Nutritional Management of Acute Pancreatitis

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KEYWORDS

• Acute pancreatitis • Nutrition • Enteral nutrition

KEY POINTS

- Acute pancreatitis (AP) remains among the most common gastrointestinal disorders requiring hospital admission.
- EN further preserves gut function by reducing gut dysmotility and ileus promoted by pancreatic and systemic inflammation.
- However, poor tolerance of EN and the spectrum of disease severity in patients with AP present unique challenges for clinicians in determining the appropriate type, timing, route, and composition of nutritional support, which results in significant variation in management across centers.

INTRODUCTION

Acute pancreatitis (AP) remains among the most common gastrointestinal disorders requiring hospital admission. The burden and cost of AP on the health care system continues to rise accounting for nearly 280,000 hospitalizations and more than $2.6 billion dollars spent annually in the United States.[1] The management of AP is largely supportive and focuses on intravenous fluid therapy, analgesics, and nutritional support. Enteral nutrition (EN) is one of the few interventions that has been shown to reduce mortality in AP[2] and plays a key role in limiting disease progression and accelerating patient recovery.

The pathogenesis of AP across all etiologies involves a complex cascade of intra-acinar pancreatic zymogen activation, most notably trypsinogen, resulting in acinar injury and upregulation of proinflammatory mediators and cytokines that contribute to a profound local and systemic inflammatory response syndrome (SIRS).[2] Nutritional support plays a key role in mitigating the sequelae of the SIRS response with specific attention to hypoperfusion of the gut barrier mediated by inflammatory and microcirculatory damage.[3] EN is thought to promote the integrity of the damaged gut barrier by

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preventing luminal mucosal atrophy, hence reducing gut permeability and the resulting translocation of gut microbiota that potentiates AP-associated SIRS, multiorgan failure, and infection (Fig. 1).[4,5] EN further preserves gut function by reducing gut dysmotility and ileus promoted by pancreatic and systemic inflammation. Ileus has been associated with infected pancreatic necrosis in patients with necrotizing AP, likely a reflection of the paradigm of bacterial translocation.[6] The inflammatory response also induces a highly catabolic state that increases metabolic demand causing a negative nitrogen balance of up to 20 to 40 g per day that promotes malnutrition.[7,8]

For these reasons, optimizing nutritional support and maintaining gut function is instrumental in the recovery of patients with AP. However, poor tolerance of EN and the spectrum of disease severity in patients with AP present unique challenges for clinicians in determining the appropriate type, timing, route, and composition of nutritional support, which results in significant variation in management across centers.[9] This review summarizes the current evidence with regard to these questions and provides recommendations in line with current consensus opinions to guide the clinical management of AP from the perspective of nutritional support.

ORAL NUTRITION AND TIMING

Historically, the initial management of AP prioritized bowel rest with *nil per os* (NPO) status with the rationale that avoiding EN would minimize pancreatic stimulation and any exacerbation of ongoing inflammation. In normal patients, oral/duodenal feeding leads to greater stimulation of pancreatic exocrine function compared with fasting and intravenous nutrition as measured by rates of duodenal trypsin secretion (Table 1).[10,11] Middistal jejunal feeding, however, does not seem to stimulate pancreas exocrine secretion.[9] AP has been shown to diminish pancreatic exocrine function and the effect seems proportional to morphologic disease severity with the lowest rates of trypsin secretion seen in necrotizing pancreatitis (see Table 1).[12] This suggests that pancreatic exocrine function may be "stunned" in AP and EN, regardless of the route, especially in necrotizing AP, may not produce appreciable pancreatic stimulation to contribute to worsening disease severity. Furthermore, EN has been shown to promote gut integrity and function, introducing the concept of

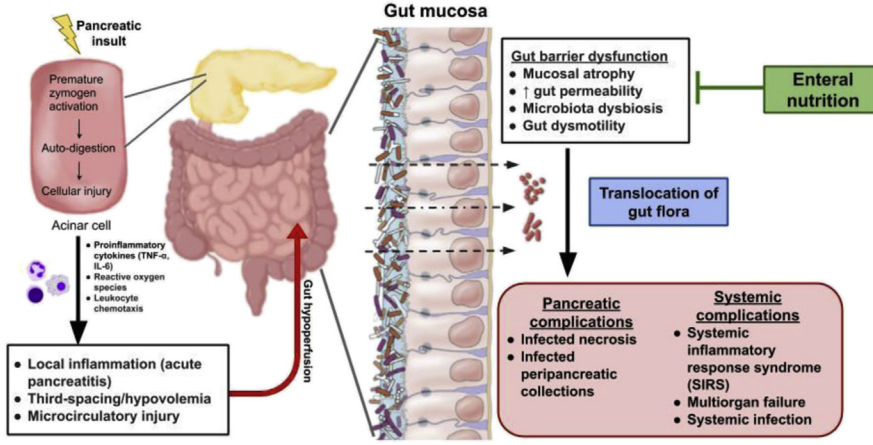

Fig. 1. Pathophysiology of acute pancreatitis and mitigation of associated gut barrier dysfunction by enteral nutrition. IL, interleukin; TNF, tumor necrosis factor.

Table 1
Pancreatic enzyme secretory response to various forms of diet

Mode of Feeding	Trypsin (u/h)
Normal patients	
Fasting (n = 7)	134 (22)
Intravenous (n = 5)	171 (33)
Duodenal total (n = 13)	408 (51)
Polymeric (n = 6)	471 (73)
Elemental (n = 7)	335 (65)
Middistal jejunal (n = 11)	119 (16)
Disease Severity	**Trypsin (u/h)**
AP	
Control, no AP (n = 8)	514 ± 86
Mild/moderate (n = 8)	214 ± 83
Necrotizing (n = 4)	32 ± 7

Duodenal trypsin secretion rates in normal patients given various modes of feeding and in patients with AP given duodenal feeding. Values are listed as group means with standard error.

Data from Kaushik N, Pietraszewski M, Holst JJ, O'keefe SJ. Enteral feeding without pancreatic stimulation. Pancreas. 2005;31(4):353-9; and O'keefe SJ, Lee RB, Anderson FP, et al. Physiological effects of enteral and parenteral feeding on pancreaticobiliary secretion in humans. Am J Physiol Gastrointest Liver Physiol. 2003;284(1):G27-36.

"gut rousing, but not resting."[13,14] In line with this, contemporary evidence supports early enteral feeding, ideally *per os* in AP.

A recent systematic review of 11 randomized control trials (RCTs) by Vege and colleagues[15] compared the role of early feeding (within 48 hours of admission) with delayed feeding across all severities of AP and found no difference in outcomes including mortality, rates of multiorgan failure, and complications related to pancreatic necrosis. Prior systematic reviews have also shown decreased length of stay (LOS)[16] and potentially lower infectious complications[17,18] with early feeding within 48 hours of admission. The American Gastroenterological Association (AGA) guidelines for AP currently strongly recommend early (within 24 hours) oral feeding as tolerated rather than keeping patients NPO based on this moderate quality body of evidence.[19] Multiple RCTs suggest initiation of oral feeding upfront with a soft low-fat, low-residue diet because it provides more calories without worsening of symptoms or difference in LOS when compared with an initial diet of clear liquids.[20–22]

It is important to acknowledge that oral refeeding is sometimes not feasible in patients with significant symptoms, gastrointestinal dysmotility, and in severe AP (SAP)/necrotizing disease. For these patients, timely initiation of EN via a nasogastric tube (NGT) or nasojejunal tube (NJT) becomes appropriate. However, the administration of prompt EN via NGT/NJT as a substitute for oral intake in patients with predicted SAP is not associated with improved outcomes. The PYTHON trial, a multicenter RCT from the Netherlands, that randomized patients with predicted SAP (defined as Acute Physiology and Chronic Health Evaluation II score of $\geq$8, an Imrie or modified Glasgow score of $\geq$3, or a serum C-reactive protein level of >150 mg/L) to either early EN via NGT within 24 hours of admission or to "on-demand" oral feeding within 72 hours, found no differences in the composite end points of major infection and death or in secondary end points of rates of pancreatic necrosis or need for intensive care unit level care.[23] Of note nearly 70% of patients in the on-demand group were able to

tolerate oral feeding in the early stages of disease and had shorter time to tolerance of full oral feeding (6 days for oral group vs 9 days for EN group). Additional studies have demonstrated no difference in inflammatory profiles/cytokine production in oral versus EN in SAP.[24] Although more research is needed to clarify the optimal timing and administration of EN in severe and acute necrotizing pancreatitis, early oral feeding in this subgroup may be trialed cautiously and directed by patient symptoms.

TYPE OF NUTRITION (ENTERAL NUTRITION VS PARENTERAL NUTRITION)

The previously held dogma of gut and pancreatic rest in AP established parenteral nutrition (PN) as the primary means of providing nutrition while patients were kept NPO. Current evidence, however, has clearly shown worse outcomes with PN relative to EN. In a technical review of 12 RCTs that compared EN with PN across all severities of pancreatitis, there was more than a two-fold reduction in the rate of multiorgan failure (odds ratio, 0.41; 95% confidence interval, 0.27–063) and nearly a four-fold reduction in infected peripancreatic necrosis (odds ratio, 0.28; 95% confidence interval, 0.15–0.51) with the use of EN.[15] Other meta-analyses have also shown increased cost, infectious complications, and LOS with the use of PN.[25,26] These findings were similarly shown in a Cochrane review by Al-Omran and colleagues of eight RCTs that also demonstrated increased mortality in the subset of patients with SAP receiving PN.[27] These findings are likely reflective of known complications inherent to PN, such as to catheter-related bloodstream infections and sepsis, metabolic derangements,[11] and compromise of gut barrier function and microbiota dysbiosis that has been demonstrated with the withdrawal of EN in critically ill patients.[28,29]

In patients unable to tolerate oral feeding within the first 48 to 72 hours because of symptoms, ileus, or SAP, EN via NGT or NJT should be prioritized over PN in line with the current strong recommendation from the AGA that was based on moderate-quality evidence.[30] Given the relative harm associated with PN, it should be reserved only for patients unable to tolerate EN over a prolonged period, when an NGT/NJT cannot be placed, or when minimal caloric needs cannot be met with EN alone.

ROUTE OF ENTERAL NUTRITION (NASOGASTRIC VS NASOJEJUNAL)

Despite clear evidence supporting the use of EN in patients intolerant of oral feeding, there is less compelling evidence for a preferred route: NGT versus NJT. A meta-analysis of three RCTs that compared NGT with NJT feeding in SAP demonstrated no difference in mortality, infectious complications, or LOS.[31] The distal delivery of EN via NJT offers a theoretic reduction in aspiration risk and middistal jejunal nutrition has been shown to minimize pancreatic stimulation. However, RCTs and meta-analyses have shown no difference in tracheal aspiration,[30] exacerbation of pain, or energy balance between the two routes.[32] These studies had several limitations including large heterogeneity, high risk of bias because of a lack of blinding, small sample sizes, and poorly specified outcomes. A large multicenter trial comparing NGT with NJT feeding in AP was unfortunately terminated because of lack of adequate patient recruitment (ClinicalTrials.gov NCT00580749). The lack of clear evidence suggesting a superior route of EN in SAP may reflect stunning of pancreatic exocrine function observed in necrotizing disease.

Although available evidence is not robust, NGT represents a more pragmatic option for EN in AP given the relative ease of bedside placement compared with endoscopic placement of NJT. There are new bedside transnasal systems that have been developed for the placement of NGT and NJT. Additional research is required to more

definitively establish the optimal and safest route of EN in SAP; however, results of the PYTHON trial demonstrating equal tolerance of oral feeding compared with tube feeding in SAP may make the comparison less relevant for clinical management.

COMPOSITION OF ENTERAL NUTRITION AND IMMUNONUTRITION

There is a wide range of EN formulations with varying purported benefits in AP and, for simplicity, is divided into three categories: (1) oligomeric feeds, (2) polymeric feeds, and (3) "immunonutrition." Oligomeric, also known as semielemental, formulations contain small peptides, medium-chain fatty acids, and simple polysaccharides that do not require digestion by pancreatic enzymes and theoretically offer greater pancreatic rest than more complex polymeric formulations that contain full proteins, complex lipids, and carbohydrates.[33,34] Two meta-analyses, however, comparing oligomeric with polymeric formulations found no difference in terms of feeding intolerance, mortality, or LOS between the two formulations.[35] There is no apparent clinical advantage to the use of oligomeric formulations and more inexpensive polymeric formulations should be readily used.

Immunonutrition broadly refers to specialized formulations containing immunomodulatory supplements that are thought to offer benefit by modifying the immune response associated with AP. The most well studied of these include formulations supplemented with one of either glutamine, arginine, omega-3 fatty acids, nucleotides, and fiber enrichment. Trials in other clinical settings involving critically ill patients given immunonutrition-supplemented EN, specifically with glutamine and arginine, have described trends toward lower infectious complications and mortality compared with standard EN.[36–38] The benefit of immunonutrition-supplemented EN in AP is less established and based on low-quality studies. A Cochrane systematic review by Poropat and colleagues[39] of 15 trials investigating EN formulations specifically containing immunonutrition components given to patients with AP found no difference in all-cause mortality or occurrence of SIRS when compared with other EN formulations. Nearly all the trials in this review were noted to be of low quality with a high risk for bias. A separate meta-analysis by Petrov and colleagues[40] similarly did not demonstrate a clinical benefit with immunonutrition formulations in regard to LOS or infectious complications.

There are trials, largely from China, showing clinical benefit of PN supplemented with glutamine or glutamine administered intravenously in SAP with regards to lower infectious complications, LOS, and resolution of inflammatory markers.[41–44] Glutamine is postulated to exert an immunomodulatory effect via increasing lymphocyte mitogenic function, whereas decreasing production of proinflammatory cytokines, such as interleukin-6 and tumor necrosis factor-α and antioxidant properties. Glutamine also supports the growth of other rapidly dividing cells, such as enterocytes.[45] These benefits have not been demonstrated in trials with glutamine-supplemented EN,[43,46] currently limiting the clinical relevance of glutamine in AP until further investigation with high-quality trials can be performed.

Patients with AP are known to have gut dysbiosis or unfavorable imbalance of gut microbiota that may contribute to associated inflammation.[3,47] The use of probiotics, substances containing live microorganisms of healthy gut flora, however, has been shown to be detrimental in AP. The PROPATRIA trial, a multicenter, double-blind, placebo-controlled RCT of nearly 300 patients with predicted SAP conducted in the Netherlands aimed to reduce infectious complications in patients with SAP through the use of enteral probiotic preparations. The study compared the use a multispecies mixture of two different *Bifidobacterium* species, three different *Lactobacillus* species,

and one *Lactococcus* species with placebo. Findings from the trial demonstrated no significant difference in the primary end point of infectious complications and a two- to three-fold increase in mortality in patients who received probiotics.[48] Until more studies can establish an acceptable safety margin and consistent dosing for probiotic administration, their use should be avoided in AP.

The benefit of immunonutrition in AP is currently unclear and, as recommended by the AGA, warrants further investigation with high-quality RCTs to support routine use. Current evidence is lacking in supporting the use of immunonutrition-supplemented EN but there may be some benefit of glutamine-supplemented PN in patients with SAP requiring PN. A Cochrane systematic review and network meta-analysis by DiMartino and colleagues[49] is ongoing to further clarify the benefit of immunonutrition supplementation in EN and PN in AP.

SUMMARY AND RECOMMENDATIONS

In addition to supportive care, nutritional support is a cornerstone of the management of AP across all disease severities. EN serves to preserve the gut barrier as a means to mitigate immune dysregulation and systemic inflammation inherent to the clinical syndrome of AP. Based on the current body of evidence, oral feeding trials should be initiated generally within 24 hours with a soft, low-residue diet as tolerated rather than routinely keeping patients NPO. Polymeric EN should be given via tube feeding for patients unable to tolerate an oral feeding challenge within 48 to 72 hours. NGT may be the preferred route of feeding in patients without gastric outlet obstruction, ileus, or of high aspiration risk because of its relative convenience and lack of evidence supporting the superiority of NJT (**Fig. 2**). It is important to actively reassess patients reported symptoms to attempt oral feeding trials as feasible. PN should be avoided because of worse clinical outcomes relative to EN and is reserved only for select situations where EN cannot be administered. Immunonutrition formulations cannot be routinely

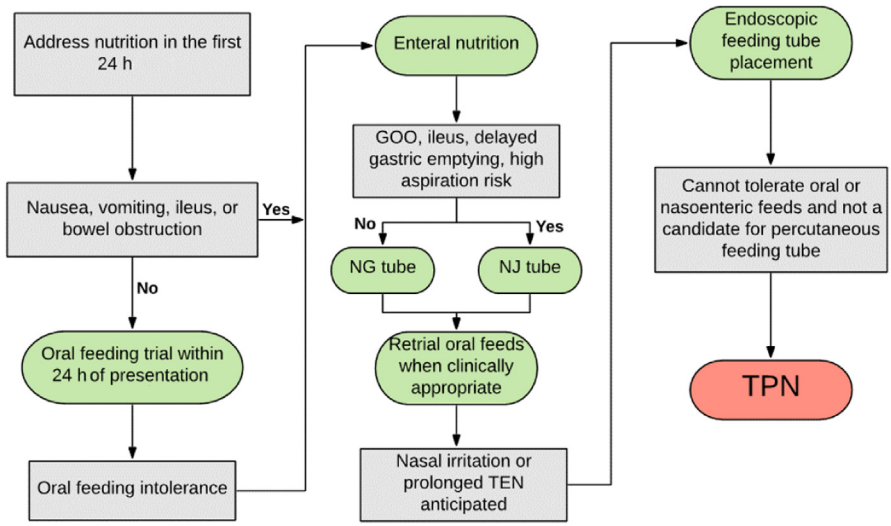

Fig. 2. Flow diagram on the suggested nutritional management of patients with moderate to severe acute pancreatitis (pancreatic necrosis). GOO, gastric outlet obstruction; NG, nasogastric; NJ, nasojejunal; TEN, total enteral nutrition; TPN, total parenteral nutrition.

recommended based on current evidence and additional investigation is required to clarify its benefit in AP. Probiotic use should be avoid in AP.

CLINICS CARE POINTS

- Oral and enteral nutrition (EN) significantly reduces the risk of mortality, infection, and organ failure in patients with acute pancreatitis and should be prioritized along with fluid therapy and analgesia.
- Oral feeding using a soft low-fat and low-residue diet should be attempted within 24 hours of presentation as tolerated by symptoms rather than keeping patients *nil per os* (NPO). Early oral feeding is safe and has been shown to decrease hospital length of stay.
- Patients unable to tolerate oral feeding trials over 48 to 72 hours should receive EN through a feeding tube. There is no difference between nasogastric or nasojejunal tubes and the choice of which to use is left to the discretion of the clinician and available resources.
- Parenteral nutrition should be avoided in acute pancreatitis because of increased rates of infection and mortality relative to EN. Its use is reserved for only select circumstances where EN is not tolerated.
- The benefit of "immunonutrition" and other nutritional supplements in acute pancreatitis requires further investigation. Probiotic use should be avoided.

DISCLOSURE

All included authors disclose no commercial or financial conflicts of interest.

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