

# Nutrition Management in Acute Pancreatitis

Meera Ramanathan, MD<sup>1</sup> ; and Abdul Aziz Aadam, MD<sup>2</sup>

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## Abstract

Acute pancreatitis (AP) is one of the most prevalent gastrointestinal conditions necessitating inpatient care. In the United States, over 275,000 patients are hospitalized for management of AP, with an estimate that over \$2.5 billion is spent annually in treatment, with incidence continuing to rise. AP is a highly inflammatory and catabolic state, putting all patients with the condition at risk of malnutrition. Numerous approaches to nutrition support in pancreatitis have been evaluated and remain controversial. In this narrative review, we aim to give an overview of indications for nutrition and approach to management of nutrition in severe and predicted severe AP based on currently available data. (*Nutr Clin Pract.* 2019;34(suppl 1):S7–S12)

## Keywords

acute pancreatitis; enteral nutrition; exocrine pancreatic insufficiency; nutrition; nutrition support; nutrition therapy

## Introduction

Acute pancreatitis (AP) is one of the most prevalent gastrointestinal conditions necessitating inpatient care.<sup>1</sup> In the United States, over 275,000 patients are hospitalized for management of AP, with an estimate that over \$2.5 billion is spent annually in treatment, with incidence continuing to rise.<sup>2</sup>

The pathophysiology of AP involves a complex sequence of events, including activation of acinar cell zymogens, which leads to autodigestion of pancreatic and surrounding tissue, activation of the immune system, and release of pro-inflammatory mediators, ultimately increasing vascular permeability. This then gives rise to the systemic inflammatory response syndrome (SIRS) and multiorgan dysfunction.<sup>3</sup> This intricate process gives rise to a vast spectrum of disease severity from transient, self-limited presentations to severe, fulminant progression of multiorgan failure and ultimately death. The 2012 revised Atlanta Classification system is often employed to identify patients in each of the classes in order to better focus treatment strategies.<sup>4</sup> The severity of AP is classified as mild, moderate, or severe depending on the extent of injury to and around the pancreatic tissue and, importantly, the extent of systemic injury<sup>4</sup> (Table 1).

Pancreatitis has consistently presented a therapeutic conundrum given the lack of medications found to be effective therapies. Management, thus, is focused on supportive interventions—most notably, aggressive hydration. Immediate and aggressive fluid resuscitative efforts assist in minimizing the untoward effects of hypovolemia in the setting of an ongoing systemic inflammatory process. Additionally, AP is known to be a highly inflammatory and

catabolic state, putting all patients with the condition at risk of malnutrition. As such, nutrition aids in restoration of energy balance and maintenance of the gut barrier function, ultimately decreasing risk of bacterial translocation. This thereby decreases risk of the complications of pancreatitis such as infection and necrosis.

## Mild-Moderate AP

The clinical course of AP has been divided into 2 distinct phases: (1) early, which is within 1 week of symptom onset, characterized by the SIRS with or without organ dysfunction, and (2) late, which is defined as >1 week into the clinical syndrome, characterized by local or systemic complications.<sup>5</sup> The majority of patients recover without incident, oral intake is tolerated without issue, and they are discharged within 48–72 hours. This suggests that early oral feeding is safe in patients with mild or moderate disease.<sup>6</sup>

From the <sup>1</sup>Division of Hospital Medicine, Northwestern University Feinberg School of Medicine, Chicago, Illinois, USA; and the <sup>2</sup>Division of Gastroenterology and Hepatology, Northwestern University Feinberg School of Medicine, Chicago, Illinois, USA.

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## Corresponding Author:

Abdul Aziz Aadam, MD, 676 North Saint Clair, Suite 1400, Chicago, IL 60611, USA.

Email: [abdul.aadam@northwestern.edu](mailto:abdul.aadam@northwestern.edu)

**Table 1.** Atlanta Classification for Grading Severity of Acute Pancreatitis.

Grade of Severity	Criteria for Classification
Mild acute pancreatitis	No organ failure No local or systemic complications
Moderate-severe acute pancreatitis	Organ failure that resolves within 48 hours (transient organ failure) Local or systemic complications without persistent organ failure
Severe acute pancreatitis	Persistent organ failure (>48 hours): Single organ failure Multiorgan failure

Twenty percent of patients presenting with AP, however, develop severe AP (SAP), with a mortality rate in this group reported to be as high as 30% because of an increased risk of developing acute multiorgan failure, extended hospitalizations including intensive care unit stays, and possible invasive treatments of local or systemic complications.<sup>7-9</sup>

### *Severe and Predicted SAP*

SAP is a highly catabolic and energy-consuming state leading to loss of nutrients, water, and electrolytes as well as dysregulation of acid-base balance.<sup>10</sup> In one study, 80% of patients were found to have at least 40 g/d protein loss, leading to a negative nitrogen balance and prolonging recovery time.<sup>11,12</sup> Intestinal permeability, secondary to damaged intestinal epithelial cells, is notably increased in the early phase of SAP, allowing for systemic translocation of inflammatory mediators, toxins, and gut microbiota.<sup>13</sup> Without early interventions, increased intestinal permeability in conjunction with metabolic derangements increases risk of infections, multiorgan dysfunction, and ultimately, worse prognosis and survival rates for patients with SAP.<sup>14</sup> Thus, nutrition support and optimization of intestinal function is imperative in the overall management of patients presenting with SAP.<sup>15</sup>

Numerous approaches to nutrition support in pancreatitis have been evaluated and remain controversial, including parenteral nutrition (PN), combined enteral nutrition (EN) and partial PN, nasojejunal (NJ) vs nasogastric (NG) tube feeding, and delayed vs early initiation of oral feeding. Physician practice is also highly variable, with one study showing that nearly 95% of patients receive nothing by mouth at the time of admission,<sup>16</sup> which was historically the approach to care in AP despite a dearth of data supporting this. In this narrative review, we aim to give an overview of indications for nutrition and approach to management of

nutrition in severe and predicted SAP based on currently available data.

## **Methods and Design**

This is a qualitative, narrative review on nutrition management in AP. We conducted a systemic online search of PubMed, Medline, and Cochran Database from January 2000 to February 2019. The following terms and keywords were used: acute pancreatitis, severe acute pancreatitis, enteral nutrition, parenteral nutrition. Additionally, reference sections were reviewed for additional sources.

### *Criteria for Inclusion and Exclusion*

The study inclusion criteria were as follows: (1) systematic reviews, meta-analyses, randomized controlled trials (RCTs), cohort studies; (2) study populations limited to adult humans. Exclusion criteria included the following: comments, reviews, letters, conference abstracts. In the case of continuing or duplicate studies, only the most recent publications were used.

## **Discussion**

Nutrition management is of principal importance in patients with AP. Numerous RCTs and meta-analyses have been conducted to evaluate various aspects of enteral feeding, including time of initiation (early vs late),<sup>17</sup> route of delivery (NG vs NJ),<sup>18</sup> and the type of diet or formula administered.<sup>19</sup> This remains a vast and dynamic field of study.

### *Enteral vs Parenteral*

PN was historically recommended for patients with AP. This approach allowed for a longer resting period for the pancreas while limiting the stimulation of exocrine pancreatic secretion, minimizing enzyme-driven inflammation, and still providing patients with nutrition.<sup>20</sup> PN offers the benefit of providing exogenous nutrients to maintain lean body mass and avoid adynamic ileus.<sup>21</sup> This had been the established school of thought, despite the known potential of increased risk of catheter-related infections, electrolyte imbalances, multiorgan dysfunction, and higher cost.<sup>22-24</sup> Though PN seemed advantageous in theory, it has been shown that lack of luminal nutrients has the potential to contribute to intestinal atrophy. Additionally, short recovery periods in AP, as well as more recent knowledge regarding the role of gut trophism in the pathophysiology of pancreatitis, has prompted a shift in this approach to nutrition support. Interestingly, a recent RCT comparing early nasoenteral feeding with on-demand oral feeding at 72 hours showed that nearly 70% of patients with severe or predicted SAP tolerated oral nutrition in the early stages of disease.<sup>25</sup> Additionally, recent studies in the management of

trauma and burn patients suggest that EN is associated with fewer complications and may offer the benefit of immune modulation, decreased incidence of SIRS/sepsis, and more cost-effectiveness.<sup>17</sup>

A 2010 meta-analysis of 8 randomized trials including 348 participants showed a benefit of EN in terms of mortality, multiorgan failure, systemic infections, and need for operative interventions when compared with PN. This was found to be consistent when subgroup analysis was done on patients with severe or predicted severe pancreatitis.<sup>26</sup> Similarly, a 2008 meta-analysis including 5 RCTs with 202 participants showed a statistically significant benefit in terms of infection rate and mortality in patients receiving EN vs PN. These results were further validated in a 2018 meta-analysis of 5 RCTs including 348 patients. Compared with PN, EN was associated with significant reduction in mortality and rate of multiorgan failure.<sup>27</sup> Another larger meta-analysis in 2018 involving 11 RCTs and a total of 562 patients demonstrated similar findings, with EN offering a lower risk of infectious complications and surgical interventions when compared with PN. There was no notable difference between developments of multiorgan failure between the 2 groups.<sup>10</sup> Thus, based on this and similar evidence, current guidelines suggest avoiding use of PN apart from situations in which either enteral feeding is not feasible or minimum caloric requirements are not met.<sup>5,28,29</sup>

### *Timing of Initiation of Feeding*

Guidelines released by the American Gastroenterological Association in 2013 and subsequently in 2018 recommend the use of early (within 24 hours) enteral feeding in AP.<sup>2,5,7</sup> This is further supported by results from a meta-analysis of 5 RCTs that suggest that an attempt at initiation of EN as early as within 24–48 hours and regardless of severity of disease may be successful.<sup>30</sup> The trophic effect of luminal nutrients with initiation of early EN has been found to have a beneficial effect on maintenance of both function and structure of the mucosa with regards to preservation of the integrity of the epithelial cell junctions, stimulation of brush border enzymes, and prevention of bacterial translocation.<sup>31</sup> A growing body of evidence suggests a resultant benefit of decreased multiorgan failure and infections.<sup>32–35</sup> A beneficial trend was also seen with regards to mortality, though statistical significance of this finding has been variable.

A 2018 systematic review by Song et al evaluating 10 RCTs showed early enteral feeding within 48 hours to be more efficacious than delayed enteral feeding or PN with regard to infected necrosis, organ failure, need for intervention, and possibly mortality.<sup>21,36</sup> This study also suggests a decreasing trend in development of SIRS with early initiation of enteral feeding, though the results were not

significant.<sup>36</sup> A recent systematic review suggested enteral feeding, either orally or via tube, within 48 hours was not associated with adverse outcomes across the spectrum of severity in AP.<sup>17</sup>

A 2014 multicenter randomized trial conducted in patients with AP at high risk of complications randomized patients to either early nasoenteric feeding within 24 hours or an on-demand oral diet 72 hours after presentation. The primary endpoint of the study was presence of a major infection (infected pancreatic necrosis, bacteremia, pneumonia) or death during a 6-month follow-up period. The study did not identify significant superiority of early nasoenteric feeding in comparison with on-demand oral feeding after 72 hours in regard to the primary endpoint of major infection or death. One-third of patients in the oral diet group ultimately required nasoenteric tube feeding due to oral feeding intolerance or need for mechanical ventilation. These results suggest initiation of nasoenteric feeding within 24 hours of presentation may not be superior to on-demand oral feeding at 72 hours. This study was notably quite small, involving a total number of 205 patients, likely limiting ability, or power, to detect a significant difference between the 2 groups.<sup>25</sup>

### *Gastric vs Jejunal*

In patients with more advanced bouts of SAP or in those patients with complications of AP, oral feeding is often not tolerated, requiring an alternative approach to nutrition support.<sup>37</sup> In these patients, it is reasonable to insert a nasoenteric tube. Comparison of NG vs NJ feeding has been limited because of methodological problems and difficulty in recruiting patients. Previously, NJ feeding was the preferred approach because it allowed for “resting” the pancreas. Studies have not shown a difference in NG vs NJ feeding,<sup>18,38–40</sup> though this remains a point of contention. A meta-analysis by Jiang et al in 2007 evaluated 3 RCTs including 131 patients. In this study, patients with SAP had similar outcomes in terms of safety, efficacy, and mortality.<sup>40</sup> These studies were limited in that risk of aspiration was not considered as a primary outcome, possibly contributing to an underestimation of negative outcomes. Additionally, positioning of the tip of the NJ tube was not clearly reported, which suggests that there may have been a component of pancreatic stimulation remaining, given inadequate distance from the ligament of Treitz.<sup>41</sup> A 2016 meta-analysis including 446 total participants showed no significant difference between groups receiving gastric feeds when compared with jejunal feeding in terms of risk of mortality, infectious complications, pain, diarrhea, need for surgical intervention, feeding intolerance, and energy balance.<sup>42</sup> A large multicenter trial comparing these approaches with treatment was started, but it was

terminated because of the inability to recruit participants (ClinicalTrials.gov NCT00580749).

Nasoenteral tubes can be placed by unguided bedside insertion, electromagnetic-guided or magnet-directed bedside insertion, or fluoroscopy- or endoscopy-guided insertion. Tubes placed at the bedside without guidance have been shown to result in malpositioning in up to 16% of cases. This presents risk of pneumothorax and infusion of formula into the pulmonary or pleural space, which can lead to catastrophic complications.<sup>43</sup> A 2015 systematic review evaluating electromagnetic-guided nasoenteric feeding tube placement showed this approach to be noninferior to fluoroscopically or endoscopically guided placement. Randomized trials are lacking in this realm,<sup>44</sup> though based on currently available data, this may offer a similarly reliable approach to placement given that endoscopically guided placement is inherently more invasive. Transpyloric tube migration often occurs spontaneously or with the assistance of a prokinetic agent. However, the assistive techniques required to do this at the bedside require experience and a sufficient amount of time. Jejunal intubation is achieved in roughly 17% of placements using this technique.

Jejunal feeding offers the benefit of bypassing any element of gastroparesis, pancreatic edema, or pseudocysts encroaching on the stomach or duodenum. However, definitive placement of a jejunal nasoenteral feeding tube often requires endoscopy, often under fluoroscopic guidance, and may require a bridle, suture, or mechanical clip placement to secure its positioning.<sup>45</sup>

For patients who require nasoenteral tube feeding for a prolonged period, typically beyond 30 days, alternative options must be considered. Extended duration of NG or NJ feeding presents hurdles such as sinusitis, discomfort for the patient, malpositioning or inadvertent removal of the tube, risk of aspiration, and trauma to the nasal passages.<sup>46</sup> For these patients, consideration should be given to placement of a gastrostomy tube, gastro-jejunostomy, or jejunostomy for those patients who cannot tolerate gastric infusions, are at risk of aspiration, or require decompression of the stomach.<sup>45</sup> Data are limited regarding this approach to nutrition in AP. Further study is needed regarding gastrostomy or jejunostomy feeding modalities in patients with AP.

### *Composition of Feeds*

Though studies evaluating composition of the ideal diet in pancreatitis are limited, success with early feeding has been observed with numerous diets, including normal-fat, low-fat, and soft diets with solid or liquid consistency.<sup>47</sup> For patients who tolerate oral intake, RCTs have shown no difference between starting patients on clear liquids with plans to advance the diet and starting with a solid diet. Importantly, this may offer the benefit of a decreased

length of hospitalization.<sup>48</sup> With regard to tube feeding for those patients who do not tolerate oral feeding, though further studies are needed, current guidelines recommend continuous feeds as the preferred approach over cyclic or bolus feeds.<sup>5</sup> The optimal formula for tube feeding remains unclear because of limited data. However, a 2018 study from Japan suggests there is no clinical benefit to using elemental formulas when compared with semi-elemental and polymeric formulations.<sup>49</sup>

### *Pancreatic Exocrine Insufficiency*

The pancreatic endocrine insufficiency seen in pancreatitis has been studied extensively. The study of exocrine pancreatic insufficiency (EPI), however, has been limited by smaller samples sizes. A meta-analysis by Hollemans et al in 2018 showed that in their population of 1495 patients (32 studies included) with AP, including patients of various severities, 27.1% developed EPI. A lower prevalence was seen in patients with mild or moderate AP when compared with those with severe pancreatitis. Alcohol-related pancreatitis, severe disease, and necrotizing pancreatitis were found to be the most commonly associated etiologies of AP with regard to EPI.<sup>50</sup> Significant heterogeneity between studies limits subgroup analyses in large meta-analyses of EPI. Additionally, a consensus has not yet been established on how to determine presence of pancreatic EPI, leading to significant variability between compared studies.

### *Prebiotics and Probiotics*

As discussed, the alterations in the mucosal barrier function, gut microbiome, and intestinal motility in AP increase risk of bacterial translocation and development of infectious complications. Numerous clinical trials have been done to evaluate the role of probiotics in promoting gut health, and some propose a benefit, though there is some inconsistency in these findings across studies, necessitating further research in this field. However, in AP, studies have shown synbiotics, the use of prebiotics and probiotics together in conjunction with EN, to have a beneficial role in treatment. Though these are smaller studies, there is suggestion that development of SIRS, organ failure, infected necrosis, and surgical interventions are decreased, though results have not shown statistical significance.<sup>51,52</sup> Larger-scale studies are needed.

### **Limitations**

Despite a multitude of studies, systemic reviews and meta-analyses evaluating the subject, timing, modality, and constitution of nutrition in AP remain controversial.<sup>7,8</sup> Many of the studies conducted thus far, and the results referred to in this review, offer data in the setting of variable timeframes—some focusing on the initial 48 hours, some

**Table 2.** Summary of Nutrition Recommendations for Severe Acute Pancreatitis.

Management of Severe Acute Pancreatitis	Recommendation
Enteral vs parenteral feeds Timing of feeding	Enteral feeding preferred Early feeding within 48 hours is preferred
Gastric vs jejunal route for tube feeding	Gastric or jejunal acceptable
Composition of feeds	Full solid oral diet as tolerated; no benefit of elemental formula for tube feeding
Pancreatic exocrine insufficiency	Replacement benefit limited to severe or necrotizing pancreatitis
Prebiotics and probiotics	Insufficient data to support standard use

on the initial 72 hours—leaving the optimal timing of initiating enteral feeding ambiguous. A reason for this may be that SAP presents a diagnostic challenge in that most patients do not present to the hospital with organ failure or notable necrosis, lending to difficulty with triaging and identification of sicker patients. Many of the currently used scoring systems take 48 hours or more to reflect SAP, at which point the patient's clinical state likely reflects severity without the need to use a score.<sup>53</sup> Similarly, given low positive predictive value for current prognostication systems, RCTs are limited, as patients are randomized before they are deemed to have SAP,<sup>54</sup> thus making assessment of the various aspects of early nutrition management a challenge. Additionally, the nature of treatment for AP and design of the studies to evaluate treatment portends a high risk of bias given difficulty with blinding participants, study personnel, and outcome assessments. Larger randomized trials are needed to be sufficiently powered to suggest stronger evidence; however, based on currently available data, early EN is the preferred approach in patients with severe or predicted SAP. The recommendations discussed based on currently available data are summarized in Table 2.

## Conclusions

Though still a topic of much debate, review of the current literature has important implications. Results supporting initiation of early EN, within 48–72 hours of presentation, seem to be promising with regard to decreased length of stay, complication rate, prognosis, mortality, and cost-effectiveness. Though support is largely from meta-analyses, the results thus far should urge physicians

to consider early EN in patients with SAP; however, large, high-quality randomized trials are needed to further determine whether there is truly a clear, unambiguous benefit.

## Statement of Authorship

M. Ramanathan and A. A. Aadam equally contributed to the conception and design of this narrative review. All authors critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

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