Nutrition in Severe Acute Pancreatitis

10

Kishore Vipperla and Stephen J. O'Keefe

Introduction

A variety of factors such as alcohol and gallstones predispose to the premature activation of the pro-enzymes within the acinar cells in the genetically susceptible individuals causing enzymatic destruction of pancreatic tissue or "autophagia" and inflammation known as acute pancreatitis (AP). AP represents a hypercatabolic metabolic state marked by high caloric and nitrogenous demand from the acute inflammatory and reparative processes. Nearly 80 % of AP patients have mild to moderate disease that resolves uneventfully within 3–5 days with bowel rest and supportive care, but ~20 % have severe AP (SAP) disease complicated by severe systemic inflammatory response syndrome (SIRS), multiorgan failure (MOF), and local complications such as necrotizing pancreatitis associated with mortality as high as 40 % [1]. Interestingly, while bowel rest is probably essential in the early treatment phase of SAP, delay in enteral feeding of these very sick patients is associated with increased morbidity and mortality, possibly because of complications arising from gut stagnation. Better understanding of the underlying pathophysiologic mechanisms and the unique nutritional challenges faced during the treatment of the SAP patients is crucial to provide the essential nutritional support; preserve the gut function and splanchnic metabolism; and potentially modulate the systemic inflammatory response through enteral feeding.

Physiology of Pancreatic Secretion

Proteolytic enzymes synthesized within the pancreatic acinar cells are secreted in their inactive forms (e.g., trypsinogen) that are activated in the intestinal lumen by the enterokinase, an intestinal brush border peptidase. Pancreatic juice is secreted at a basal rate (~20 %) and further stimulated by meals (~80 %) in three interrelated phases: cephalic, gastric, and intestinal phases [2]. In the "cephalic phase" mere sight of food, chewing, and swallowing cause pancreatic secretion mediated by direct vagal cholinergic stimulation of the acinar cells. In the "gastric phase" mechanical distention caused by the ingested food provides a major stimulus for pancreatic enzyme

K. Vipperla, M.D.
Division of General Internal Medicine, Section of Hospital Medicine, University of Pittsburgh School of Medicine, 200 Lothrop Street, W933 MUH, Pittsburgh, PA 15213, USA

S.J. O'Keefe, M.D., M.Sc. (✉)
Department of Gastroenterology, Hepatology, and Nutrition, University of Pittsburgh School of Medicine, 200 Lothrop Street PUH, Mezzanine Level-C Wing, Pittsburgh, PA 15213, USA
e-mail: sjokeefe@pitt.edu

C.E. Forsmark and T.B. Gardner (eds.), *Prediction and Management of Severe Acute Pancreatitis*,
DOI 10.1007/978-1-4939-0971-1_10,

secretion in addition to the gastric acid secretion mediated by a gastropancreatic vagovagal reflex. Finally, in the "intestinal phase" passage of acidic gastric contents through the pylorus incites the maximal stimulatory phase of pancreatic secretion mediated by complex neural (cholinergic excitation of the entero-pancreatic reflex) and humoral (cholecystokinin [CCK] and secretin) pathways. CCK is released from the duodenal I-cells in response to peptides, amino acids, and fatty acids that are present in the chyme and is mediated by vagal neurotransmitters such as acetylcholine, gastrin-releasing peptide (GRP), and vasoactive intestinal peptide (VIP). Secretin is released by the duodenal mucosa in response to the acidic chyme and is the major mediator of pancreatic water and bicarbonate secretion. Importantly, when the undigested nutrients reach the terminal ileum pancreatic secretions are suppressed through a negative-feedback mechanism known as "ileal brake" that is mediated by the release of enteroendocrine gut peptides such as glucagon-like peptide-1 (GLP-1) and peptide-YY (PYY) [3]. Importantly, the rate of gastric emptying and duodenal delivery of nutrients, as well as their physicochemical characteristics (i.e., the proportion of fat, carbohydrate, and protein content), determine the duration and composition of the pancreatic secretory response.

Pathophysiology of Acute Pancreatitis

The inflammatory cascade of events in AP is believed to be triggered by the intracellular influx of calcium with inappropriate activation of the pancreatic zymogen (pro-enzyme) resulting in pancreatic parenchymal proteolysis or "autophagia" [4]. Pancreatic acinar cell injury results in activation of the periacinal myofibrocytic nuclear factor-kappa B (NF-κB) and mitogen-activated protein (MAP) kinase pathways that generate a flood of proinflammatory cytokines such as tumor necrosis factor-α (TNF-α), interleukins (IL)- IL-1b, IL-17, and IL-18 [5]. Subsequent IL-6 release and cytoattraction of neutrophils amplify this cytokine cascade. Activation of one of the cytokines, endothelin-A, causes arterial vasoconstriction and ischemic death of pancreatic as well as the intestinal tissue [6]. The fluid sequestration or "third spacing" secondary to pancreatic inflammation decreases the intravascular volume compromising tissue perfusion and microcirculation that further exacerbates the ischemic injury. Besides the local inflammation in the pancreatic bed, the proinflammatory cytokines released into the blood circulation can cause systemic inflammation and organ failure. The consequent SIRS escalates and manifests as acute respiratory distress syndrome (ARDS, from bronchial mucosal injury) and bowel ischemia that compromises the gut mucosal defense barrier causing bacterial translocation and systemic infections. To make matters worse, prolonged fasting can be detrimental as lack of luminal nutrients further aggravates the already disturbed gut function and splanchnic metabolism.

Nutritional Support in AP

The initial treatment of AP is focused on symptomatic control of nausea and abdominal pain using narcotic analgesics and antiemetic agents; aggressive fluid resuscitation and restoration of electrolyte balance; and initiation of specific treatment addressing the inciting etiological factor [7]. Nutritional support is a key supportive measure that serves two important purposes. First, nutrients provide the building blocks for the tissue repair and healing. Secondly, enteral nutrition can potentially improve the clinical outcomes of SAP by preserving the gut function and modulating the systemic inflammation and preventing organ failure, which are associated with high morbidity and mortality. The disease severity, determined by the severity and duration of symptoms, laboratory and radiographic evidence of organ failure, and stability of hemodynamic parameters, dictates the timing and mode of nutrition (Fig. 10.1). Most importantly, resting the bowel to avoid or minimize pancreatic secretion during AP has been the standard of care.

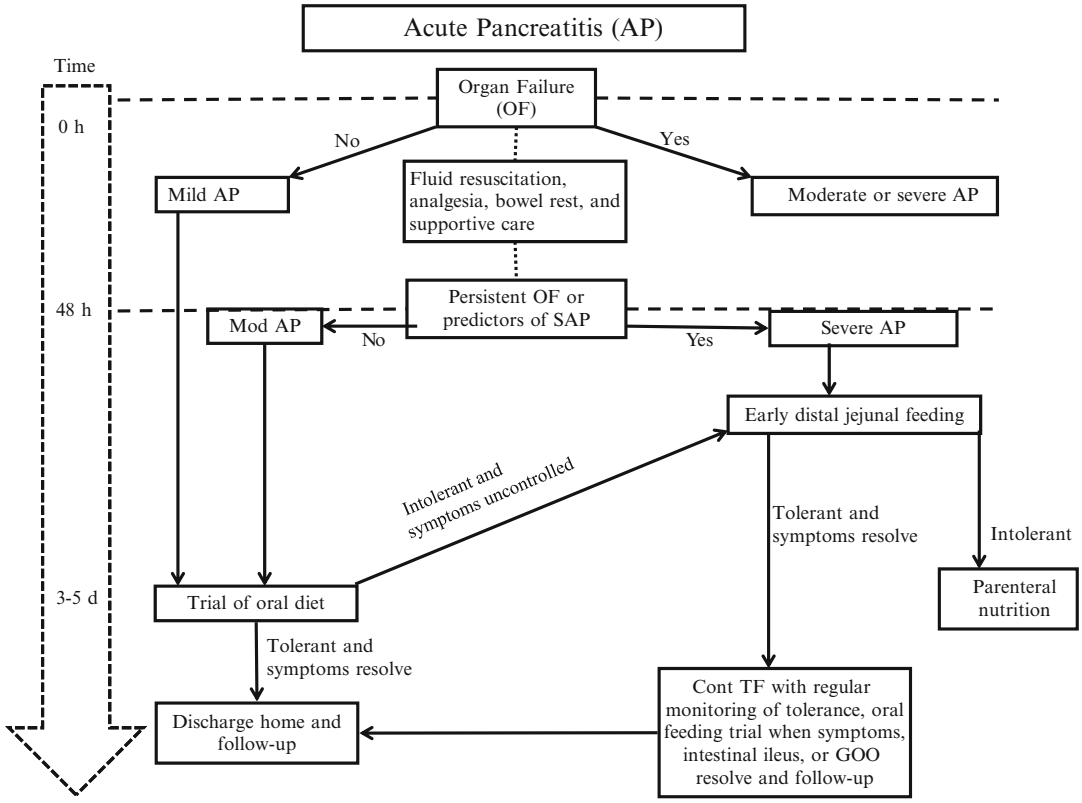

Fig. 10.1 Nutritional support in acute pancreatitis. Bowel rest is important during the first 48 h. Oral feeding can be initiated at 3–5 days in mild to moderate AP patients when symptoms resolve. Enteral feeding can be begun as early as 48 h after the initial resuscitation period in predicted severe AP patients in an effort to preserve gut mucosal function and splanchnic metabolism and modulate the inflammatory cascade to mitigate SIRS, OF, and high morbidity and mortality associated with severe AP

Nutrition can be held for up to a week without significant malnutritional consequence in patients with mild AP, but early enteral feeding should be started when AP is predicted to be severe or associated with complications such as necrotizing AP in order to sustain these profoundly catabolic hypermetabolic states and to maintain gut function and prevent ileus, stagnation, and bacterial overgrowth [8]. Risk stratification and prediction of severity of AP earlier in the course are very helpful in determining the timing and mode of nutritional support. Hence, the conventional practice of prolonged fasting patients with moderate to SAP for "pancreatic rest" has transformed into one where earlier enteral feeding is being advocated in anticipation of better clinical outcomes.

NPO-Pancreatic Rest

Nil per os (NPO) or bowel rest has been the cornerstone of AP treatment traditionally based on the assumption that ingestion of food stimulates pancreatic secretion and worsens leakage of enzymes that aggravate the pancreatic injury and inflammation [9]. Resting the pancreas is expected to decrease pancreatic secretion and mitigate the inflammation and pain, but strong evidence to prove the merits of the concept of "pancreatic rest" is lacking. On the other hand, AP is often associated with delayed gastric emptying and intestinal ileus that cause anorexia, abdominal pain, nausea, and vomiting that prevent the patient from tolerating oral fluids and diet.

However, depriving these patients of the essential nutrients during a highly catabolic process aggravates the nitrogen loss and is likely detrimental to the healing and repair of the inflamed pancreas. In addition, starvation compromises the mucosal integrity and promotes bacterial overgrowth due to diminished intestinal motility. An impaired mucosal defense barrier increases the gut permeability to inflammatory cytokines and intestinal bacterial translocation that worsen the SIRS. The fact that the enteric microorganisms are commonly isolated from infected pancreatic necrosis further underscores the risk of early bacterial translocation in AP. Unfortunately prophylactic antibiotics have not proven to be effective in decreasing the infection risk. Hence, oral or enteral nutritional support should be provided as soon as possible to preserve the gut function.

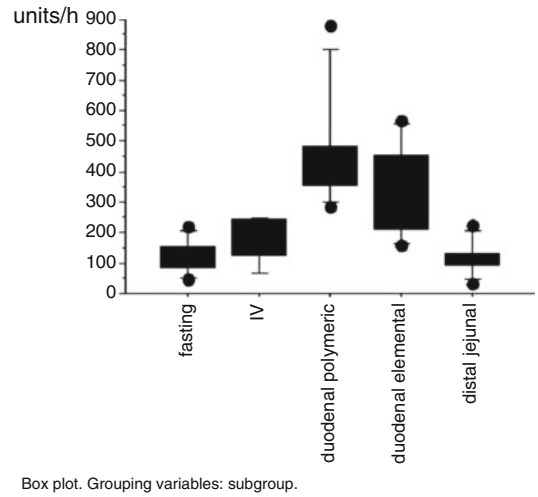

Fig. 10.2 The effect of site of nutrient delivery on trypsin secretion. Reprinted with permission from from O'Keefe S. Physiological response of the human pancreas to enteral and parenteral feeding. Curr Opin Clin Nutr Metab Care 2006; 9(5)

How Can We Safely Rest the Pancreas?

The pancreas continues to produce "basal secretion" that is rich in bicarbonate and fluid by volume and poor in protein enzyme output during an AP episode in spite of absolute bowel rest. An ideal nutrition support for AP should minimally stimulate pancreatic secretions or perhaps suppress them and yet be able to provide the required energy and protein. While only PN can completely avoid pancreatic stimulation, all forms of oral and conventional enteral feeding have been shown to stimulate pancreatic secretion to some degree in human studies [10]. The meal composition (i.e., proportion of fat, carbohydrate, and protein) and site of nutrient delivery influence the composition and duration of pancreatic secretion. High-fat diet stimulates pancreatic secretion through CCK and infusion of an elemental diet containing low fat and free amino acids was shown to reduce the pancreatic secretion by ~50 % when compared to a polymeric diet containing intact protein [10]. Trypsin secretion was shown to be lower with increasing distance of the tip of the feeding tube from ligament of Trietz (LOT) favoring distal jejunal feeding over gastric feeding for the least stimulation of pancreatic secretion (Fig. 10.2) [11]. Infusion of enteral feeding into the mid-jejunum at 60 cm distal to the LOT has been shown to have no stimulatory effect on the pancreas when compared to the infusion in the proximal duodenum, which resulted in fourfold increase in basal trypsin secretion [12]. Bypassing the oral, gastric, and intestinal phases of pancreatic secretion probably explains the lack of stimulatory effect of EN delivered to distal jejunum. Besides avoiding the stimulation of pancreatic trypsin secretion, delivery of EN into the mid-distal jejunum has been shown to activate the intestinal inhibitory peptide-mediated "ileal-brake" as evidenced by significantly elevated serum GLP-1 and PPY levels, but not CCK, as noted on measurement of these gut peptides in response to distal jejunal feeding [11]. These observations strongly support distal jejunal feeding as the most rational form of nutritional support in SAP.

Enteral Feeding

The concept of nutritional support in AP has evolved significantly in the past two decades with a growing understanding of early inflammatory mechanisms in AP and fascinating evidence on improved survival and reduced rate of complications with early initiation of oral or enteral feeding. Consequently, there has been a gradual shift in the treatment approach from recommendation of strict NPO to that of early EN with the expectation of being able to suppress the systemic inflammatory response. Sound evidence from several randomized controlled trials (RCTs) and meta-analyses comparing the outcomes of EN to PN in AP has clearly shown the superiority of EN in decreasing mortality, infectious complications rate, MOF, and length of hospitalization [13, 14]. The beneficial effects of EN have been ascribed to its ability to prevent mucosal atrophy and maintain the integrity of gut barrier. Avoidance of central venous access catheter-associated risks such as blood stream infections and vascular thrombosis, PN-related metabolic complications such as hyperglycemia, and importantly affordability of EN support at ~15 % cost of PN make EN a more attractive form of nutrition. EN was shown to be safe, effective, and even better in terms of mitigating the inflammatory effects of AP when compared to PN in mild-moderate as well as SAP [15, 16].

Route of EN

Severe abdominal pain, nausea, vomiting, and ventilator support requiring sedation in the ICU preclude oral feeding in patients with SAP. EN can be provided via nasogastric (NG), nasoduodenal, or nasojejunal (NJ) feeding. Gastric feeding is relatively easy and facilitates early enteral nutrition as nasogastric feeding tube placement is a simple procedure and can be performed at bedside. Eatock et al. and Kumar et al. have demonstrated in their RCTs that both gastric and jejunal feeding routes are well tolerated, and there was no significant difference between these groups in terms of mortality, length of hospital stay, infectious complications, or MOF [17, 18]. Eatock et al. compared the inflammatory responses and clinical course between NG versus NJ feeding of objectively graded SAP patients and found NG feeding as simple, cheap, and as good as NJ feeding as no significant differences were noted in the APACHE II scores, C-reactive protein levels, analgesic requirement, and mortality [17]. However, these studies failed to investigate the importance of pancreatic rest as both forms of feeding were stimulatory and positioning of the jejunal tube well down the jejunum was not proven. A systematic review noted nasogastric feeding to be safe and well tolerated with no difference in mortality or tolerance found between the NG and NJ groups, though it was acknowledged that a well-powered RCT is needed for a more conclusive and firm evidence [19]. However, the need for frequent gastric suctioning for delayed gastric emptying and/or gastric outlet obstruction from compression by duodenal swelling makes gastric feeding ineffective and even potentially dangerous by increasing the risk of aspiration of gastric contents. Further, the theoretical risk of pancreatic stimulation still exists with NG feeding.

Distal jejunal (DJ) feeding has been shown to be more effective than PN in delivering the nutrition and at the same time allowing the pancreas to rest [20]. In patients having gastric outlet obstruction from pancreatic inflammation or fluid collection related duodenal compression, a nasogastrojejunal (NGJ) tubing system, a double lumen tube with proximal gastric decompression, and distal jejunal feeding ports can be used to serve both the purposes without the need for two separate tubes [21]. When gastric decompression is not needed, a NJ feeding tube is usually placed under endoscopic or fluoroscopic guidance to infuse the nutrients far (~40 cm) beyond the LOT [22]. Only well-trained gastroenterologists or radiologists can place a NJ feeding tube successfully, which makes jejunal feeding a less readily available option with potential delays in "prompt or early" nutrition in some cases. In many centers, nasoduodenal feeding tubes are placed by

nursing teams, as the primary method of enteral feeding. Patients who require surgical intervention for AP-related complications could have a surgical enterostomy tube (jejunostomy) placed at the same time when the need for prolonged EN is anticipated.

Timing of EN (Window of Opportunity)

The first priority is to resuscitate the patient to maintain intravascular volume and prevent renal failure. Depending on the patient's preexisting nutritional state, nutritional support should not be delayed beyond 5–7 days of fasting to suppress severe net nitrogen losses, which can be as high as 20–40 g/day [23]. Evidence from studies on EN in critically ill patients with head injuries, burns, trauma, and postoperative and other non-pancreatitis-related medical problems have suggested benefits of reduced length of stay and delayed infectious complications when patients were fed within 36 h compared to those who received it after 36 h [24]. In a systematic review of RCTs comparing EN and PN in mild and SAP, significant differences between the two forms of feeding in terms of reductions in MOF, pancreatic infectious complications, and mortality were observed only in those who had their EN administered within 48 h of admission [25].

Although observational studies have shown that early enteral feeding is associated with better outcome, the best timing of enteral feeding in the AP patients has not yet been studied in large RCTs [8]. The current recommendation of "early EN" is based on the assumption of exploiting the "window of opportunity" during the initial course of disease when luminal nutrients reinforce the gut function and splanchnic metabolism to potentially ameliorate the SIRS [26]. It is still unclear whether interventional feeding is better than no feeding, or whether slow (trophic) feeding is as good as full feeding in the initial management, bearing in mind that most cases of SAP nowadays are obese [8].

Composition of EN

The average daily nutrition requirement in an adult is 25–35 kcal/kg of energy and 0.8–1.5 g/kg of protein. Despite the fact that the disease produces accelerated catabolism, there is no evidence that feeding at higher rates improves outcome, as energy stores in all but the previously malnourished can cover excess loss. Peptide-based formulas with low fat (long-chain fatty acids/LCFA) and isotonic solutions are ideally fed into the jejunum. Tube feeds are generally categorized into elemental, semi-elemental, and polymeric or standard formulas based on the characteristics of their individual carbohydrate, fat, and protein nutrient components. Elemental formula is a completely predigested formula consisting of amino acids, simple sugars, and essential fatty acids. Semi-elemental formula contains peptides, glucose polymers, and medium-chain triglycerides that are easier to digest compared to standard polymeric formulas, which contain non-hydrolyzed proteins, complex carbohydrates, and long-chain triglycerides. Earlier studies used (semi) elemental formulas based on the knowledge that they stimulate pancreatic secretions less than the polymeric formulas [27]. However, recent meta-analysis comparing polymeric and (semi) elemental feeds in patients with AP did not find any difference in the risk of intolerance to feeding, infectious complications, or death [28]. Despite these results, we prefer to use semi-elemental formulae because our studies have shown that pancreatic insufficiency can result from SAP and we want to ensure what is delivered is absorbed [27].

Tolerance of Tube Feeding

In general, enteral feeding is simple to use and safe. Although diarrhea is common in all ICU patients, EN is rarely the cause. Other medications such as antibiotics, sorbitol, and fiber deficiency are more common causes. Importantly, dysbiosis (disturbed microbiotal composition and their beneficial metabolites such as short

chain fatty acids) of the colonic microbiota as a result of fasting, use of proton-pump-inhibitors, and antibiotics is believed to be an important factor responsible for the diarrhea in these sick patients. Interestingly, diarrhea in the critically ill patients was shown to improve with fiber supplementation that had the potential to improve the microbial mass and function [29]. The other limitations of enteral feeding are intolerance and complications that are commonly associated with the feeding tube such as nasopharyngeal discomfort and mucosal erosions, otitis media, sinusitis, esophageal erosions, and acid reflux. In the case of NG feeding, gastric residual volumes (GRV) are measured every 4 h as a measure of tolerance to feeding. GRV <500 mL is an acceptable mark of continuation or advancement of rate of feeding, considering the significantly higher risk of aspiration noted beyond this mark [30]. The risk of aspiration, which is greater for NG than NJ mode of feeding, can be minimized by elevation of the head of the bed by 30–45º, confirmation of the position of the tip of the feeding tube by abdominal radiographs when dislodgement is suspected, gross inspection of the tracheal aspirates for presence of tube feeds in the intubated patients, and consideration of using a prokinetic agent (e.g., metoclopramide).

Maintenance of Tube Feeding

Certain maintenance and monitoring measures are paramount for the best performance of the feeding tubes. Nasal feeding tube must be secured properly using a device such as a "nasal bridle" to prevent accidental dislodgement. The tubes need to be flushed with 30 mL of tap water once every 4–6 h (now easily programmable on infusion pumps) to minimize the risk of clogging from congealed feed. Most importantly, the feeding tubes must be reserved for feeding. If alternative delivery is impossible, medications should be carefully administered as crushed or liquid preparations via the G-port, but should never be administered through the J-port. GRV should be <500 mL for medication deliver through the G-port. Kinking of the enteral feeding tube within the intestinal lumen can often present as "clogging" that does not respond to declogging maneuvers. Abdominal radiograph should be obtained to identify kinking that can be resolved by slowly withdrawing the J-tube until flow is restored.

Feeding must be initiated at a slow rate and then gradually advanced as tolerated. In either NG or NJ feeding, generally a liquid elemental nutrient formula can be initiated at 25 mL/h for the first 24 h, and then gradually advanced by 25 mL/h daily over the next 2–3 days to achieve the final goal rate calculated to provide 25 kcal energy/kg ideal body weight/day. Having said that, lower rates of feeding throughout the acute episode may be optimal, as it preserves gut function and reduces side effects. In the case of NGJ system, the gastric port (G-port) is connected to a low-pressure (50 mmHg) intermittent suction while feeding is started until the GRVs drop below 500 mL/4 h, whence the G-port can be clamped and monitored as described above.

Enteral feeding is continued until the patient's clinical condition improves and appetite returns. Tolerance of <10 % of the goal rate of feeding can be considered a failure of enteral feeding. Failure to tolerate EN requires consideration of PN for nutritional support in the second week.

Immunonutrition and Probiotics

Enrichment of enteral feeding formulas with glutamine, arginine, omega-3 fatty acids, antioxidants such as vitamins and micronutrients (concept of "immunonutrition") in order to boost the gut immune system has garnered significant research attention. While experimental models revealed promising observations, small-scale clinical studies in humans have yielded mixed results and a recent systematic review has not found any benefits of immunonutrition in clinical outcomes of AP in terms of incidence of MOF, length of hospitalization, or mortality [28]. Similarly studies on probiotic and prebiotic supplementation purported to reduce small intestinal bacterial overgrowth, reinforce the gut barrier, and modulate gut immunity have also resulted in inconsistent results. Importantly, mortality was shown to be higher (16 % vs. 6 %) in a RCT

that evaluated the effectiveness of multispecies probiotic prophylaxis in predicted SAP patients [31]. While these results are difficult to explain, they exemplify the critical state of the GI tract in severe disease and the need to be cautious and always avoid excessive forced feeding. Overall, the evidence recommends against probiotic prophylaxis in SAP and there is no strong enough evidence to recommend immunonutrition for the routine management of SAP.

Parenteral Feeding

PN was conceptualized as an ideal way to deliver nutrients to meet the high metabolic demands of AP, as it does not stimulate pancreatic secretion and thereby offering a more practical method of resting the pancreas. But bypassing the entero-pancreatic axis nutrient assimilation and providing intravenous glucose disturb the glucose metabolism causing hyperglycemia, hyperinsulinemia, and insulin resistance, resulting in higher rate of complications. Experimental and clinical data suggest that PN is associated with stronger proinflammatory responses, impaired cellular and humoral immunity, compromised gut defense barrier, increased bacterial translocation, and risk of systemic infections [32]. More importantly, the lack of intestinal luminal nutrients from fasting while receiving TPN has grave consequences in the form of gut mucosal atrophy and dysfunction of gut immune system, with suppression of Th_2 response and activation of adhesion molecules, increased neutrophil adherence, migration, and activation systemically causing end-organ damage such as ARDS [33]. Bowel rest also impairs intestinal blood flow and gut motility potentiating the risk of small intestinal bacterial overgrowth, bacterial translocation, and endotoxemia in the setting of increased intestinal barrier permeability [34]. Acute pancreatitis and PN are known to increase intestinal production of IL-6, associated with intestinal barrier dysfunction, and increase the risk of sepsis from enteric organisms/colonic microbiota.

In addition, the inherent risks associated with the central venous access catheter used for administering the PN such as of bleeding, bloodstream infections, and venous thromboses make it a poorer option. Serum electrolytes potassium, magnesium, and phosphorous and calcium need to be monitored closely and corrected appropriately while receiving PN.

Overall, an overwhelming body of evidence argues against general use of PN support and it should be reserved for patients who have failed enteral feeding and are becoming nutrient-depleted. In practice, PN is rarely needed when a NGJ tube can be placed and managed appropriately by experienced personnel.

Conclusion

- Bowel rest allows the inflamed pancreas to rest, but delay in enteral feeding can compromise the gut mucosal integrity, promote bacterial overgrowth and translocation, and exacerbate the systemic inflammation and risk of infection. Moreover, starvation aggravates the negative nitrogen balance and catabolism, thus impairing tissues healing and repair.
- PN provides the protein and nutrients for tissue repair without stimulating the inflamed pancreas. However, PN exacerbates systemic inflammatory responses, gut mucosal atrophy, and the risks of central venous catheter-related thrombosis and septicemia, and PN-associated metabolic complications (e.g., hyperglycemia) can outweigh the benefits of nutrition support.
- EN offers the advantage of delivering the nutritional support while it preserves gut mucosal integrity, supports splanchnic metabolism, and thereby potentially mitigates the systemic inflammatory response. Moreover, it avoids the complications of parenteral nutrition and causes minimal stimulation of pancreatic secretion by distal jejunal feeding.
- In general, recommendations for mode of nutritional support depend on the underlying nutritional state, the severity of pancreatitis,

and existence of complications. Early organ failure correlates well with mortality in SAP, and there is evidence that early slow (25 cm^3/h) enteral feeding may prevent progression of organ failure. Overfeeding from EN or PN introduces further complications and must be avoided in SAP.

- Oral feeding trials can be initiated within 3–4 days of supportive care and bowel rest in AP patients with mild to moderate disease severity.
- Early enteral feeding (within 48 h of onset of pain) may improve outcome in patients with significant symptoms and laboratory and radiographic evidence of SAP by suppressing systemic inflammation and organ failure, but RCT are needed to confirm this.

References

1. Windsor JA, Petrov MS. Acute pancreatitis reclassified. Gut. 2013;62(1):4–5.
2. O'Keefe SJ. Physiological response of the human pancreas to enteral and parenteral feeding. Curr Opin Clin Nutr Metab Care. 2006;9(5):622–8.
3. Van Citters GW, Lin HC. Ileal brake: neuropeptidergic control of intestinal transit. Curr Gastroenterol Rep. 2006;8(5):367–73.
4. Sah RP, Garg P, Saluja AK. Pathogenic mechanisms of acute pancreatitis. Curr Opin Gastroenterol. 2012; 28(5):507–15.
5. Norman J. The role of cytokines in the pathogenesis of acute pancreatitis. Am J Surg. 1998;175(1):76–83.
6. Inoue K, Hirota M, Kimura Y, Kuwata K, Ohmuraya M, Ogawa M. Further evidence for endothelin as an important mediator of pancreatic and intestinal ischemia in severe acute pancreatitis. Pancreas. 2003; 26(3):218–23.
7. Tenner S, Baillie J, DeWitt J, Vege SS, American College of Gastroenterology. American College of Gastroenterology guideline: management of acute pancreatitis. Am J Gastroenterol. 2013;108(9): 1400–15.
8. Hegazi R, Raina A, Graham T, Rolniak S, Centa P, Kandil H, et al. Early jejunal feeding initiation and clinical outcomes in patients with severe acute pancreatitis. J Parenter Enteral Nutr. 2011;35(1):91–6.
9. Ragins H, Levenson SM, Signer R, Stamford W, Seifter E. Intrajejunal administration of an elemental diet at neutral pH avoids pancreatic stimulation. Studies in dog and man. Am J Surg. 1973; 126(5):606–14.
10. O'Keefe SJ, Lee RB, Anderson FP, Gennings C, Abou-Assi S, Clore J, 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.
11. Kaushik N, Pietraszewski M, Holst JJ, O'Keefe SJ. Enteral feeding without pancreatic stimulation. Pancreas. 2005;31(4):353–9.
12. Vu MK, van der Veek PP, Frölich M, Souverijn JH, Biemond I, Lamers CB, et al. Does jejunal feeding activate exocrine pancreatic secretion? Eur J Clin Invest. 1999;29(12):1053–9.
13. Marik PE, Zaloga GP. Meta-analysis of parenteral nutrition versus enteral nutrition in patients with acute pancreatitis. BMJ. 2004;328(7453):2.
14. Al-Omran M, Albalawi ZH, Tashkandi MF, Al-Ansary LA. Enteral versus parenteral nutrition for acute pancreatitis. Cochrane Database Syst Rev, 2010 Jan 20 (10):CD002837.
15. McClave SA, Greene LM, Snider HL, Makk LJ, Cheadle WG, Owens NA, et al. Comparison of the safety of early enteral vs parenteral nutrition in mild acute pancreatitis. J Parenter Enteral Nutr. 1997; 21(1):14–20.
16. Kalfarentzos F, Kehagias J, Mead N, Kokkinis K, Gogos CA. Enteral nutrition is superior to parenteral nutrition in severe acute pancreatitis: results of a randomized prospective trial. Br J Surg. 1997;84(12): 1665–9.
17. Eatock FC, Chong P, Menezes N, Murray L, McKay CJ, Carter CR, et al. A randomized study of early nasogastric versus nasojejunal feeding in severe acute pancreatitis. Am J Gastroenterol. 2005;100(2):432–9.
18. Kumar A, Singh N, Prakash S, Saraya A, Joshi YK. Early enteral nutrition in severe acute pancreatitis: a prospective randomized controlled trial comparing nasojejunal and nasogastric routes. J Clin Gastroenterol. 2006;40(5):431–4.
19. Petrov MS, Correia MI, Windsor JA. Nasogastric tube feeding in predicted severe acute pancreatitis. A systematic review of the literature to determine safety and tolerance. JOP. 2008;9(4):440–8.
20. Abou-Assi S, Craig K, O'Keefe SJ. Hypocaloric jejunal feeding is better than total parenteral nutrition in acute pancreatitis: results of a randomized comparative study. Am J Gastroenterol. 2002;97(9):2255–62.
21. O'Keefe S, Rolniak S, Raina A, Graham T, Hegazi R, Centa-Wagner P. Enteral feeding patients with gastric outlet obstruction. Nutr Clin Pract. 2012;27(1): 76–81.
22. O'Keefe SJ. A guide to enteral access procedures and enteral nutrition. Nat Rev Gastroenterol Hepatol. 2009;6(4):207–15.
23. Bouffard YH, Delafosse BX, Annat GJ, Viale JP, Bertrand OM, Motin JP. Energy expenditure during severe acute pancreatitis. J Parenter Enteral Nutr. 1989;13(1):26–9.
24. Marik PE, Zaloga GP. Early enteral nutrition in acutely ill patients: a systematic review. Crit Care Med. 2001;29(12):2264–70.
25. Petrov MS, van Santvoort HC, Besselink MG, van der Heijden GJ, Windsor JA, Gooszen HG. Enteral nutrition and the risk of mortality and infectious complications in patients with severe acute pancreatitis:

a meta-analysis of randomized trials. Arch Surg. 2008;143(11):1111–7.
26. McClave SA, Heyland DK. The physiologic response and associated clinical benefits from provision of early enteral nutrition. Nutr Clin Pract. 2009;24(3): 305–15.
27. O'Keefe SJ, Lee RB, Li J, Stevens S, Abou-Assi S, Zhou W. Trypsin secretion and turnover in patients with acute pancreatitis. Am J Physiol Gastrointest Liver Physiol. 2005;289(2):10.
28. Petrov MS, Loveday BP, Pylypchuk RD, McIlroy K, Phillips AR, Windsor JA. Systematic review and meta-analysis of enteral nutrition formulations in acute pancreatitis. Br J Surg. 2009;96(11):1243–52.
29. O'Keefe SJ, Ou J, Delany JP, Curry S, Zoetendal E, Gaskins HR, et al. Effect of fiber supplementation on the microbiota in critically ill patients. World J Gastrointest Pathophysiol. 2011;2(6):138–45.
30. McClave SA, Martindale RG, Vanek VW, McCarthy M, Roberts P, Taylor B, et al. Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.). J Parenter Enteral Nutr. 2009;33(3):277–316.
31. Besselink MG, van Santvoort HC, Buskens E, Boermeester MA, van Goor H, Timmerman HM, et al. Probiotic prophylaxis in predicted severe acute pancreatitis: a randomised, double-blind, placebo-controlled trial. Lancet. 2008;371(9613):651–9.
32. Marik PE, Pinsky M. Death by parenteral nutrition. Intensive Care Med. 2003;29(6):867–9.
33. King BK, Kudsk KA, Li J, Wu Y, Renegar KB. Route and type of nutrition influence mucosal immunity to bacterial pneumonia. Ann Surg. 1999;229(2):272–8.
34. Fong YM, Marano MA, Barber A, He W, Moldawer LL, Bushman ED, et al. Total parenteral nutrition and bowel rest modify the metabolic response to endotoxin in humans. Ann Surg. 1989;210(4):449–56. discussion 456–7.