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## Chapter

# Advances in Nutritional Therapy of Acute Pancreatitis

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## Abstract

Acute pancreatitis (AP) is a frequent abdominal acute inflammatory disorder and the leading cause of hospital admissions in gastrointestinal units. Clinical manifestations of AP vary from a mild edematous form to severe fulminant pancreatitis with major devastating complications. To date, experimental therapeutic agents remain scarce for the treatment of this disease. Nutritional therapy with appropriate nutrient supplementation is key to limiting the acute inflammation and preventing and managing complications associated with AP. This chapter focuses on novel therapeutic agents for nutritional intervention including enteral versus parenteral nutrition strategies, and nutritional supplements such as probiotics, glutamine, omega-3 fatty acids, and vitamins in the treatment of AP.

**Keywords:** nutritional support, nutritional supplements, acute pancreatitis, antioxidants, nutritional therapy

## 1. Introduction

Acute pancreatitis (AP) is defined by an inflammation of the pancreas, where several organs and other systems are involved with a potential immune response in a

severe course [1] with a consecutive augmented release of hydrolytic enzymes, cytokines, and toxins, which may result in failure of several systems. Hypermetabolism is observed with a negative nitrogen balance and also augmented metabolism [2–6]. Global incidence of AP ranges from 13 to 45 cases per 100,000 population with a global estimate of 33.74 cases per 100,000 population, causing an uneven burden across the globe. Gallstones (40%–70%) and alcohol (25%–35%) are two of the most common etiologies [7–10]. AP occurs frequently with a mild clinical course. However, when necrotizing pancreatitis is observed, mortality rises up to 15% of cases [11]. When infection of pancreatic necrosis is present, organ failure or both, mortality rises to 30% [12]. Also, severe pancreatitis can cause sustained hyperglycemia, producing diabetes [13, 14]. Interventions (i.e., surgical, endoscopic, and radiological) are frequently used in some patients with AP [15], requiring nutritional support [6].

Clinical therapy in AP differs according to the severity of the disease. Therefore, adequate identification of patients with mild, moderate, or severe AP (SAP), who need nutritional support, is of great importance. Atlanta classification authors defined and stratified the severity of AP [16]: Mild AP is described with absence of organ failure or local complications; moderate-severe AP with transient organ failure and/or local complications; and SAP when persistent organ failure is observed with more than 48 hours, which usually have an ominous prognosis [16]. The first step of the clinical approach of AP consists of close monitoring of vital signs, general support with vigorous fluid resuscitation, pain relief, nutrition, correction of metabolic disorders, identification of complications, and prevention of recurrence [17]. Most of the patients have a mild course of the disease with good prognosis in most cases, but near 15% of cases develop complications (local and systemic). Local complications are mainly pancreatic pseudocyst, acute necrotic collection, acute peripancreatic fluid collection, and walled-off necrosis; systemic complications are defined as multi-organ failure or as an exacerbation of a pre-existing condition [18]. A mean of 15–20% of AP patients will course a severe form of the disease, but mortality is present in only 2–3% of patients because of complications [19, 20].

## **2. Nutritional support in clinical AP**

### **2.1 Overview**

Nutritional therapy and nutritional supplements have great advantages in maintaining the integrity of intestinal barrier, providing major immunomodulatory and antioxidant effects, but more importantly restoring energy balance [21]. The main benefit of nutritional support lies in its immunologic effect, including maintenance of normal intestinal mobility and IgA production, prevention of bacterial overgrowth and infection, diminished bacterial translocation, promoting adequate intestinal permeability [22], decreasing the inflammatory response [22–24], and disease severity, and also promoting a better resolution of the disease process (i.e., duration of systemic inflammation, hospital length of stay) [23, 25]. Clinical evidence suggests that dietary antioxidants and supplements have the potential in protecting against the augmented inflammatory response of the pancreas and oxidative stress during the initial phase of AP. This includes the use of glutamine, antioxidants, probiotics, omega-3 fatty acids, as well as different formulations of enteral and parenteral nutrition [21, 26–28].

## 2.2 Metabolic response to acute pancreatitis

### 2.2.1 Inflammation

Nutritional status during AP is affected by several factors, more importantly in the inflammation cascade. It is fed with increased secretion of tumor necrosis factor (TNF) secondary to hypotension, ischemia, endotoxin, hypoxemia, and reperfusion. Nitric oxide synthesis also increased activating the arachidonic acid pathway and inducing the activation of cyclooxygenase (COX). TNF and interleukin (IL) 1 are synergistic, leading to augmented neutrophil activation and permeability [29]. IL-1 also increases T-cell and macrophage activation, fever, and COX and nitric oxide synthase production [29]. IL-8 is an endogenous chemoattractant, present for a longer period, and is notably proinflammatory. IL-6 is frequently used as a biomarker of severity of the inflammatory response. It has both proinflammatory and anti-inflammatory activities [29]. However, the intestinal epithelial barrier is the first line of defense during AP and carries out the production of immunoglobulin A (IgA). AP is also characterized by causing weakening of this defense system because of increased capillary leakage and decreased activity of tight junctions in preserving the integrity of intestinal barrier secondary to inflammatory mediators. When the intestinal barrier is compromised, intestinal bacteria can penetrate the bloodstream. Invading microorganisms are recognized in minutes by multiple components of innate immunity [29]. Peak inflammatory cytokine production is observed 24–36 hours after initial symptoms of pain, and subsequent systemic manifestations and distant organ failure 2–4 days later [30]. This dysregulation of the immune system leads to a major organic and systemic inflammation and immune paralysis, causing a worsening clinical course during AP [29].

### 2.2.2 Metabolic changes

Inflammatory cytokines (TNF, IL 1, and 6) as well as stress hormones (cortisol, catecholamines, and glucagon) are produced during AP. As a result, a dysregulation of basal metabolism is similar to trauma or sepsis [23, 31, 32]. When overwhelming inflammation is observed, it produces augmented protein catabolism, characterized by a decremented production of gluconeogenesis by exogenous glucose, increased energy expenditure and insulin resistance, and an augmented dependence of fatty acid oxidation for energy substrates. Energy needs are in constant change according to the severity and stage of AP, comorbidities, as well as complications during the clinical course of AP [23, 32]. In the same sentence, impaired nutrient digestion and absorption occurred during AP produce nutritional deficiencies. This can be particularly severe in undernourished patients, as well as alcoholic patients, who are at great risk of AP. Without the correct and opportune nutritional support, patients develop malnutrition in a rapid manner, as well as water retention and decreased muscle function [33].

In patients with AP, resting energy expenditure (REE) measured by indirect calorimetry (IC) is increased by 61% and by 82% in complicated by infection  $\pm$  SD of measured REE was 111%  $\pm$  15% in mild pancreatitis, 126%  $\pm$  10% in SAP, and 120%  $\pm$  11% in pancreatic sepsis, compared with predicted REE by Harris-Benedict equation [3]. The substrates for the production of acute-phase occurred during AP covered by amino acid released from protein breakdown observed in about 80% of patients with severe necrotizing pancreatitis [31]. In the same way, nitrogen loss can

be up to 20–40 g/d and these patients have a tenfold higher death rate than those with normal balance [34]. Regarding carbohydrate metabolism, hyperglycemia is frequently observed in patients with AP, as a result of an imbalance of insulin resistance, increased hepatic glucose production, and impaired insulin secretion caused by beta-cell damage [35]. Hyperglycemia is associated with necrosis and its infectious complications. Clinical therapy should include blood glucose control in a strict manner [36]. Hypertriglyceridemia is also common during AP, and it can be caused by any complication related to AP, or it can produce pancreatitis. Elevated serum triglycerides and impaired lipid clearance are caused by lipid catabolism, resulting from decreased insulin secretion [36]. Severe hypertriglyceridemia is considered when serum triglycerides > 11.3 mmol/L, and in the absence of gallstones and significant alcohol consumption, it can cause AP [9, 36].

Micronutrient deficiencies are commonly observed in AP. On the other hand, chronic alcohol consumption can cause micronutrient deficiencies due to impaired storage and utilization of nutrients, inadequate intake, and decreased absorption. These deficiencies include vitamin B1, B2, B3, B12, C, A, folic acid, and zinc [37, 38]. Moreover, deficiencies in patients with severe complicated pancreatitis often require hospital admission.

### **3. Nutritional support in AP**

#### **3.1 Nutritional requirements**

Energy requirements should be estimated with IC if possible or should be given 25–35 kcal/kg/d as energy goal, the estimated protein requirements range over 1.2–1.5 g/kg/d. This may improve nitrogen balance and is related to a decrease in 28-d mortality in critically ill patients [39]. A mixed source of energy from carbohydrates, fat, and protein should be provided [40, 41]. In severe AP, carbohydrates/day should be 3–6 g/kg and up to 2 g/kg of lipid/day.

#### **3.2 Enteral nutrition vs. parenteral nutrition**

Enteral nutrition (EN) is feasible, safe, and beneficial in all types of pancreatitis [42]. It is currently acknowledged that EN properly applied may be essential to enhance AP-associated malnutrition and its general effects; on the other hand, bowel rest has been associated with atrophy of the intestinal mucosa and an increase in infectious complications [43]. About 60% of patients with AP have experienced gut barrier dysfunction [8, 44]. It is important to mention that EN has immunomodulatory effects that preserve the integrity of the intestinal mucosa, in addition to stimulating intestinal motility and reducing the excessive growth of bacteria, [8, 45] and diminishing endotoxin and bacterial translocation [46–49].

The 2016 American Society for Parenteral and Enteral Nutrition/society of critical care medicine guidelines recommend EN over parenteral nutrition (PN) and show a decrease in infectious morbidity (42.6% vs. 16.1%,  $P < .0001$ ) and mortality (16.4% vs. 6.1%,  $P = .02$ ); [50] EN also decreases levels of TNF, IL-1, IL-6, and IL-8 [47]. A meta-analysis of eight randomized clinical trials found that EN considerably reduced mortality, organ failure, and surgical intervention compared with PN [51]. EN vs. PN mortality rates showed an increase in survival with EN (4% vs. 15.9%). In patients with SAP, EN is preferred to PN, whether administered orally or by tube, it preserves

the intestinal barrier function to prevent bacterial translocation. The New England Journal of Medicine demonstrated, in a multicenter randomized study, that both early tube feeding and oral diet after 72 hours given to patients with AP at high risk of complications are equivalent in reducing infection rates or death [46]. Multiple meta-analyses have been found that support the use of EN in PN, such as a Cochrane study in which eight randomized controlled studies were carried out in patients with PA comparing EN with PN, it was found that EN reduced mortality, systemic infections, and multi-organ failure [52]. Another study carried out on 381 patients confirmed the benefit of EN over PN in patients with SAP, and the results showed lower mortality, fewer infectious complications, a lower rate of organ failure, and surgical intervention [49]. Several trials have suggested that the optimal EN route is the nasogastric route, putting it as an alternative to the nasoduodenal or nasojejunal routes [53–55]. As demonstrated in multiple trials involving a sample of 157 SAP patients, the results were that nasogastric feeding is safe and well tolerated compared with nasojejunal feeding [41, 56]. Nevertheless, as shown by multiple randomized trials that have associated total PN (TPN) with risks of infection and other complications [57]. PN should still be minimized unless the enteral route is not available, not tolerated, or not meeting caloric requirements [58, 59]. PN causes increased inflammatory cytokines, leading to a proinflammatory state in the gastrointestinal tract [58, 60]. Overall, PN is more expensive than EN or oral nutrition and associated with more complications [61].

### **3.3 Nutrition support in mild and moderate AP**

In the care of patients with mild-to-moderate AP, food can be given orally once nausea, vomiting, and abdominal pain have subsided and appetite has returned [62, 63]. The conventional way of feeding patients with AP is increasing, that is, once the abdominal pain has disappeared and the pancreatic enzymes have decreased, the first 24 hours are given clear liquids to later consume a low-fat soft diet for 24 hours to check tolerance, and then start a solid low-fat diet [57]. However, a randomized study determined that providing a soft diet with clear liquids to patients with mild AP did not show significant differences in the two participating groups. In addition, it was determined that starting treatment with a solid diet is associated with a shorter hospital stay (mean of 5 vs. 8 days of starting with clear liquids,  $p < 0.001$ ). On the other hand, a current open-label randomized trial [64] demonstrated no difference in tolerance to refeeding when comparing both the stepped and immediate full-calorie diets. Likewise, it was mentioned that fasting caused by constant abdominal pain in patients with moderate AP should not exceed five days, and if this is the case, a catheter should be placed [62, 63, 65].

Theory mentions that nasojejunal feeding is preferred over nasogastric feeding because it is assumed to be more tolerable for patients [66]. In nasojejunal feeding, placing the tube in the jejunum beyond the duodenum avoids stimulation of the already inflamed pancreas, causing less pain. However, there are studies that compared nasojejunal and nasogastric feeding and did not find significant differences [67, 68]. The current indication is that continuous feeding over bolus feeding is recommended for patients requiring tube feeding [3, 66]. EN demonstrated better feeding tolerance and decreased interruptions due to high residuals and vomiting in the continuous infusion when compared with the bolus group [69, 70].

The method of administration of the nasogastric diet is through interrupted boluses (200–300 mL 5–6 times a day) under control of gastric residual volume (GRV) or continuous infusion (30–50 mL/h), unlike NE via NJT that is administered

in continuous infusions. Gradually increasing the flow rate: from 20 to 30 ml/h to 100 to 125 ml/h. To avoid complications (regurgitation, aspiration, or pneumonia), EN *via* the nasogastric route should be interrupted at GRV > 200 mL. The EN must cover a minimum of 60% of the energy requirement. When intolerance to EN occurs, resulting in effects such as diarrhea, the rate of feed delivery should be decreased. When this is not enough, a switch to PN should be considered. The continuous evaluation of the nutritional requirement and the laboratory investigations must be carried out weekly with the objective of optimally carrying out the nutritional support and if required, the modification of the type or formula if indicated. In addition, it is essential to carry out adequate care of the tube (in EN) or catheter (in PN) to avoid infections and other complications related to the catheter and the tube [1, 71]. Due to its nature, parenteral nutrition is reserved only for patients who present intolerance or are unable to receive enteral nutrition [52, 72].

### **3.4 Nutrition support in severe AP**

At the international level [62, 63, 65, 73, 74], it is mentioned that in patients with SAP, nutritional support should be provided through enteral feeding (grade of recommendation: A). Even if complications such as fistulas, ascites, and pseudocysts occur, EN is preferred over PN (grade of recommendation: C) [63, 65]. After surgery for pancreatitis, EN is recommended through intraoperative jejunostomy (grade of recommendation: C) [65]. Since enteral tube feeding can provide safe nutritional support in AP even in cases where gastric outlet is obstructed [75] in this case, the tip of the tube should be placed distal to the obstruction (grade of recommendation: C) [65]. However, early EN (enteral tube feeding within 24 hours of presentation) has not been shown to improve outcomes in SAP patients, compared with oral feeding starting at 72 hours. [76]

The only real contraindication to EN is prolonged paralytic ileus. However, according to the European Society for Parenteral and Enteral Nutrition guidelines, it is advisable to combine PN with a small content of an elemental or immunopotentiating diet (10–30 ml/h) continuously infused into the jejunum. Regarding delivery times, continuous infusion is preferred over bolus administration (grade B recommendation) [65, 66].

### **3.5 Time of enteral support**

EN should be initiated when the patient has an established condition for gut permeability and should start after adequate resuscitation and stable hemodynamic status. Many studies have shown the advantages of early enteral feeding in SAP and how convenient it is for the prognosis [77]. A meta-analysis conducted by Petrov [78] showed that the timely administration of EN during the first 48 hours of admission improved the reduction of multiorgan failure, complications of infectious origin, and mortality rate in comparison with PN. After this period, there were no significant differences observed in comparison with PN. Starting EN before 48 hours provide several advantages in more successive studies and another meta-analysis. Many studies have shown this association, and a more recent meta-analysis, improving the time, demonstrated that starting EN within 24 hours after hospital admission was associated with lower complications for predicted severe or SAP, but not for mild to moderate pancreatitis. [76, 79–82]. A multicenter randomized controlled trial compared early EN within 24 h versus an on-demand oral diet of 72 h, with tube feeding

provided on day 4 if the oral diet was not tolerated. This study showed that patients with moderate pancreatitis, who do not require intensive care, can use an oral diet on demand and only through a tube from day 4 if the oral diet is not successful [76].

### **3.6 Gastric vs. small bowel feeding**

In response to decreased efficiency in pancreatic secretion during PA, nasogastric feeding has been considered to be similar to nasojejunal feeding when the following parameters are assessed: pain, aspiration, compliance with energy balance, and mortality; this even though it was previously believed that feeding through the small intestine could decrease the stimulation of the pancreas and digestion [55].

Feeding in the stomach is the most used because it is easier and cheaper, and it optimizes the time for the patient who requires EN, since through the intestine, not only a special technique is required, but also more time for the correct one tube placement. However, this technique is mainly used for patients who do not tolerate gastric feedings, such as obstructions, edema, severe gastroparesis, or pseudocysts. Likewise, the use of jejunal probes is indicated for post-operative patients in different conditions where it is required [65, 83].

### **3.7 Polymeric vs. semielemental formula**

Formulations used in EN and PN are compounds based on the following nutritional requirements: protein 1.2–1.5 g/kg/d, carbohydrates 3–6 g/kg/d (glucose concentration, aim: <10 mmol/L), lipids up to 2 g/kg/day, (triglyceride concentration, aim: <12 mmol/L), Sodium 1–2 mmol/kg/d, potassium 1–2 mmol/kg/d, chlorine 2–4 mmol/kg/d, phosphorus 0.1–0.5 mmol/kg/d, magnesium 0.1–0.2 mmol/kg/d, and calcium 0.1 mmol/kg/d. Naturally, this formula could be adapted for the clinical condition of the patient, depending on the above-mentioned serum concentrations [79]. Enteral formulas are classified into elemental (monomeric), semi-elemental (oligomeric), and standard (polymeric) formulas and differ in protein and fat concentration. Elemental formulas contain amino acids, simple sugars, and very low fats; semi-elemental formulas contain peptides of various chain lengths, a simple sugar, glucose polymers or starch, and medium-chain triglycerides, and polymeric formulas contain intact proteins, complex carbohydrates, and long-chain triglycerides [84].

Nevertheless, polymeric formulas are safe and comply with the same nutrimental function as elemental and semi-elemental formulas if administered *via* nasojejunal tube in AP patients [85–87]. A meta-analysis by Petrov et al including 1070 patients found no significant difference in feeding tolerance (RR = 0.62; 95%CI: 0.10–3.97), infection (RR = 0.48; 95%CI: 0.06–3.76), and death (RR = 0.63; 95%CI: 0.04–9.86) [85–89]. It should be remembered that semi-elemental or elemental formulas are at least sevenfold as expensive as polymeric feeds [90, 77, 91].

### **3.8 Parenteral nutrition**

EN is the first way of nutrition, however, if it is not possible to use it or there is intolerance to it, parental nutrition (PN) can be used, which is used after the fifth or seventh day of admission to increasing, in this way, the correct clinical development of the patient and decrease the hospitalization days [40, 59, 89, 92, 93] EN intolerance is generally accompanied by diarrhea and in such cases, PN nutrition is considered. It is recommended that PN must have a gradual increment starting from day one up to



day three in the following way 50%, 75%, and 100%, and must include carbohydrates, proteins, and lipids. The control of the hemodynamic status of the patients has to be overseen even before starting the nutrition in order to avoid the re-feeding syndrome in such a way that the formula can be readapted if required [1].

An important consideration is that glucose should not be more than the maximal level of glucose oxidation (4–7 mg/kg/min or 5–6 g/kg/d), and a target blood glucose range of 7.7–10 mmol/L is recommended [94, 95]. Intravenous lipid emulsions can be safely started, and the recommended dose is 0.8–1.5 g/kg/d [40, 41]. Intravenous lipid emulsions dose may need to be reduced or discontinued if serum triglyceride concentrations are greater than 4.5 mmol/L [96, 97]. In PN-exclusive nutrition, a daily dose of multivitamins and trace elements should be administered. Micronutrients should be supplemented in patients with confirmed or suspected deficiencies of estimated nutritional requirements gradually from day 1 to day 3. The hemodynamic status must be watched to avoid water/electrolyte and acid-base imbalances [1, 41].

#### **4. Nutritional supplements and antioxidants in AP**

Various supplements such as probiotics, glutamine, omega-3 fatty acids, and different formulations of enteral and parenteral nutrition have been studied with the aim of reducing inflammation and improving outcomes in AP [28]; however, their clinical benefit is still unclear.

##### **4.1 Vitamins**

AP carries great oxidative stress and an acute systemic inflammatory response, [98] which is the reason why it is suggested that patients with AP have lower serum levels of anti-oxidant vitamins and may benefit from supplementation [99]. Vitamin A, vitamin C, vitamin E, selenium, and N-acetyl cysteine are important immunonutrients and have been inversely associated with AP [98]. It has been described that they may reduce inflammation and improve outcomes in SAP. Nevertheless, only a few small studies with varied doses and duration of vitamins have studied this effect with non-conclusive results: Musil et al. [21] found that plasma concentrations of vitamin A and vitamin C were significantly lower in AP patients compared with controls ( $P < 0.05$ ) [100]. Recently, another study reported that vitamin D has been inversely associated with gallstone-related AP [98].

It has also been assessed the vitamin supplementation in combination with other antioxidants or in vitamin-only therapy and yielded mixed outcomes: In a multicenter randomized, double-blind, placebo clinical trial by Siriwardena et al. the use of intravenous combination of antioxidant therapy containing vitamin C, was not clinically justified to continue in AP [101]. Subsequently, another group comparing vitamin C (N-acetylcysteine) in combination with standard medical treatment in early AP suggested that antioxidant supplementation reduced the length of hospital stay and complications in these patients [102].

Another study with high vitamin C doses, involving 84 AP patients and 40 healthy subjects in China, demonstrated therapeutic efficacy on the disease, and they proposed that promoting anti-oxidizing capability in these patients, may block lipid peroxidation and improve cellular immune function [103]. This hypothesis cannot yet be proven, as another group studied multiple vitamin-based antioxidant therapy

(vitamin A, vitamin C, and vitamin E) in a randomized study involving 39 patients, in which there was no proven benefit [104].

## 4.2 Curcumin

Curcumin (CUR) has been described as an important antioxidant, anti-apoptotic, anti-cancer, and anti-inflammatory supplement, [105–109], acting as a free radical scavenger [42, 110], and increases the expression of anti-oxidant enzymes like superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), hemo oxygenase-1 (HO-1), and others [111]. Also, CUR exerts an anti-inflammatory effect through its ability to diminish the activation of nuclear factor  $\kappa$  B (NF $\kappa$ B, p65/p50), [112], which reduces the expression of inflammatory cytokines like IL-1 $\beta$ , IL-6, TNF $\alpha$ , cyclo-oxygenase 2, lipoxygenase 5, and inducible nitric oxide synthase [113].

In experimental models of AP, CUR decreased the level of serum amylase, the number of myeloperoxidase, NF $\kappa$ B, and apoptotic cells. Furthermore, pancreatic inflammation, edema, and necrosis of fat cells also decreased after inducing pancreatitis with L-arginine. Histopathological features in experimental pancreatitis were normalized by effect of CUR [114]. Similar findings were reported by Yu [115] in an AP induced with caerulein. Finally, a clinical study in tropical pancreatitis suggested the beneficial effect of CUR by decreasing the level of lipid peroxidation and reinforcing the activation of the endogenous antioxidant enzymes [116]. Thus, the potential benefits of CUR alone or combined with other antioxidants contained in micro or nano-formulations [116] continue to be evaluated and applied in AP.

## 4.3 Gut microbiome impact in AP

The human gastrointestinal tract has a rich microbiota, consisting of a vast number of microorganisms and >5000 genes. About 80–90% of the gut microbiome are Firmicutes and Bacteroidetes, being the most prevalent bacteria [55]. The gut microbiome influences the immune system through its effect on systemic metabolism.

In acute pancreatitis, the microbiome is altered by the increased intestinal permeability [117], resulting in important dysbiosis [118]. Changes in the intestinal microbiota during AP depend on the course of the disease, with a decrease in the diversity of microorganisms in acute necrotic pancreatitis [119]. Also, the need for aggressive medical therapy with acid suppression and reduced oral feeding creates a microbial imbalance [117, 118].

Increased intestinal permeability has been demonstrated in a significant percentage of patients with AP [120], with circulating bacterial DNA representative of gut bacteria in 68.8% of patients with AP. Zhang and colleagues showed that patients with AP had more Proteobacteria and Bacteroidetes and fewer Actinobacteria and Firmicutes in their feces, compared with normal controls [121]. The clinical significance of gut dysbiosis is poorly understood, but these patients have been found to have worse outcomes .

Mechanisms of microbiome alteration include 1. poor intestinal mobility: resulting in the growth of Gram negative and anaerobic microflora, in addition to the accumulation of substances that will inhibit the growth of probiotics, [122]. 2. Gut mucosal ischemia: Inflammation in the environment generated by AP can cause ischemia injury due to the release of proinflammatory cytokines, which together, with the increased migration of cells of the immune system, alters the microbiota destroying the bacterial glycocalyx [123]. 3. Oxidative stress: The subsequent inflammation in the

tissue leads to the release of reactive oxygen species, and the oxidative state present in the tissue allows the presence of oxygen-tolerant bacteria [124].

Different strategies are recommended to recover the intestinal microbiome in the treatment of AP, mainly with the use of probiotics. These are live microorganisms that confer a health benefit through the inhibition of pathogenic microorganisms, the induction of growth of the mucous layer, and inhibiting apoptosis of epithelial cells. The most used probiotics are *Lactobacillus*, *Bifidobacterium*, *Streptococcus*, and *Lactococcus lactis* among others [125, 126]. Other strategies as antibiotics are not widely used in patients with AP since their prophylactic use does not reduce mortality, and in spite of this, Ahuja et al. [127] reported that the pancreatic acini were able to regulate the intestinal microbiota through the secretion of antimicrobials and different pro-inflammatory cytokines, which still must be proven.

#### **4.4 Glutamine**

For unfed sterocytes, glutamine represents an important substrate [30]. Long-term parenteral nutrition can cause glutamine deficiency, which in turn leads to intestinal dysfunction [47]. Supplementing PN with glutamine is recommended for patients with critical illnesses associated with a catabolic response, as it helps preserve the cell mass of the stomach-associated lymphatic tissue and antibacterial defenses [30, 51].

It has been shown that glutamine can be associated with a decrease in infectious complications, as a result of a meta-analysis of 12 RCTs (RR = 0.58; 95% CI: 0.39–0.87) and mortality (RR = 0.30, 95% CI: 0.15–0.60). In this study, statistically significant benefits were shown among patients who received total PN but not EN [128]. The above findings were confirmed in another study that determined the advantages of intravenous glutamine [129]. Among the most recent studies was found that enteral glutamine showed an improvement in the organ failure score, it did not obtain significant benefits in infected necrosis and mortality [130]. One study showed that giving PN with glutamine supplementation reduced overall complications by 25% compared to the PN-only group by 47% [131]. Overall, giving intravenous glutamine appears to be beneficial in patients with total PN, however, the beneficial effects of enteral glutamine should be investigated in the future. Glutamine is recommended as a supplement in the following doses 0.3 to 0.5 g/kg/d [130, 132, 133].

#### **4.5 Omega-3 fatty acids**

Remarkable immunomodulatory benefits are described from dietary polyunsaturated fatty acids, especially lipoxins, resolvins, and protectins, [134, 135]

A randomized study found that enteral formula enriched with  $\omega$ -3 FA in the treatment of AP reduced the total time of jejunal feeding and hospital length [136]. Also, more studies evaluated the effects of  $\omega$ -3 FA supplemented in the PN during SAP. Wang et al. performed a randomized, double-blind trial of 40 SAP patients receiving PN with the same amount of nutrients but different lipid contents, including soybean oil-/fish oil-based fat solutions. It was observed that patients with  $\omega$ -3 FAs-supplemented PN had higher levels of eicosapentaenoic acid and decreased pro-inflammatory cytokines, together with improved respiratory function and a minor renal replacement therapy time, suggesting an attenuated systemic response to pancreatic and organ injury [137]. Another study by the same authors who included 56 patients receiving an isocaloric and isonitrogenous PN with fats of all  $\omega$ -6 FAs or

4:1  $\omega$ -6: $\omega$ -3 FAs demonstrated that  $\omega$ -3 FAs-supplemented PN augmented the expression of IL-10, and human leukocyte antigen-DR in SAP patients [137]. In the same way, during the first hours of SAP, supplementation with  $\omega$ -3 fish oil emulsion in PN decreased SIRS, and improved the balance of pro-/anti-inflammatory cytokines and thus improved AP-associated severe [138]. Moreover, a meta-analysis of eight small RCTs showed that omega-3 fatty acids supplementation was beneficial in the total mortality, infectious complications, and length of hospital stay, especially when received parenterally. Nonetheless, large and well-designed RCTs are required to elucidate the efficacy of omega-3 FA supplementation during SAP.

## 5. Conclusions

Nutritional therapy since the onset of AP constitutes a critical component in the management of patients that should be performed and assessed in the first hours of hospital admission. If the patient has mild disease and the on-demand oral diet of low-fat solid foods is tolerated, and not limited to clear liquids or if the enteral nutrition support is well tolerated during SAP, a daily reassessment of tolerance should be performed. The correct time to start enteral support should be performed in the first 24–48 hours after onset of AP. In contrast, early EN may not be better than an on-demand oral diet at 72 h. If it is not tolerated, then the enteral route through a nasogastric or nasojejunal feeding tube should be attempted. The use of a standard polymeric formula is recommended in gastric and jejunal feeding; nonetheless, daily assessment of tolerance should be carried out. PN is considered the last option because of the considerable risks of infection, and other complications. Lastly, various nutritional supplements used during AP have mixed clinical outcomes that should be more elucidated to bring certainty of their use to achieve better clinical outcomes.

## Conflict of interest

The authors declare no conflict of interest.

## Acronyms and abbreviations

AP	acute pancreatitis
SAP	severe acute pancreatitis
TNF	tumor necrosis factor
COX	cyclooxygenase
IL	interleukin
REE	resting energy expenditure
IC	indirect calorimetry
EN	enteral nutrition
PN	parenteral nutrition
TPN	total parenteral nutrition
GRV	gastric residual volume

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