

Nutrition in acute pancreatitis

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Abstract

Acute pancreatitis (AP) has varying severity, and moderately severe and severe AP has prolonged hospitalization and requires multiple interventions. These patients are at risk of malnutrition. There is no proven pharmacotherapy for AP, however, apart from fluid resuscitation, analgesics, and organ support, nutrition plays an important role in the management of AP. Oral or enteral nutrition (EN) is the preferred route of nutrition in AP, however, in a subset of patients, parenteral nutrition is required. EN has various physiological benefits and decreases the risk of infection, intervention, and mortality. There is no proven role of probiotics, glutamine supplementation, antioxidants, and pancreatic enzyme replacement therapy in patients with AP.

Key Words: Acute pancreatitis; Enteral; Parenteral; Nutrition; Malnutrition

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Core Tip: Nutrition improves the outcomes of acute pancreatitis (AP). In mild AP, solid food can be given when the patient is pain-free and hungry. In moderately severe and severe pancreatitis, feeding can begin as early as possible if there are no contraindications for an oral diet. If the patient does not tolerate an oral diet, tube feeding can be tried; and in case of gastric outlet obstruction or gastroparesis, nasojejunal tube feeding is preferred. Parenteral nutrition should be provided in case of complete intolerance or contraindications to oral/enteric feed or supplemented along with enteral feed if energy targets are not met.

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INTRODUCTION

Acute pancreatitis (AP) is an acute inflammatory condition of the pancreas, leading to systemic inflammation, organ failure, infection, morbidity, and mortality. It is a frequent cause of emergency visits and its incidence is rising globally[1]. AP is a catabolic state and malnutrition sets in early, progresses rapidly, and is associated with poor prognosis. The management of AP is centered on fluid resuscitation, early nutrition, adequate analgesia, various organ supports, management of local complications, and rehabilitation of the patient. There is no pharmacotherapy available for AP, however, nutritional intervention has shown various benefits in the management of AP. Hence, nutritional management is the cornerstone in the management of AP and is to be emphasized on regular basis to achieve a better outcome in AP. In this review, we shall discuss the practical aspects of nutrition in AP under two categories: (1) Mild AP; and (2) Moderately severe AP (MSAP) and severe AP (SAP).

NUTRITIONAL MANAGEMENT IN MILD AP

Among the patients of AP, nearly 80%-85% will have acute interstitial pancreatitis, usually with mild severity and no risk of mortality. Mild AP is usually self-limiting with an uncomplicated course. Patients do not have local complications or organ failure, and pain subsides early. A low-fat, soft oral diet can be initiated as early as possible when patients feel hungry and are pain-free. Compared with the stepwise introduction of diet from a liquid diet to an oral diet, a full-calorie solid oral food is similarly tolerated and is associated with better calorie intake and a shorter hospital stay[2-4].

NUTRITIONAL MANAGEMENT IN MSAP AND SAP

Acute necrotizing pancreatitis occurs in 15%-20% of patients, which can be MSAP or SAP with a 5%-30% risk of mortality depending on organ failure and infective complications[5]. These MSAP and SAP will be associated with prolonged hospitalizations, infectious complications, requiring invasive interventions, malnutrition, morbidity, and mortality.

Etiopathogenesis of malnutrition in AP

Studies on resting energy expenditure (REE) in AP are limited and have shown that most patients with severe AP and AP with sepsis are hypermetabolic based on gold standard indirect calorimetry ($> 110\%$ of predicted energy expenditure by Harris-Benedict equation)[6,7]. Hyperglycemia is often observed during AP and is related to pancreatic necrosis and infections. It is characterized by hyperglucagonemia and relative hypoinsulinemia in the early phase leading to increased gluconeogenesis, while relative hypoinsulinemia extends into the late phase also[8]. Hence, glucose monitoring and control are essential.

In necrotizing AP, severe inflammation in the early phase and sepsis in the later phase leads to increased protein catabolism[9]. In necrotizing AP, skeletal muscle mass and muscle density decrease significantly and rapidly within a month, and it was observed that a decrease in muscle density of $\geq 10\%$ in 1 mo was an independent predictor of mortality[10]. There is increased lipolysis and impaired lipid clearance due to relative hypoinsulinemia and serum triglyceride levels require monitoring in those with severe hypertriglyceridemia as etiology of AP and those in intravenous lipid emulsions.

Malnutrition develops rapidly, is common, especially in necrotizing AP, and is multifactorial (Figure 1). The probable causes are: (1) Decreased oral intake due to pain, nausea and vomiting secondary to gastroparesis or gastric outlet obstruction, intra-abdominal hypertension (IAH) and inappropriate fasting; (2) Increased catabolism in severe AP, and AP with sepsis; (3) Alcoholism; (4) Intestinal failure due to ileus or enteric fistulas; and (5) Exocrine and endocrine dysfunction during AP [11].

Nutritional assessment of patient and energy requirement

The purpose of nutritional assessment is to assess if a patient is at risk of malnutrition, and the current nutritional status of the patient and to plan personalized nutritional support for a patient depending on the severity of AP and the patient's current clinical status. Nutritional risk is defined by the present nutritional status and risk of impairment of present status, due to increased requirements caused by stress metabolism of the clinical condition. All patients with predicted mild to moderate AP need to be screened using validated tools like nutritional risk screening (commonly known as NRS)-2002 or nutrition risk in the critically ill (commonly referred to as NUTRIC) score, and those with predicted severe AP need to be considered at nutritional risk with no screening[12]. This helps to identify patients at high nutrition risk, and these are more likely to benefit from early enteral nutrition (EN) with improved outcomes[13]. There are various definitions of the diagnostic criteria for malnutrition, and Global Leadership Initiative on Malnutrition (commonly known as GLIM) criteria for the diagnosis of

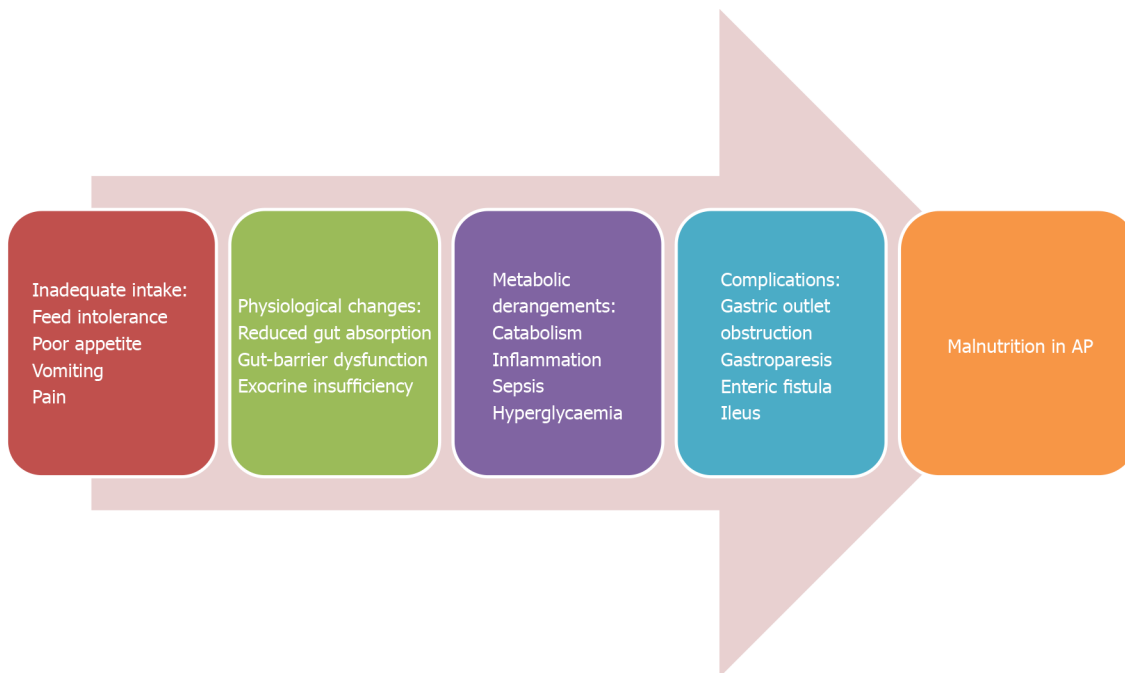


Figure 1 Various probable causes of malnutrition during the course of acute pancreatitis. AP: Acute pancreatitis.

malnutrition were proposed by major nutritional societies for a uniform definition globally[14]. Serum markers like albumin, pre-albumin, or transferrin should be avoided in nutritional assessment in AP, as those serum markers are not truly reflective of malnutrition[15].

Indirect calorimetry is the gold standard for the assessment of calorie requirement, especially in critically ill patients but rarely used given its limited availability. The predicted REE can be calculated using predictive equations like the Harris-Benedict equation or by a simpler weight-based equation of 25-30 kcal/kg/day[13]. In healthy adults, the Harris-Benedict equation can provide an approximate estimate of REE in kcal/day, and the same equation can be used for critically ill patients without any modification. Adjusted body weight is preferred for patients with obesity, edema, or ascites[16].

In those who are not critically ill, like mobile patients without organ failure, an additional 10%-20% of the calculated value from the equation is added to account for physical activity and thermogenesis. In patients who are not critically ill and with malnutrition like low BMI (BMI < 18.5 kg/m²), an additional 300-500 kcal is added to improve their nutritional status[16]. The protein requirements are higher than the healthy controls given higher protein catabolism, especially in severe AP and AP with sepsis. Weight-based protein intake (1.2-2 g/kg/day) can be used to target daily protein requirements[13]. A mixed source of energy from carbohydrates, proteins, and fats is preferable. Micronutrients should be supplemented in patients with suspected or confirmed deficiencies, especially in patients with a history of chronic alcohol consumption or pre-existing malnutrition. In patients on total parenteral nutrition (PN), daily supplementation of multivitamins and trace elements is required as per the recommended daily allowances[11].

A proportion of patients with MSAP or SAP on tube feeding cannot tolerate a complete feed that achieves all calorie requirements owing to various reasons like pain, vomiting, and others[17]. In a randomized controlled trial (RCT) of critically ill patients, permissive underfeeding (40%-60% of estimated caloric requirements) as compared to standard enteral feeding (70%-100% of estimated caloric requirements) was found to have similar clinical outcomes like mortality, infections, and hospital stay with no serious adverse events. An important caveat in that study is that both groups received a similar protein intake of 1.2-1.5 g/kg/day[18]. Hence, in critically ill patients who cannot tolerate entire calorie targets, we can continue with permissive underfeeding. In patients with poor tolerance to tube feeding or those on PN, trophic feeding, *i.e.* small-volume enteral feeding to stimulate the gut, not to meet the calorie requirements, may help to maintain the intestinal physiology, prevent mucosal atrophy, and improve gut barrier dysfunction[19].

Preferred route of nutrition

An oral diet is preferred in patients who can take it orally. In patients, who are not able to feed orally, EN by tube feeding is preferred over PN[12]. In addition to meeting the nutritional targets, EN has additional advantages like beneficial gastrointestinal, immunological, and metabolic responses[20]. In conditions with contraindications to EN (Table 1), patients should be assessed for initiating PN (Figure 2)[21,22].

Table 1 Contraindications of enteral nutrition[22]**Contraindications of EN**

Uncontrolled shock (low dose EN can be initiated once the shock is controlled with fluids and vasopressors with close monitoring for any signs of bowel ischemia).

Uncontrolled hypoxemia, hypercapnia, or acidosis (EN can be initiated in patients with stable hypoxemia, and compensated or permissive hypercapnia and acidosis.)

Active upper gastrointestinal bleeding (EN can be initiated once bleeding is controlled)

Gastric aspirate of > 500 mL/6 h

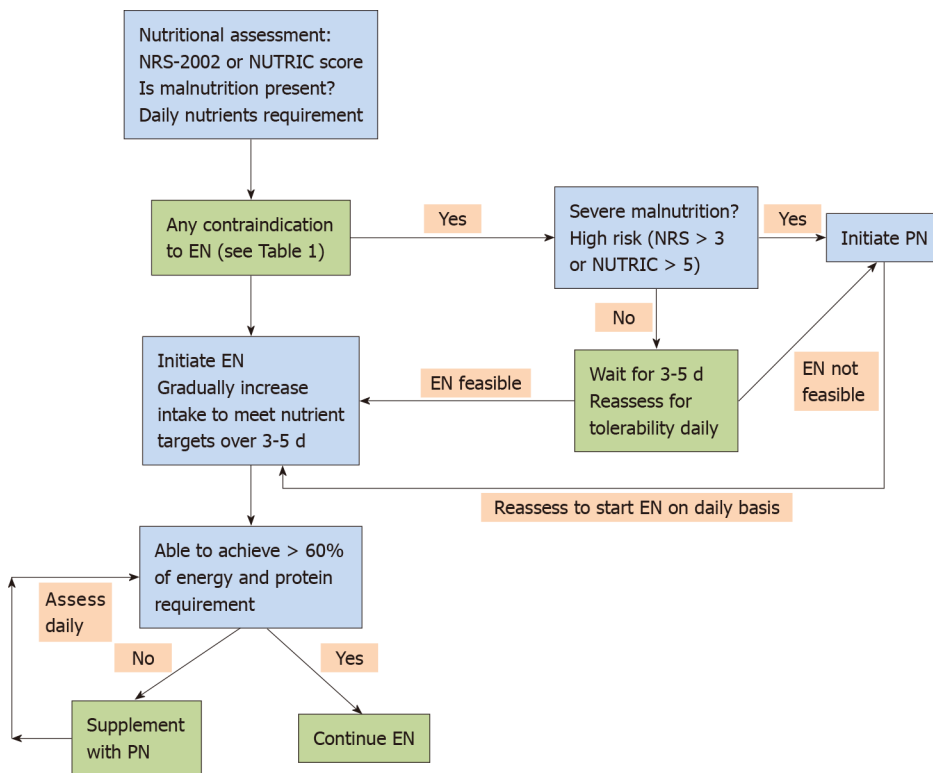
Abdominal compartment syndrome or intra-abdominal pressure of > 20 mm Hg

Bowel obstruction or ileus

Bowel ischemia

High-output fistula without distal feeding access

EN: Enteral nutrition.



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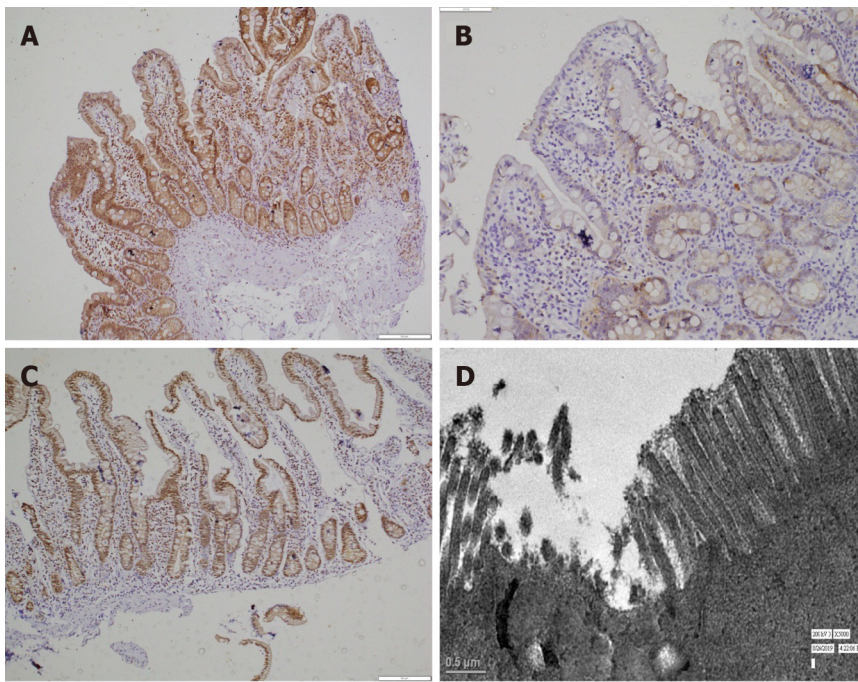
Figure 2 Flowchart of the initiation of nutrition in patients with acute pancreatitis. EN: Enteral nutrition; NRS: Nutritional risk screening; NUTRIC: Nutrition risk in the critically ill; PN: Parenteral nutrition.

Physiological benefits of early EN in AP

The earlier concept of “pancreatic rest” in AP by continuing patient fasting has fallen out of favor, as the benefits and safety of early EN in AP are now well established in RCTs[12,23]. The gut barrier dysfunction in AP is implicated in increased bacterial translocation and subsequent infection of pancreatic necrosis or collections. EN can improve gut barrier dysfunction and preserve the gut mucosal integrity, prevent bacterial translocation, stimulate gut motility, and improve splanchnic circulation[12, 24,25] (Figure 3). EN is the recommended mode of nutritional support in AP. Compared with PN, EN decreases systemic infections, multiorgan failure, hospital stay, mortality, and the need for surgical interventions and the benefit is more pronounced in severe AP (Figure 4)[23,24,26,27].

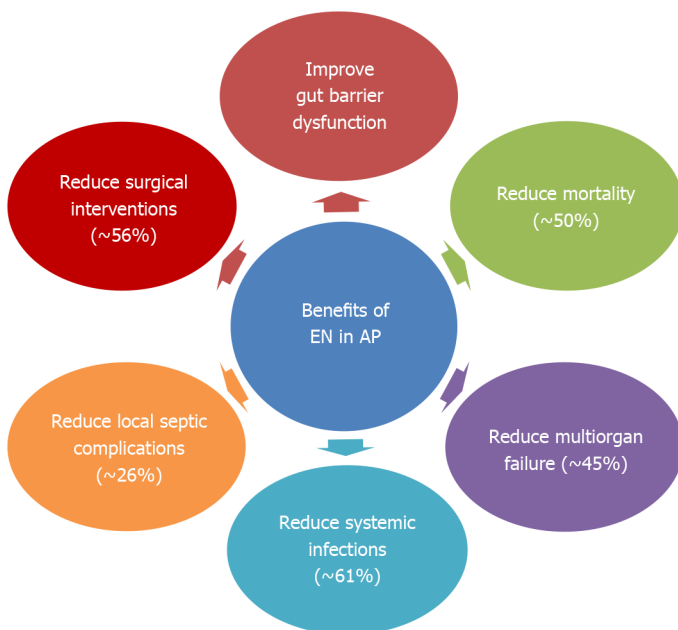
Optimal timing for initiating early EN in AP

EN must be started after adequate fluid resuscitation and at least a relatively stable hemodynamic



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Figure 3 Gut barrier dysfunction and its restoration after enteral nutrition. A: Duodenal biopsy from control shows intact claudin-3 positivity on immunohistochemistry in both villi and crypts throughout the mucosa ($\times 200$); B: Biopsy taken from acute pancreatitis (AP) shows loss of claudin-3 positivity in the duodenal villi and crypts ($\times 200$); C: Biopsy taken from AP post-enteral nutrition shows positivity (significant improvement) in the duodenal villi and crypts ($\times 200$). Ultrastructural changes in duodenal epithelia of patients with AP on electron microscopy show disordered microvilli.



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Figure 4 Evidence-based physiological and clinical benefits of enteral nutrition compared with total parenteral nutrition in acute pancreatitis[24,26]. AP: Acute pancreatitis; EN: Enteral nutrition.

status. Meta-analyses have shown that early EN started within 24-48 h of admission is feasible, tolerated, and associated with lower mortality, organ failure, and infections[28,29]. Two recent RCTs found no difference in mortality, organ failure, or infections between early EN started within 24 h or an oral diet started after 72 h of admission[30,31]. Another prospective cohort study observed that the 3rd d after hospital admission was the best cutoff to reduce infections, with better tolerance and nutritional improvement[32]. A possible explanation is that most of the patients in these two RCTs were not critically ill, and that the benefit of early EN is more pronounced in severe AP compared with other

categories of severity[26]. Hence, patients who are not critically ill can be safely started on an oral diet when symptoms improve or an enteral diet, *i.e.* tube feeding, can be considered after admission if an oral diet is not tolerated. In critically ill patients not tolerating an oral diet, existing data suggest that the EN must be initiated within 48-72 h of admission[5,21]. A RCT is required to justify the benefits of early EN within 24-48 h in this specific group of critically ill patients.

Choice of formulation for EN

EN can be provided by elemental or semi-elemental or polymeric diets. Elemental diets are completely predigested commercial formulations with the simplest form of nutrients. They contain simple carbohydrates and individual amino acids, are low in fat, and contain medium-chain triglycerides. Semi-elemental formulations are commercial feeds with partially predigested enteral formulations (simple carbohydrates, oligopeptides of varying length, and medium-chain triglycerides), whereas polymeric formulations have intact macronutrient components (complex carbohydrates, whole proteins, and long-chain triglycerides). Most earlier studies showing benefits with early EN compared with parental nutrition or no nutrition were done with a semi-elemental diet while some recent studies done with polymeric formulations also showed benefits[33-35]. A pilot RCT compared a semi-elemental diet with a polymeric diet and showed that both were similarly tolerated and absorbed while hospital stay and weight loss were lower with a semi-elemental diet[36]. A meta-analysis compared semi-elemental and polymeric formulations indirectly using PN as a reference and found that feeding tolerance, complications and mortality were similar in both groups[33]. Hence, the guidelines recommend a standard polymeric diet for EN in AP including critically ill patients[12,13].

A polymeric diet can be from two sources: commercial formulations and kitchen-based preparations. Commercial formulas became more desirable, as they are easy to prepare, less prone to microbial contamination, and provide the desired amount of nutrients. However, commercial formulations are more expensive and have less palatability compared with the kitchen-based diet. Kitchen-based diets are easily available, cost-effective in healthcare settings with limited resources, more palatable, and more acceptable to patients. The concerns of a kitchen-based diet are a long time in preparation, increased risk of microbiological contamination, and uncertainty on their nutritional value, especially with nonstandardized recipes[37,38]. In a recently conducted pilot RCT in patients with MSAP and SAP, we observed that both a kitchen-based diet and commercial polymeric formulations were similarly tolerated (personal communication). In summary, EN in any form is beneficial, and the choice should depend on the availability of formulations and cost.

Preferred route of EN

Nasogastric tube feeding is cheaper, easier to insert, and convenient compared to nasojejunal tube feeding. Physiologically, the nasojejunal tube is thought to decrease pancreatic stimulation and secretion, and probably decrease pain and complications, but RCTs have found no differences between nasogastric and nasojejunal feeding in complication rate, refeeding pain, and hospital stay. A recent Cochrane review concluded that there is insufficient evidence to prove superiority or equivalence or inferiority of nasojejunal feeding over nasogastric feeding[39-42]. So, all patients who do not tolerate oral diet should be initiated on EN through the nasogastric or nasojejunal route. Nasojejunal tube feeding should be preferred if a patient has delayed gastric emptying, gastric outlet obstruction due to pancreatitis, or patients with high-risk of aspiration[21].

Continuous vs intermittent bolus feeding

Although intermittent bolus feeding is physiological and has theoretical advantages, existing data showed an increased incidence of diarrhea with intermittent feeds without additional clinical benefit in critically ill patients[43]. Hence, continuous feeding is preferred over intermittent feeding in EN in critically ill patients, although direct evidence is not available in patients with AP.

Role of PN in AP

Although EN is the preferred nutrition over PN in AP, the following are the indications for PN in AP (Figure 2): (1) Complete intolerance to EN; (2) Unable to meet nutritional targets with EN alone; and (3) Contraindication to EN.

Role of other supplements in AP

Immuno-nutrition: (1) Glutamine: Glutamine, a nonessential amino acid, is essential for the survival, proliferation, and function of immune cells. During catabolic/hypercatabolic circumstances, the requirement for glutamine increases rapidly during hypercatabolic states and may lead to impairment of the immune function. A meta-analysis showed the benefit of glutamine supplementation by a reduction in infections, mortality, and hospital stay, and a subgroup analysis showed that those benefits were seen only in patients receiving PN and intravenous glutamine[44]. The risk of bias in the included studies was due to the small sample size and heterogeneity in the severity of the disease. According to European Society for Clinical Nutrition and Metabolism guidelines, intravenous L-glutamine at a dose of 0.2 g/kg/day should be given in patients on total PN owing to contraindications or nonfeasibility of

EN[12]; and (2) Antioxidants: A meta-analysis assessed the effects of antioxidants (including glutamine and other antioxidants) and observed that the antioxidants resulted in a reduction in complications and hospital stay but not mortality[45]. As the results were attributed to glutamine, and a recent Cochrane review did not find any clinical benefit of antioxidants, guidelines do not recommend antioxidant mixtures in AP[12,46].

Probiotics: In experimental models of AP, probiotics were shown to decrease intestinal permeability and hence proposed to reduce infections and mortality[47]. However, in a meta-analysis of clinical trials on patients with AP, there was no benefit of probiotics on infections or mortality, and in one of the RCTs, a multispecies probiotic combination was associated with increased mortality compared to a placebo[48,49]. Currently there is no evidence to support the use of probiotics in AP and the guidelines do not recommend probiotics[12].

Pancreatic enzyme replacement therapy: In a meta-analysis, the prevalence of exocrine insufficiency in AP during admission was 65%, more commonly seen with severe AP and persisted during follow-up in 35% of cases[50]. In an RCT, pancreatic enzyme replacement therapy in AP did not show any statistically significant clinical benefit and only 35% of patients had exocrine insufficiency[51]. Although the data are inadequate, there may be a role of enzyme supplementation in AP with exocrine insufficiency to improve absorption and nutrition[12]. However, recent evidence does not support the generalized use of pancreatic enzyme replacement therapy (PERT) in patients with AP.

SPECIAL SITUATIONS

IAH

Normal intra-abdominal pressure is 5-7 mmHg in critically ill patients and IAH is diagnosed when intra-abdominal pressure (IAP) is increased to ≥ 12 mmHg. As most patients with IAH will have ileus, abdominal distension, or high gastric residue, EN can be initiated *via* the nasojejunal route in patients with IAH[12,52].

If the IAP is < 15 mmHg, early EN can be initiated preferably *via* the nasojejunal route or nasogastric tube. If the IAP > 15 mmHg, it is preferable to initiate the feed *via* the nasojejunal route with caution at a slow rate (20 mL/h) and increase it gradually, as tolerated, monitor IAP, and withhold EN if the pressure increases further. In case of an IAP of > 20 mmHg or presence of abdominal compartment syndrome, EN is to be avoided until the IAP reduces, and PN should be initiated[12]. In postoperative patients with an open abdomen, EN, if possible, is associated with mortality benefit, lesser complications, and higher fascial closure rates. Hence, EN should be initiated and tried at least in small amounts and rest supplemented by PN[12].

Post-endoscopic or minimally invasive necrosectomy

Oral nutrition or if not tolerated, EN is safe and can be initiated within the first 24 h after the procedure provided there are no other contraindications to EN[12].

CONCLUSION

In conclusion, AP is associated with increased morbidity and mortality. Many patients require prolonged hospitalization, multiple interventions, and develop malnutrition. Nutritional supplementation is an important part of the armamentarium to improve the outcomes in patients with AP. Oral or EN is the preferred route and can be started as early as possible. In mild AP, an oral diet can be started whenever a patient is free of pain and feeling hungry. In MSAP and SAP, if oral feeding is not tolerated, then tube feeding can be initiated. However, some patients may require PN. There is no clear benefit of probiotics, immuno-nutrition, and PERT; and they should not be recommended based on current evidence.

FOOTNOTES

Author contributions: Gopi S and Gunjan D contributed to the conceptualization, drafting of the manuscript; Saraya A and Gunjan D critically revised the manuscript.

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