Nutritional Aspects of Acute Pancreatitis

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KEYWORDS

• Nutrition • Acute pancreatitis • Enteral • Parenteral

KEY POINTS

- Acute pancreatitis is associated with a catabolic and hypermetabolic state.
- Nutrition support is critical in severe acute pancreatitis (SAP).
- Early enteral nutrition is safe and beneficial in SAP and its use is linked to better glycemic control, reduced infectious complications, and reduced multiorgan failure and mortality.
- Enteral nutrition may be provided by the gastric or jejunal route in patients with SAP.
- Nasogastric tube feeding seems to be feasible in SAP; however, further randomized controlled trials are needed.

INTRODUCTION

Acute pancreatitis (AP) is often a self-limited inflammation of the pancreas with an excellent prognosis. Most patients with AP have mild or moderately severe pancreatitis that is associated with low morbidity and mortality, thus patients recover within a few days, and usually do not require nutritional support.[1] Historically, most of the patients admitted with a diagnosis of AP were kept nil per os to avoid further stimulation of an already inflamed organ.[2] This concept has been challenged and does not apply to cases of AP unless there is significant gastrointestinal tract dysfunction present. Depending on disease severity, maintaining hemodynamic and respiratory stability, preventing and treating end-organ damage, and treating infection are prioritized more highly than nutritional needs.[3]

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There is scientific evidence that enteral nutrition (EN) is beneficial in critically ill patients with sepsis, trauma, burns, and severe pancreatitis, with demonstrable improvement in total and intensive care unit (ICU) length of stay, infectious complications, and multiorgan failure compared with patients who receive parenteral nutrition (PN) or are kept NPO.[4–7] In contrast, early initiation of PN in critically ill patients, usually within 24 hours, has been associated with an improved nitrogen balance but increased risk of infection complications and length of hospitalization even compared with patients in whom EN was started later.[8–10] Early EN may be more beneficial because it attenuates the catabolism associated with sepsis by maintaining the gut barrier integrity and reducing the translocation of bacteria and bacteria-derived endotoxin into the systemic circulation.[11,12]

AP is a highly metabolic disease process with activation of an inflammatory cascade that leads to catabolic stress, formation of reactive oxygen species, and activation of immune responses that can rapidly overwhelm innate immune regulation and inherent antioxidant capacity.[13–15] Approximately 20% of AP cases are severe, manifesting as the systemic inflammatory response syndrome (SIRS) associated with multiorgan dysfunction (MOD) and a 15% to 40% mortality.[16,17] The exaggerated, uninhibited, and self-perpetuating inflammatory response is the cause of early mortality in severe AP (SAP), defined as within the first week of presentation. Infection of peripancreatic fluid and/or pancreas or other organs and necrosis of the pancreas is associated with late mortality (after the first week of presentation).[4,18–23]

For AP, resting the pancreas has been advocated to help resolve inflammation, and oral feeding was usually held until the patient was free of pain and nausea. Most cases of mild and moderately severe acute pancreatitis are self-limited, and patients recover within a few days, thus nutrition support is not necessary because oral feeding can be started as soon as the patient can tolerate it.[24–26]

Predicting the severity of AP, and thus patients in whom therapeutic interventions including nutrition could prove helpful, has been difficult.[27] Severity scores can help identify patients at risk for increased morbidity, prolonged hospitalizations, and mortality who could be targets for institution of early treatment, including nutrition, but the scores are limited as predictors of disease severity because most patients, even with a high score, usually survive.[8,27–29] Nonoperative supportive care and delay of procedures are strongly recommended for patients with SAP, because early surgery is associated with a substantial increase in morbidity and mortality; thus, nutritional support becomes an important part of the patient's care, because prolonging the time to any invasive intervention decreases mortality.[26,30,31]

In AP, the initial insult, which has been called the sentinel AP event, causes a liberation of proinflammatory cytokines and chemokines; increased levels of reactive oxygen species; activation and recruitment of neutrophils and macrophages; and vascular and lymphatic dilation mediated by cathepsin 3, intracellular calcium, tumor necrosis factor, nuclear factor kappa-B, platelet activating factor, heat shock protein, and others that contribute to disease severity, possibly determined by associated genetic mutations, epigenetic events, and the native oxidative stress response.[8,9,32,33] Ultimately, the complex inflammatory cascade, which the pancreas can self-regulate up to a point, leads to acinar cell death by apoptosis or necrosis, the latter associated with SAP.[34] Extra-acinar inflammation is modulated by neuropeptidases and oxidative stress that cause vascular permeability and stimulate neutrophil infiltration, with associated gland ischemia and reperfusion injury because nitrous oxide production is affected, and leakage of reactive oxygen species and proinflammatory cytokines to the systemic circulation, which leads to the local and systemic complications associated with SAP.[35–37]

Bacterial translocation across the intestinal barrier to the mesenteric lymph nodes and then to the systemic circulation has been well described in critically ill patients, and is a major cause of local and systemic complications, and the morbidity and mortality seen in SAP.[4,21,38,39] Oxidative stress leads to the formation of thiobarbituric acid reactive substances (a by-product of lipid peroxidation), downregulation of the heat shock protein, and a lack of commensal flora caused by NPO status, decreased intestinal motility caused by SAP-associated ileus, the use of systemic antibiotics, and decreased intestinal short chain fatty acid levels caused by fasting promote enteropathogen proliferation and bacterial endotoxemia as measured by the presence of systemic antiendotoxin immunoglobulin (Ig) M and IgG antibodies, which are markers of increased intestinal barrier permeability.[2,17,21,40,41] The proinflammatory state that started with the acinar injury is enhanced by altered intestinal blood flow and augmented inflammation that promotes intestinal permeability. Some studies suggest lower than expected levels of endotoxemia for the severity of the disease process in SAP, and that a proliferation of virulent intestinal lumen bacteria that stimulate the activation of inflammatory cytokines such as interleukin-1, tumor necrosis factor alpha (TNF-α), and interleukin-8 ultimately spills into the systemic circulation, causing the subsequent complications.[8]

The understanding of the inflammatory progression has led to the institution of treatment using antiinflammatory cytokines, inflammatory factor inhibitors, and even antioxidants with poor to no clinical results as shown by a recent Cochrane Systemic Review that found low-quality studies and no clinical benefit of direct pharmacologic interventions for AP.[42]

However, nutritional therapy (EN) for SAP, which functions as immunonutrition, merits further discussion. As described byMcClave,[8] "the strongest evidence for impact of nutrition therapy on patient outcome is in severe acute pancreatitis."

MALNUTRITION IN ACUTE PANCREATITIS

All patients with pancreatitis should be classified as having a moderate to high nutritional risk because of the complex disease process and the subsequent impact on nutritional status.[1,43] Prolonged nil per os status and/or delay in specialized nutrition support (SNS) initiation and/or advancement of feeding regimens also contribute to the nutritional risk for patients with AP. Furthermore, in those individuals with concurrent alcoholism, there is an even higher risk of malnutrition. These patients require supplementation of both thiamin and folate to prevent Wernicke encephalopathy and anemia. Therefore, nutritional assessment of these patients within the first 24 to 48 hours of admission is required to formulate a plan for the appropriate nutritional intervention.

CHANGES IN ABSORPTION AND METABOLISM IN ACUTE PANCREATITIS

The pancreas is composed of 2 major types of tissues: the acini, exocrine tissue that is responsible for digestive secretions released into the duodenum; and the islets of Langerhans, which secrete the hormones insulin, glucagon, and somatostatin. The primary exocrine secretions include digestive enzymes and bicarbonate. Protein-digesting enzymes include trypsinogen, chymotrypsinogen, procarboxypeptidases, and elastase. Proteolytic enzymes are secreted as zymogens. When trypsinogen is activated to trypsin, the other zymogens are activated in a cascade phenomenon. Pancreatic amylase is the primary enzyme involved in carbohydrate digestion, and pancreatic lipase, colipase, phospholipase A2, and cholesterase are needed for lipid digestion. Gastric acid is the stimulus for the release of secretin from the duodenal mucosa (S cells), which in turn stimulates the secretion of water, electrolytes, and bicarbonate.

The extreme inflammatory response noted in AP can potentially impair both exocrine and endocrine functions. If this occurs, impaired synthesis or release of enzymes leads to maldigestion. Furthermore, the proposed pathophysiology of AP involves tissue damage from activated proteolytic enzymes. However, the extent of maldigestion is difficult to quantify and does not necessarily correlate with serum levels of lipase and amylase.

THE NIL PER OS CONUNDRUM IN ACUTE PANCREATITIS

Historically, individuals with AP were made NPO because oral intake increases the rate and synthesis of pancreatic enzymes, which vary with the dietary composition, and to avoid further stimulation of the pancreas until the pain subsided. This practice is no longer consistent with published data and the evidence-based guidelines that are explored here.[1,3] Fasting decreases pancreas exocrine output, but the understanding of the role that an intact gut barrier plays in critical illness, and especially in SAP, led to studies that revealed that enteral feeds distal to the papilla caused minimal exocrine pancreas stimulation in patients with SAP and healthy controls. Because EN has been shown to improve morbidity and possibly mortality in SAP (discussed later) there is no justification for keeping patients NPO; some studies even suggest that gastric feeding, in contrast with direct jejunal feeding, is as beneficial and well tolerated in patients with SAP, supporting the view that the maintenance of gut integrity by EN is much more important than the mode of enteral delivery.[42,44–47]

NUTRITIONAL ASSESSMENT

During AP, the inflammatory cascade drives the increased metabolic demand requiring additional macronutrients and micronutrients to support the immune system and tissue regeneration after pancreatic injury. Nutritional intake supports intestinal integrity and prevents mucosal permeability and subsequent bacterial translocation, both of which can contribute to the infectious complications seen in AP. Nutrition therapy as EN is critical to maintain intestinal integrity and support the metabolic demand that ensues during the disease process and therefore plays a vital role in reducing the morbidity and mortality associated with AP.[43]

On admission to the hospital, a nutrition screening should identify all patients with AP having moderate to high nutritional risk. The nutrition assessment determines the presence and degree of malnutrition and allows a nutrition plan of care to be formed. For those patients admitted to the ICU, calculation of a Nutritional Risk in Critically Ill (NUTRIC) score to determine nutritional risk can assist in determining the appropriate nutrition therapy for the patient. Patients with a NUTRIC score of greater than or equal to 5, should start EN and meet the energy and protein goal within 24 to 48 hours.[48] In addition to determining risk of malnutrition, a malnutrition diagnosis can be confirmed by the presence of greater than or equal to 2 of the following criteria[49]:

- Insufficient energy intake
- Weight loss
- Loss of muscle mass
- Loss of subcutaneous fat
- Presence of edema or fluid accumulation
- Diminished functional status as measured by handgrip strength or reduction in activities of daily living

These criteria can be ascertained by completing a nutrition-focused physical examination, assessing caloric intake before and during the hospital admission, and

determining changes in body weight. This system of diagnosis has replaced the historical use of serum proteins (ie, albumin, prealbumin, transferrin, and retinol-binding protein) that more accurately describe the acute phase response and changes in body weight, which alone cannot identify malnutrition.

Determining Calorie and Protein Needs

Indirect calorimetry is the gold standard for measuring the resting metabolic rate of critically ill adults. When indirect calorimetry is not available, weight-based nomograms can be used to estimate energy and protein needs. In the ICU, it is recommended to have a reassessment of nutritional needs weekly as a minimum because the severity of disease can rapidly change (Table 1).[48]

Table 1
Monitoring nutrition care plans for hospitalized patients with acute pancreatitis

Parameters	Mild AP	Moderate to Severe AP
Intake/output	Weekly	Daily
Vitals	Daily	Daily
Anthropometrics		
Height	Baseline	Baseline
Weight	1–2 times/wk	Daily
Usual body weight	—	Admission
Nutritional Assessment		
Nutrition screening	Admission	Admission
Nutrition-focused physical examination	Weekly	Weekly or as needed
Abdominal examination	Weekly	Daily
Indirect calorimetry (when available)	—	2–3 times/wk
Nutrition-related History		
Food intolerances	Baseline	Baseline
Presence of nutrient deficiencies	As indicated	As indicated
Nutritional intake before admission	Baseline	Baseline
Laboratory Parameters		
White blood cell count	2–3 times/wk	Daily until stable
Hemoglobin/hematocrit	2–3 times/wk	Daily until stable
Triglycerides, serum	Weekly	Weekly
Lactic dehydrogenase	Weekly	Daily until stable
Liver-associated enzymes	2–3 times/wk	Daily until stable
Serum glucose	Daily	3 times daily
Serum amylase/lipase	2–3 times/wk	2–3 times/wk
C-reactive Protein	Weekly	Weekly
Blood urea nitrogen, creatinine	Daily	Daily until stable
Serum electrolytes	Daily until stable	Daily until stable
Arterial blood gas (when available)	—	As indicated
Vitamins/minerals/trace elements	As indicated	As indicated
Interleukin-6	—	As indicated
Nitrogen balance	—	As indicated
NUTRIC score		Admission

Using weight-based nomograms, determining caloric/protein requirements varies based on the severity of AP. In mild AP, 25 to 30 kcals/kg/d of energy, and 1.2 to 1.5 g/kg/d of protein can be used initially. If the disease progresses to moderate SAP, caloric demand is estimated to increase up to 35 kcals/kg/d.[50] Plasma glucose levels should be maintained less than or equal to 10 mmol/L (180 mg/dL) and plasma triglyceride levels maintained at less than or equal to 3 mmol/L (266 mg/dL).[51]

NUTRITION THERAPY IN ACUTE PANCREATITIS

Historically, on hospital admission, medical management evolved around minimizing pancreatic stimulation by keeping patients NPO. There is now a much better understanding of the role of nutrition (oral and tube-delivered nutrients) in minimizing the inflammatory cascade by the maintenance of gut barrier function and modulation of the immune and inflammatory responses.[52–54] Reduction in the duration of NPO and the use of aggressive nutrition support in severe pancreatitis has led to improved outcomes for this patient population. The degree of malnutrition and the severity of AP require customization and tailoring nutrition therapy for each patient. Patient with mild AP and who are not malnourished on diagnosis do not require SNS.[49] In contrast, malnourished patients with moderate AP, and certainly SAP, should start SNS within 24 to 48 hours of hospital admission.[50]

Because of the rapid disease progression seen in AP, establishing a plan for frequent monitoring is necessary to detect changes in the severity of pancreatitis. Mild pancreatitis might present at the onset of the inflammatory cascade and can rapidly progress to moderate to severe pancreatitis and thus may require more aggressive nutritional intervention. Some studies suggested that EN increases intestinal blood flow demands, which paradoxically could contribute to and enhance bacterial leak and translocation, and serve to highlight the importance of initiating enteral feeds before the gut barrier is disrupted.[25] It has also been described that target calories are reached 75% of the time, indicating the need for frequent nutritional reassessment[47] (see **Table 1**, which underscores the need for frequent monitoring of these patients).

NUTRITION IN MILD ACUTE PANCREATITIS

On admission with a diagnosis of mild AP, an oral diet is preferred. Approximately 80% of patients successfully transition to an oral diet within 7 days of hospital admission and experience minimal morbidities.[48] The optimal timing to initiate an oral diet and the type of oral diet prescribed are debatable. Numerous studies indicate that initiation of oral or enteral feeding in any form in mild AP decreases length of hospitalization, and a recent meta-analysis by Márta and colleagues[3,4,10,13,24,25,55–57] comparing EN with NPO in all types of AP found a general benefit of EN compared with fasting patients. Oral feeding with a low-fat regular diet is as well tolerated as, and nutritionally more beneficial than, a clear liquid diet (CLD) in this subset of patients. Eckerwall and colleagues[25] randomized 60 subjects with AP into a fasting group and an oral feeding group in which diet was advanced as tolerated. This study indicated that hospital length of stay (LOS) significantly decreased in the oral feeding group, suggesting that dietary prescription should be assigned at hospital admission to patients identified with mild AP (4 vs 6 days; $P<.05$). Various dietary patterns have been investigated, including the CLD, low-fat, soft, or regular diet. Jacobson and colleagues[58] pooled more than 350 subjects with mild AP to assess differences in hospital LOS and reoccurrence

of abdominal pain after initiation of a liquid versus solid diet. Prescribing a solid diet, despite the percentage contribution of fat kilocalories, compared with a CLD was associated with a decreased hospital LOS (1.18 days; 95% CI, 0.82–1.55; $P<.00001$) without increased abdominal pain.[56–58] Monitoring and evaluation of dietary tolerance includes nausea, vomiting, and increased abdominal pain. An additional 2 randomized trials showed benefit of solid diet compared with liquid diet with shorter length of hospital stay with solids.[57,58] Therefore, patients with mild AP can be started on a low-fat oral diet after a short initial fasting period. Increased levels of amylase and lipase contribute to the overall assessment of the patient but are not required to drive decisions on advancing the diet.[48] For those patients whose disease progresses to moderate severe or severe pancreatitis or who are unable to advance to a regular diet within 7 days of hospital admission, the use of EN, as outlined later, should ensue.[48] Mild AP has an overall good prognosis and thus is less likely to benefit from or require interventions beyond supportive care.

IMPROVING TOLERANCE TO AN ORAL DIET

Although guidelines for the nutritional management of AP typically do not include a description of the size and timing of meals, extrapolation from other disease states leads clinicians to adjust to small, frequent meals to improve dietary tolerance, especially in patients experiencing nausea, vomiting, and early satiety.[59–61] Patient education should include the number and estimated kilocalories required per meal to better address adequate nutrient delivery.[61] Adjustment of the dietary fat content and consistency can also be considered to improve dietary tolerance.[62] If early satiety is present, increased dietary fat intake may result in delayed gastric emptying and ultimately decreasing oral intake. In this case, reducing the total amount of fat prescribed at each meal and/or converting to liquid fat sources might improve oral intake and promote gastric emptying.[62,63]

Tolerance to an oral diet is challenging because of the increased nausea, vomiting, and abdominal pain that are characteristic of AP. Various medications can be considered to treat symptoms associated with dietary intolerance. Antiemetic and prokinetic agents can combat nausea and vomiting by increasing peristalsis, blocking hormone signaling, and improving gastric emptying and have proved to be an effective strategy for improving gastrointestinal symptoms. Fiber supplementation is not routinely recommended for patients in the ICU because of the impact on delayed gastric emptying. For patients recovering from moderate to severe pancreatitis or with mild pancreatitis, consideration for initiating soluble fiber in those experiencing diarrhea as a result of the pancreatic inflammation may decrease nutrient loses. In addition, the use of antidiarrheals taken before meals can reduce the frequency of bowel movements and improve the consistency to promote absorption. **Table 2** provides an overview of medications to consider for improving enteral (oral and tube-delivered nutrients) tolerance.

NUTRITION IN MODERATELY SEVERE ACUTE PANCREATITIS

This subgroup of patients with AP have transient organ failure that usually subsides within 48 hours, and most have a good to excellent prognosis. Most studies group mild and moderate SAP together so it is difficult to know the impact of EN in this group of patients. As with all types of AP, EN support decreases hospital LOS, and is preferred to NPO or PN.[55] As described earlier, continuous monitoring for nutritional needs, supportive care, and deterioration to SAP is necessary.

Table 2
Medication management used in acute pancreatitis to improve enteral tolerance

Medication	Examples	Symptom	Mechanism	Administration
Pancreatic enzymes	Pancrelipase	Diarrhea, steatorrhea	Replaces pancreatic enzymes to improve fat, protein, and carbohydrate digestion	Take with meals
Prokinetic agents	Metoclopramide, erythromycin, bethanechol	Nausea, vomiting, early satiety	Increased peristalsis, improved gastric emptying	Take 10–15 min before meals
Antiemetic agents	Ondansetron, prochlorperazine	Nausea, vomiting, early satiety	Block dopamine and/or serotonin signaling	Take 30–45 min before meals
Soluble fiber	Guar gum, banana flakes, pectin	Diarrhea	Increases water absorption in the gastrointestinal tract. Thickens stool consistency	Mixed into hot or cold beverages/ foods
Antidiarrheals	Loperamide, diphenoxylate and atropine, codeine, opium tincture	Diarrhea	Decreases the number and frequency of bowel movements by slowing peristalsis	Take 30–60 min before meals

NUTRITION IN SEVERE ACUTE PANCREATITIS

The focus of nutritional therapy should be on patients with SAP, because they are more ill and are unable to tolerate oral feeds for a longer period of time. Aggressive fluid resuscitation is initially required to promote urinary output of 0.5 mL/kg/h and is linked to improved outcome.[51] The hypermetabolic and inflammatory state that characterizes SAP leads to rapid nutritional deterioration, increased caloric requirements, and rapid protein losses. These deficiencies are augmented by keeping the patients NPO, which leads to progressive nutrition deficit, and a negative nitrogen balance. The latter has been associated with increased morbidity and mortality, and a prolonged hospitalization and overall poor recovery.[1,13,15]

The use of SNS must be considered to meet the metabolic demand associated with the early phase of AP. A NUTRIC score indicating high nutrition risk can be calculated to support the initiation of early EN.[48] There is evidence for the therapeutic benefit of EN as treatment of SAP, and thus for effectively using enteral feeds as a form of immunonutrition as summarized from meta-analysis and a frequently revised Cochrane Review on the subject.[13] EN has been associated with decreased bacterial gut translocation and peripheral blood enterotoxin levels, and decreases TNF-α and C-reactive protein levels within 48 hours of its initiation.[4,64] Serum albumin level, an indirect measure of nutritional status, has been shown to improve with EN.[65] EN with an elemental diet containing omega-3 fatty acids, and possibly also omega-6 fatty acids, may also have a positive effect on neurogenic inflammation.[8] Individual studies and meta-analyses also indicate a significantly decreased relative risk of infection, and subsequent decreased need for surgical interventions as well as significant decrease in hospital and ICU LOS in patients with SAP on EN. In contrast, PN in patients with SAP was associated with poorer general outcomes, was more expensive than EN, and carried the inherent risks of infection and thrombosis.[1,55] Early peripheral

PN has been associated with a decreased risk of infection, but nutritional needs may not be met.

A few, but not all, meta-analyses show a significant decrease in multiorgan failure and mortality for EN, but all show a trend toward an improvement of these two important outcomes.[15,55,66–68] **Table 3** summarizes the impact of EN on clinical outcomes. Current guidelines support the use of a standard, polymeric formulas (see **Table 3**) delivered via a nasogastric and/or nasojejunal tube within the first 48 to 72 hours of hospital admission.[60] There may be a potential benefit for the use of specialized, immune-enhancing enteral formulations, but continued research in this area is warranted before changing current recommendations.[15]

IMMUNONUTRITION IN ACUTE PANCREATITIS

Various nutrients have been investigated to determine their effects on the immune response, inflammation, white blood cell recruitment, and disease outcome in AP.[69,70] Those that show some promise include omega-3 fatty acids, glutamine, and arginine.[48,71] Various micronutrients that are in demand during acute inflammation include vitamins A, C, E, B_6, folate, B_{12}, and pantothenic acid, in addition to iron and zinc. All of these nutrients have various roles in cell-mediated immunity and, when their levels are low, they can contribute to the poor/delayed immune response seen in AP.[71] Deficiencies of these nutrients are more common in chronic pancreatitis, but nutrition-focused physical examination can assist in identifying micronutrient deficiencies in patients with moderate to severe malnutrition.[72] If micronutrient deficiency is suspected, serum levels can be evaluated once inflammation has resolved, although the accuracy of these parameters as a reflection of total body stores is questionable.

Arginine

Arginine is a nonessential amino acid that plays a role in ureagenesis, immune function, wound healing, cell growth and differentiation, and vasodilation. The rationale for supplementing arginine in AP relates to the relative arginine deficiency that may occur during critical illness and sepsis. With supplementation of arginine, it is proposed that levels of nitric oxide would increase with subsequent improvement in blood flow and tissue perfusion. In contrast, there has been concern that the vasodilation mediated by nitric oxide could lead to hemodynamic instability by diverting blood flow.[67] Additional benefits include provision of substrate for collagen synthesis and enhanced T-cell function. Current American Society for Parenteral and Enteral Nutrition (ASPEN) guidelines do not routinely recommend immunonutrition in medical ICU patients, but it seems that a dose of 15 to 30 g of arginine is safe.[73]

Table 3
Effect of enteral nutrition compared with parenteral nutrition on clinical outcomes

	Infection	Organ Failure	LOS	SIRS	Mortality
McClave et al,[15] 2006	++	++	+	NR	None
Al-Omran et al,[13] 2010	NR	NR	+	None	++
Blaser et al,[3] 2017	++	NR	NR	None	NR
Petrov et al,[4] 2008	++	None	NR	NR	++

The plus symbols (+) indicate a nonsignificant difference; double plus (++) indicates a statistically significant difference.

Abbreviation: NR, not reported.

Glutamine

Glutamine is a nonessential amino acid under investigation for its antioxidant properties and the role in enhancing intestinal health and preventing bacterial translocation in critically ill patients. With mixed results on glutamine supplementation in the ICU and concern over safety in various critically ill patients, ASPEN does not endorse glutamine supplementation in patients with AP.[48]

Omega-3 Fatty Acid

Few studies have investigated the use of fish oil supplementation and/or the use of omega-3 fatty acids for modulating the inflammatory response in AP.[54,74] Although these studies show promise, the small sample sizes and heterogeneous methodologies make conclusions on the efficacy difficult at this time. Therefore, current recommendations do not support the use of oral, enteral, or parenterally delivered fish oil for treatment of AP at this time.[43,48] The potential benefits of immunonutrients are summarized in **Table 4**.

Improving tolerance to enteral nutrition

Intolerance to EN, such as abdominal pain, nausea, vomiting, and excessive gas production, is common in moderate AP to SAP. Strategies should be used to support tolerance before transitioning to PN. Tolerance can be improved through adjustments of the EN infusion rate, EN formula, and medications. Drug therapy can be used to optimize tolerance to diet and EN depending on the symptoms present and the underlying cause of these symptoms.

The first step in improving tolerance is to provide EN early as maintenance for intestinal integrity. In addition, the tip of the feeding tube can be advanced from the stomach into the small intestine in patients experiencing delayed gastric emptying and/or at risk for aspiration. Enteral formula changes from a standard, polymeric formula to a hydrolyzed formula can improve tolerance by improving the digestibility of nutrients in the gastrointestinal tract while pancreatic enzymatic action is insufficient (**Table 5**). An alternative to formula selection is for the infusion rate to be adjusted to improve tolerance. Typically, a slower infusion over a longer period of time (continuous) is better tolerated by individuals with compromised absorption. Selection of a

Table 4
Effect of enteral nutrition, supplements, and immunonutrition in acute pancreatitis

EN	Stimulates blood flow and intestinal microcirculation, inhibits bacterial overgrowth, and maintains integrity of the enteric barrier
L-Arginine	By nitric oxide pathway may improve intestinal blood flow, maintain the gut barrier, and improve pancreas blood flow
Glutamine	Antioxidant; stimulates release of heat shock protein, which controls intrapancreatic trypsin activation
Polyunsaturated fatty acids/ omega-3 fatty acids	Blunt inflammation by affecting chemotaxis and shunting to less aggressive inflammatory pathways, and regulates neurogenic inflammation
Docosahexaenoic acid	Inhibits intracellular signaling, stabilizes DNA and inhibits inflammatory cytokine activation, induces acinar apoptosis rather than necrosis
Zinc	Affects tight junctions, decreases permeability, indirectly affects glutathione production, and inhibits oxidative stress
Antioxidants	Replenish antioxidant capacity against reactive oxidant species

Table 5
Enteral nutrition formulations suggested for use in acute pancreatitis

Formulas	Indication	Characteristics
Polymeric formulas	Should be first trial if no indication of malabsorption and intact GI anatomy	Protein: intact protein lipid: triglycerides Carbohydrate: dextrin, oligosaccharides
Partially hydrolyzed	Indication of malabsorption, enteral feeding intolerance, or change in GI anatomy	Protein: peptides Lipid: medium-chain fatty acids, structured lipids, omega-3 fatty acids Carbohydrate: maltodextrin, oligosaccharides
Elemental	Indication of malabsorption, or change in GI anatomy	Protein: crystalline amino acids, dipeptides/tripeptides Lipid: medium-chain fatty acids, omega-3 fatty acids Carbohydrate: maltodextrin, <2% partially hydrolyzed cornstarch

Abbreviation: GI, gastrointestinal.

continuous infusion is preferred in the ICU to allow for delivery of a smaller volume into the gastrointestinal tract each hour. When these tactics have failed to improve EN tolerance, medication modifications can assist to improve tolerance.

EN delivery may have to be monitored more carefully in obese patients because nutritional goals may not be met as rapidly, and prolonging the time to reach them has been associated with poorer outcomes, including increased mortality.[16]

Nausea related to poor gastric and intestinal motility is commonly seen with the initiation of oral nutrition and EN in AP. Consideration should be given to the use of antiemetics and/or prokinetic agents to improve these symptoms and allowing the continuation and advancement of the diet and/or enteral feeding. As gastrointestinal function returns to baseline, these medications can often be discontinued.

Diarrhea is also commonly associated with AP. There is no role for pancreatic enzymes in interstitial pancreatitis but in necrotizing pancreatitis or in prolonged disease course it is prudent to provide them. Poor mixing of pancreatic enzymes with the food bolus leads to maldigestion and malabsorption.[59] Dosing guidelines vary worldwide, although most recommend monitoring for the presence of steatorrhea, clinical symptoms associated with fat maldigestion (ie, bloating, gas, essential fatty acid deficiency), and/or quantification of fecal fat.[75] None of the US Food and Drug Administration–approved pancreatic enzymes were used for EN until the recent release of an in-line digestive cartridge that allows mixing of lipase with the EN formula ex vivo. Although there are limitations to this product, its use seems superior to other methodologies for pancreatic enzyme delivery, with approximately 90% of fats being hydrolyzed within a 4-hour period.[75]

In addition to pancreatic enzymes, antidiarrheal medications slow the movement of the intestinal muscles through the opioid receptor to inhibit peristalsis, which promotes the contact of the enteral contents with the villi and microvilli lining of the gastrointestinal tract. The goal of antidiarrheal therapy is to decrease the number and frequency of bowel movements and ultimately improve intestinal absorption. Although use of antidiarrheal therapy is safe and effective, caution is needed in patients with hepatic injury or those who may have loperamide-induced AP.[76,77] **Table 3** provides a snapshot of the medications available that support improved tolerance to diet and EN. All EN parameters (formula, infusion rate, and tube location) and

medications used to improve digestions and absorption must be considered before consideration of failure of enteral feeding and initiation of PN.

WHEN TO START ENTERAL NUTRITION

The best time to initiate EN is not clear, but the inflammatory response and cascade associated with SAP peaks at 72 hours, which is therefore considered the therapeutic window for any intervention[25,78] Most studies defined early nutrition as being within 24 to 48 hours of presentation. A recent prospective study of patients with moderately severe AP and SAP found that starting EN by day 3 of presentation was associated with a significant decrease of pancreatic and extrapancreatic infections.[79] A few studies have shown increased intestinal permeability after 72 hours or more in patients with mild AP, indicating that the mechanism for disease is more complex, and that the poorer outcomes are related to a host of factors that by then have become active and uncontrollable. This finding may explain why instituting EN within 24 to 48 hours of presentation improves patient outcome, and why starting it later may be less beneficial.[15,25,65,78,80]

Current nutrition practice guidelines support early initiation of EN in SAP within 24 to 48 hours from admission.[1,48]

PROBIOTICS

With basic science advancements in the area of metabolomics, tools are now available to understand the metabolic action of the gut microflora and its impact on gut permeability and modulation of the immune system. These data should help guide clinical investigations on the use of probiotics in patients with AP, focusing on strain-specific actions while clarifying the dose required for the biological actions intended from the use of probiotics. Initial experimental pancreatitis model trials with probiotics showed promising results by reducing the severity of pancreatitis, improving histopathologic scores, reducing bacterial translocation, and reducing late-phase mortality.[1–3] A randomized controlled trial of probiotics in AP was stopped early because of increased risk of mortality (increased rate of fatal bowel ischemia, multiorgan failure) in those who received a multispecies probiotic with *Bifidobacterium*.[81,82]

A more recent randomized trial by Cui and colleagues[83] involving 70 patients with SAP showed beneficial effects of probiotics in combination with EN by the significant reduction in upper gastrointestinal bleeding, infection, and abscess in the probiotic group. A systematic review of 6 randomized controlled trials of a total of 536 patients showed that probiotics had neither beneficial nor adverse effects on the clinical outcomes in SAP.[84] At present, probiotics should not be used in AP based on available clinical evidence.

ENTERAL NUTRITION SHOULD BE THE RULE, NOT THE EXCEPTION

The notion that the pancreas and/or the gastrointestinal tract need to be rested in cases of AP is not supported by data. Current guidelines for management of AP recommend immediate oral feeding in patients who tolerate it and have no contraindications, such as a risk of aspiration, and resolving abdominal pain.[1] There is no benefit to administering a liquid diet, and a low-fat regular diet can be prescribed to patients with mild AP.[1,14] In SAP, EN is preferred to PN, and the direct gastric and jejunal routes of feeding seem to be equivalent. Some studies also indicate that combination EN and PN improves outcomes compared with PN alone in

matched cohorts, adding to the notion that maintenance of the gut barrier is how EN affects outcomes in AP.[85]

The nutritional practices in AP were addressed in a Dutch observational study in which 90% of the patients had mild AP.[45] Eighty percent of the patients were kept NPO for an average of 2 days, and 17% of the patients with mild AP were fed enterally using a nasojejunal feeding tube. Of the small group with SAP, only 3 patients were kept NPO, and 75% received PN with or without EN; 56% received EN only. It is encouraging to see the shift toward EN in the SAP group, but the practice of starving patients, which lasted more than 5 days in 5% of the cohort, and the use of PN is pervasive, which is highlighted by another study that found that only 2% of patients with SAP received EN alone but 64% were on combination EN plus PN.[66] This finding highlights the need to standardize treatment and to continuously educate and disseminate information, which can probably be done more effectively with multidisciplinary care including earlier consultation with the nutrition team.

LIMITATIONS

There are numerous limitations to the available data on nutrition therapy in AP. In most meta-analyses about 50% of the patient cohorts had mild to moderate SAP, or would be classified as such using the currently accepted diagnostic criteria. The role of EN in these two subgroups is not clear, but the prognosis is usually favorable so they are less likely to benefit from or require nutritional intervention. Based on the meta-analyses, selecting the patients with SAP who are most likely to benefit from immunonutrition is difficult, which makes generalization of even the most robust meta-analyses more difficult. The type of enteral formula that should be used, such as polymeric versus semielemental or elemental, is not clear. The studies also do not indicate how to treat acute exacerbations of chronic pancreatitis or idiopathic recurrent AP. A publication bias of studies showing a positive impact of EN also needs to be considered.

SUMMARY

The goal of nutritional support in AP is to reduce inflammation, prevent nutritional depletion, correct a negative nitrogen balance, and improve outcomes. EN in SAP has a positive impact on disease burden, and should be preferred to PN, which has a negative impact on patient outcomes. It maintains the integrity of the gut barrier, decreases intestinal permeability, downregulates the systemic inflammatory response, maintains intestinal microbiota equilibrium, and reduces the complications of the early phase of SAP (first week of the disease), improving morbidity and possibly improving mortality, and it is less expensive.[55,66,86] EN should be initiated within 24 hours in patients with SAP or predicted SAP, so practitioners who are taking care of them need to have a good knowledge of severity scoring systems and nutrition guidelines.[27,45] Nutritional practices for AP are widely variable and need to be aligned with the current evidence-based recommendations. The role of EN for mild or moderately SAP is not clear, but in most cases oral feeds with a low-fat regular diet can be started as soon as tolerated, because a CLD is not superior. PN should be reserved only for patients in whom EN is not tolerated or is contraindicated because PN is associated with a higher rate of infectious and metabolic complications, and greater morbidity and length of hospitalization.[16,87–89] Further studies to understand optimal timing for initiation of nutrition, route of delivery of EN, and the type of nutrition and nutrients are necessary.

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