[63]</sup> Based on the current research, patients with gastric feeding intolerance and ineffective prokinetic drugs, as well as patients with a high risk of aspiration, should be given nasojejunal feeding.

Current studies on AP have also shown that early nasogastric tube EN is not superior to oral feeding.<sup>[10,75]</sup> For mild AP, both American and European guidelines recommend early oral feeding as long as patients can tolerate it.<sup>[42,63,64,76]</sup> However, AP is often complicated with abdominal pain, nausea, vomiting, and even paralytic intestinal obstruction, resulting in difficulties when implementing early oral feeding. Summary of articles regarding comparison of nasojejunal or nasogastric feeding in SAP is presented in Table 2.

## **TIMING OF NUTRITION SUPPORT**

### **Early enteral nutrition versus delayed enteral nutrition?**

Studies of early EN versus delayed EN in critically ill patients have shown that early EN reduces mortality and infection rates in critically ill patients,<sup>[40,80,81]</sup> and studies of AP have also shown that delayed feeding significantly increased the risk of pancreatic necrosis compared with early feeding.<sup>[42,70]</sup> However, the PYTHON study showed no significant benefit in terms of infection and mortality in patients with early nasal feeding compared with oral feeding after 3 days.<sup>[75]</sup> In fact, studies of early initiation of EN in critically ill patients and in patients with SAP have not been confirmed by large high-quality RCTs;<sup>[82]</sup> nevertheless, current guidelines consistently recommend early implementation of EN; as the timing of EN initiation varies from study to study, no consensus recommendation has been reached on a specific time for initiation, which can be within 24–72 h if available.<sup>[42,64,83,84]</sup>

The early stage of SAP is often combined with hypovolemia and distributive shock. For SAP patients with unstable hemodynamics, the primary focus is resuscitation and respiratory support<sup>[63,85]</sup> and EN should be started within 24–48 h after resuscitation or after hemodynamic stabilization, which is defined as adequate perfusion pressure, stable doses of vasoactive drugs, stabilized or decreasing levels of lactate and metabolic acidosis, and mean arterial pressure  $\geq 60$  mmHg associated with improved outcomes.<sup>[61]</sup> In the NUTRIREA-2 study,<sup>[86]</sup> early EN and PN were performed in patients admitted to the ICU with mechanical ventilation and vasoactive drugs within 24 h of admission, and it was found that diarrhea, vomiting, gastrointestinal ischemia, and pseudointestinal

**Table 1: Summary of articles regarding comparison of enteral and parenteral nutrition in severe acute pancreatitis**

Author	Findings	Type of analysis	Outcomes
Yao <i>et al.</i> <sup>[43]</sup>	Lower overall mortality (RR: 0.36, 95% CI: 0.20-0.65) and multiple organ failure rate (RR: 0.39, 95% CI: 0.21-0.73) in EN	Meta-analysis including 5 RCTs (348 patients) comparison of EN and PN in SAP	EN is preferred rather than PN in SAP patients
Cao <i>et al.</i> <sup>[55]</sup>	Lower risk of infections (OR: 0.236, 95% CI: 0.120-0.464), pancreatitis-related complications (OR: 0.456; 95% CI: 0.234-0.888), organ failure (OR: 0.334; 95% CI: 0.167-0.670), multiple organ (OR: 0.306; 95% CI: 0.128-0.736), dysfunction syndrome (OR: 0.251; 95% CI: 0.095-0.666), and mortality (OR: 0.251; 95% CI: 0.095-0.666) in EN	Meta-analysis including 6 RCTs (295 patients) comparison of EN and TPN in SAP	EN is safer compared to TPN in SAP patients
Al-Omran <i>et al.</i> <sup>[47]</sup>	Lower mortality (RR: 0.50, 95% CI 0.28-0.91), multiple organ failure (RR: 0.50, 95% CI: 0.37-0.81), and systemic infections (RR: 0.39, 95% CI: 0.23-0.65). Shorter length of hospital stay (reduction 2.37 days, 95% CI: -7.18-2.44). Lesser need for operative interventions (RR: 0.44, 95% CI: 0.29-0.67) in EN	Systematic review including 8 RCTs (348 patients) comparison of EN and TPN in AP	EN should be considered the standard in AP patients
Marik and Zaloga <sup>[65]</sup>	Lower incidence of infection (RR: 0.45, 95% CI: 0.26-0.78), reduced surgical interventions to control pancreatitis (RR: 0.48, 95% CI: 0.22-1.0), and a reduced length of hospital stay (mean reduction 2.9 days, 1.6-4.3 days, $P < 0.001$ ) in EN	Meta-analysis including 6 RCTs (263 patients) comparison of EN and PN in AP	EN should be the preferred route of nutritional support in patients with acute pancreatitis
Petrov <i>et al.</i> <sup>[66]</sup>	Lower risk of multiple organ failure (RR: 0.44; 95% CI: 0.23-0.84), pancreatic infectious complications (RR: 0.46; 95% CI: 0.27-0.77), and mortality (RR: 0.46; 95% CI: 0.20-0.99)	Meta-analysis including 11 RCTs (268 patients) comparison of EN and PN in AP	EN is more effective than PN
Yi <i>et al.</i> <sup>[67]</sup>	Lower mortality (RR: 0.37, 95% CI: 0.21-0.68), infections (RR: 0.46, 95% CI: 0.27-0.78), MODS (RR: 0.44, 95% CI: 0.22-0.88), and surgery rates (RR: 0.41, 95% CI: 0.23-0.74) in EEN. Comparable duration of hospitalization (RR: -14.10, 95% CI: -36.48-8.26) and nutrition (RR: -1.50, 95% CI: -9.56-6.56)	Meta-analysis including 8 RCTs (381 patients) comparison of TEN and TPN in SAP	TEN was significantly superior to TPN in SAP
Li <i>et al.</i> <sup>[34]</sup>	Lower rate of mortality (OR: 0.31, 95% CI: 0.18-0.54), complications (OR: 0.41, 95% CI: 0.22-0.77), MODS (OR: 0.17, 95% CI: 0.06-0.52), surgery (OR: 0.17, 95% CI: 0.05-0.62), and shorter duration of hospitalization (mean difference, OR: -0.59, 95% CI: -2.56-1.38) in TEN	Meta-analysis including 9 RCTs (500 patients) comparison of TEN and TPN in SAP	TEN is safer and more effective than TPN for patients with SAP
Wu <i>et al.</i> <sup>[35]</sup>	Lower rate of mortality (RR: 0.43, 95% CI: 0.23-0.78), infectious complications (RR: 0.53, 95% CI: 0.39-0.71), and shorter duration of hospitalization (mean difference -2.93, 95% CI: -4.52-1.34) in EN, MODS (RR: 0.63, 95% CI: 0.39-1.02) in EN and PN	Meta-analysis including 11 RCTs (562 patients) comparison of EN and PN in SAP	EN is recommended as an initial treatment option for patients with SAP
Liu and Gao <sup>[68]</sup>	Lower rate of infection incidence (OR: 0.25, 95% CI: 0.10-0.623), mortality (OR: 0.59, 95% CI: 0.37-0.94) in pancreatitis (SAP)	Meta-analysis including 10 RCTs (488 patients) comparison of TEN and TPN in SAP	TEN was significantly superior to TPN in SAP

RR: Risk ratio, OR: Odds ratio, CI: Confidence interval, EN: Enteral nutrition, RCT: Randomized controlled trial, PN: Parenteral nutrition, SAP: Severe acute pancreatitis, TEN: Total enteral nutrition, TPN: Total parenteral nutrition, EEN: Early enteral nutrition, MODS: Multiorgan dysfunction syndrome, AP: Acute pancreatitis

obstruction presented less in the early PN group than in the early EN group, but mortality and infection rates were not significantly different between the two groups. Subsequent hematological analysis<sup>[87]</sup> also showed that although the level of citrulline, which reflects the quality of intestinal epithelial cells, was significantly increased in the early EN group, it was also accompanied by an increase in the level of entero-fatty acid-binding protein, which reflects intestinal ischemia, suggesting that early EN requires attention to intestinal blood flow and intestinal function.

The early stage of SAP is often characterized by circulatory instability and reduced peritoneal perfusion, as well as microvascular leakage and massive fluid loss due to

pancreatic inflammation, causing visceral vasoconstriction, intra-abdominal hypertension (IAH), and even abdominal compartment syndrome (ACS), which can affect intestinal blood flow and intestinal function.<sup>[88]</sup> Animal studies have shown that increased intra-abdominal pressure (IAP) leads to decreased abdominal perfusion pressure, decreased superior mesenteric artery and portal venous blood flow,<sup>[89]</sup> decreased perfusion of visceral organs, and decreased microcirculatory blood flow,<sup>[90]</sup> resulting in intestinal mucosal and systemic circulatory acidosis.<sup>[91]</sup> A study by Smit *et al.* included 59 cases of SAP, of which 29 were continuously monitored for IAP; 13 cases (44.8%) were found to progress to ACS, of which 10 cases underwent open decompressions and revealed varying degrees of intestinal

**Table 2: Summary of articles regarding comparison of nasogastric versus nasojejunal tube in enteral nutrition in severe acute pancreatitis**

Author	Findings	Type of analysis	Outcomes
Nally <i>et al.</i> <sup>[71]</sup>	No significant difference in the delivery of 75% of nutritional targets (pooled RR: 1.02, 95% CI: 0.75-1.38) or no increased risk of change to TPN (pooled RR: 1.05, 95% CI: 0.45-2.48), diarrhea (pooled RR: 1.28, 95% CI: 0.62-2.66), exacerbation of pain (pooled RR: 1.10, 95% CI: 0.47-2.61), or tube displacement (pooled RR: 0.44, 95% CI: 0.11-1.73) in both groups	Meta-analysis including 4 RCTs (258 patients) comparison of NGT and NJT in EN in SAP	NG feeding is efficacious and represents a viable alternative to NJ feeding in patients with SAP
Zhu <i>et al.</i> <sup>[72]</sup>	No significant difference in the incidence of mortality (RR: 0.71, 95% CI: 0.38-1.32), infectious complications (RR: 0.77, 95% CI: 0.45-1.30), the digestive complications (RR: 1.02, 95% CI: 0.57-1.83), and achievement of energy balance (RR: 1.00, 95% CI: 0.97-1.03) between the NG and NJ groups	Meta-analysis including 4 RCTs (237 patients) comparison of NGT and NJT in EN in SAP	NG nutrition was as safe and effective as NJ nutrition in patients with SAP
Chang <i>et al.</i> <sup>[73]</sup>	No significant differences in the incidence of mortality (RR: 0.69, 95% CI: 0.37-1.29), tracheal aspiration (RR: 0.46, 95% CI: 0.14-1.53), diarrhea (RR: 1.43, 95% CI: 0.59-3.45), exacerbation of pain (RR: 0.94, 95% CI: 0.32-2.70), and meeting energy balance (RR: 1.00, 95% CI: 0.92-1.09) between the two groups	Meta-analysis including 4 RCTs (237 patients) comparison of NGT and NJT in EN in SAP	Nasogastric feeding was not inferior to NJ
Eatock <i>et al.</i> <sup>[77]</sup>	No significant difference in the time to commencement of feed (Mann-Whitney <i>U</i> -test, CI: -2.0-0.0), the time to full rate of feeding at 100 ml/h (Mann-Whitney <i>U</i> -test CI: -9.0-12.0), the proportion admitted to the ICU (Mann-Whitney <i>U</i> -test CI: -12.0-5.0; Fisher's exact test CI: -0.42-0.18), and target calories supplement (Mann-Whitney <i>U</i> -test CI: 0.0-0.0)	Pilot randomized control trial including 50 patients comparison of NGT and NJT in EE in SAP	The simpler, cheaper, and more easily used NG is as good as NJ feeding in SAP
Kumar <i>et al.</i> <sup>[78]</sup>	No significant difference in the final outcome (i.e., discharge, surgery, or death; <i>P</i> =0.76)	Randomized control trial including 31 patients. comparison of NGT and NJT in EE in SAP	EN at a slow infusion is well tolerated by both NJ and NG in SAP
Singh <i>et al.</i> <sup>[79]</sup>	During the hospital stay, the presence of any infectious complication was 23.1% and 35.9% (significantly different), respectively. The effect size of the difference of infectious complications was -12.8 (95% CI: -29.6-4.0).	Randomized control trial including 78 patients comparison of NGT and NJT in EE in SAP	Early enteral feeding through NG was not inferior to NJ in patients with SAP

RR: Risk ratio, CI: Confidence interval, RCT: Randomized controlled trial, TPN: Total parenteral nutrition, EN: Enteral nutrition, SAP: Severe acute pancreatitis, NGT: Nasogastric tube, NJT: Nasojejunal tube, NG: Nasogastric, NJ: Nasojejunal, ICU: Intensive care unit, EE: Energy expenditure

ischemia and necrosis (small bowel/terminal ileum/sigmoid colon/colon, local or total ischemic necrosis).<sup>[88]</sup> Thus, special attention should be given to gastrointestinal function and blood flow when providing early EN in SAP. Usually, IAH requires gastrointestinal decompression, which also causes difficulties in implementing early EN. Summary of articles regarding comparison of early and delayed EN in SAP is listed in Table 3.

In addition, whether EN increases IAP and whether it is tolerated by patients with IAH are also issues that need to be considered. In a study of 60 patients with SAP, early EN (within 48 h) did not cause IAH compared with delayed EN (initiated after 8 days) but increased feeding intolerance. Further analysis found that feeding intolerance was significantly increased when IAP was  $\geq 15$  mmHg, regardless of early or delayed EN. Nevertheless, early EN still reduced ICU length of stay, ameliorated MODS, and reduced infections.<sup>[96]</sup> For patients with IAH, when IAP  $\leq 20$  mmHg, EN should be given earlier, while feeding intolerance and changes in IAP should be monitored carefully; if feeding intolerance fails to improve or IAP still increases after active measures are taken, enteral

feeding should be reduced or suspended; for patients with grade III or higher IAP and ACS, EN should be delayed.<sup>[11,97]</sup>

Combining the recent recommendations of the European Society for Critical Care Medicine and the European Society for Parenteral Enteral Nutrition, early EN should be performed within 24–48 h if hemodynamically stable, and when there are no contraindications to EN; in cases of circulatory instability, hypoxia/acidosis, intestinal ischemia, ACS, and gastric residual volume  $>500$  ml/6 h, EN needs to be delayed. SAP *per se* as well as weak bowel sounds and diarrhea are not reasons to delay EN.<sup>[40,98]</sup>

#### Timing of parenteral nutrition initiation

There is a consensus that early and adequate EN reduces infection and ICU length of stay and improves prognosis.<sup>[92]</sup> However, patients with SAP usually present with gastrointestinal dysfunction or feeding intolerance, resulting in insufficient feeding. At the same time, SAP is often complicated by intestinal obstruction, ACS, and mesenteric ischemia, which are also contraindications of EN. Currently, it is generally accepted that PN can

**Table 3: Summary of articles regarding comparison of early and delayed enteral nutrition in severe acute pancreatitis**

Author	Findings	Type of analysis	Outcomes
Qi <i>et al.</i> <sup>[81]</sup>	Lower rate of local infectious complications (OR: 0.51, 95% CI: 0.29-0.88) and MODS (OR 0.30; 95% CI: 0.09-0.96) only in EEN in pSAP and SAP	Meta-analysis including 8 RCTs (727 patients) comparison of EEN (<24 h) with DEN (>24 h) and PN in AP patients	EEN is safe and provides benefits for pSAP or SAP, but not for MAP and MSAP patients
Jin <i>et al.</i> <sup>[92]</sup>	Lower secondary infection rates (OR: 0.161, 95% CI: 0.036-0.718) and abdominal distension complications (EEN=8.8% vs. DEN=38.5%) in EEN	Prospective analysis of 104 patients comparison of EEN ( $\leq 3^{\text{rd}}$ day) and DEN ( $> 3^{\text{rd}}$ day) in MSAP or SAP	EEN could reduce the risk of secondary infection and improve the nutritional status of patients with acute pancreatitis, with a better tolerance
Song <i>et al.</i> (2018) <sup>[12]</sup>	Lower mortality (RR: 0.53, 95% CI: 0.35-0.81), MOF (RR: 0.58, 95% CI: 0.43-0.77), surgery (RR: 0.50, 95% CI: 0.33-0.75), systemic and local infection rates (RR: 0.75, 95% CI: 0.61-0.93) in EEN	Meta-analysis including 10 RCTs (1051 patients) comparison of EEN ( $\leq 48$ h) and DEN ( $> 48$ h) or PN in pSAP, SAP	EEN is efficient and safe for the patients with SAP or pSAP
Bakker <i>et al.</i> <sup>[93]</sup>	Lower composite endpoint (adjusted OR: 0.44, 95% CI: 0.20-0.96) and organ failure (OR: 0.42; 95% CI: 0.19-0.94) in EEN	Meta-analysis of 8 RCTs (165 patients) comparison of EEN ( $\leq 24$ h) and DEN ( $> 24$ h) in all severity degrees of AP	EEN was associated with a reduction in complications compared with DEN
Li <i>et al.</i> <sup>[94]</sup>	Lower risk of mortality (RR: 0.27, 95% CI: 0.10-0.78), organ failure (RR: 0.42, 95% CI: 0.24-0.77), hyperglycemia (RR: 0.34, 95% CI: 0.18-0.64), and catheter-related septic complications (RR: 0.15, 95% CI: 0.02-1.11) in EEN	Meta-analysis of 12 RCTs (625 patients) comparison of EEN ( $\leq 24$ h, 24-72 h) and DEN ( $\geq 72$ h) TPN in SAP, pSAP	EEN within 24 h of admission presented significantly better effect in reducing mortality than EEN at 24-72 h
Feng <i>et al.</i> <sup>[95]</sup>	Lower risk of multiple organ failure (RR: 0.67, 95% CI: 0.46-0.99)	Meta-analysis including 6 RCTs (1007 patients) comparison of EEN ( $\leq 48$ h) and DEN ( $> 48$ h) or PN in AP	EEN is superior to DEN for patients with acute pancreatitis

RR: Risk ratio, OR: Odds ratio, CI: Confidence interval, MODS: Multiorgan dysfunction syndrome, EEN: Early enteral nutrition, SAP: Severe acute pancreatitis, pSAP: Predicted SAP, RCT: Randomized controlled trial, DEN: Delayed enteral nutrition, PN: Parenteral nutrition, AP: Acute pancreatitis, MAP: Mild acute pancreatitis, MSAP: Moderately severe acute pancreatitis, MOF: Multiorgan failure, TPN: Total parenteral nutrition

be supplemented when EN is insufficient; however, controversies still exist regarding the time to add PN when enteral feeding is insufficient.<sup>[82]</sup> Timing of SPN in SAP patients may refer to studies in critically ill patients, as there is a paucity of evidence exclusively in SAP. Studies have shown that early addition of PN may increase infectious complications and length of hospital stay, while conversely, delayed PN may lead to low feeding and poor clinical outcomes if PN is delayed.<sup>[99,100]</sup>

According to the characteristics of energy metabolism, critical illness is comprised of two different phases, namely, the acute phase and chronic rehabilitation phase. The acute phase includes two periods: an early period (1–2 days) with unstable metabolism and increased catabolism and a late period (3–7 days) with muscle wasting and stabilization of metabolic disturbances.<sup>[40]</sup> Worse still, pancreatic inflammation triggers an SIRS, increases metabolic rates, and generates a catabolic state.<sup>[71]</sup> The early acute phase of critically ill patients is characterized by increased cytokine production, sympathetic excitation (massive release of catecholamines), and more catabolic hormones than synthetic hormones (glucocorticoids, glucagon, thyroxin) as same as a result of trauma, infection, and shock. Patients in a high catabolic state usually present with accelerated glycogen breakdown, enhanced gluconeogenesis, and

accelerated breakdown of skeletal muscle proteins and cellular structural proteins. The hypercatabolic state produces large amounts of endogenous calories; thus, the addition of SPN in this phase can easily lead to overfeeding.<sup>[101]</sup>

Recent studies and guidelines favor late administration of SPN, suggesting initiating SPN when EN does not meet 60% of the target requirement in 1 week; earlier SPN can be given for patients with high nutritional risk.<sup>[40,63]</sup> Early implementation of SPN could be given to patients at high nutritional risk with NRS 2002  $\geq 5$  or NUTRIC score  $\geq 6$  and if EN cannot meet 60% of target energy and protein requirements within 48–72 h.<sup>[102]</sup> Although the debate on the timing of adding PN will remain, ultimately, the clinical workup will be individualized based on the patient's pathophysiology and metabolic changes, balancing nutritional risks and benefits.

## CONCLUSION

Nutritional support is an important part of SAP treatment, and EN is preferred to PN; early tube feeding for SAP, both gastric and postpyloric, is optional. EN should be implemented as early as possible (within 48 h), but gastrointestinal function needs to be monitored closely. SPN needs to be added if EN cannot meet the target

energy intake, and the timing needs to be combined with the nutritional risk assessment, usually after 7 days, but can be advanced for those with high nutritional risk.

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### Conflicts of interest

There are no conflicts of interest.

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