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REVIEW

# Nutrition Support in Acute Pancreatitis

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**Summary**

In the majority (80%) of patients with acute pancreatitis, the disease is self limiting and, after a few days of withholding feeding and intravenous administration of fluids, patients can again be normally fed orally. In a small percentage of patients, the disease progresses to severe necrotic pancreatitis, with an intense systemic inflammatory response and often with multiple organ dysfunction syndrome. As mortality is high in patients with severe disease and as mortality and morbidity rates are directly related to the failure of establishing a positive nitrogen balance, it is assumed that feeding will improve survival in patients with severe disease. The aim of nutritional support is to cover the elevated metabolic demands as much as possible, without stimulating pancreatic secretion and maximizing self-digestion. The administration of either total parenteral nutrition or jejunal nutrition does not stimulate pancreatic secretion.

Recently, a series of controlled clinical studies has been conducted in order to evaluate the effectiveness of enteral nutrition with jejunal administration of the nutritional solution. The results have shown that enteral nutrition, as compared to total parenteral nutrition, was cheaper, safer and more effective as regards the suppression of the immunoinflammatory response, the decrease of septic complications, the need for surgery for the management of the complications of acute pancreatitis and the reduction of the total hospitalization period. It did not seem to affect mortality or the rate of non-septic complications. In conclusion, enteral nutrition should be the preferred route of nutritional support in patients with acute pancreatitis.

## Introduction

The management of acute pancreatitis differs according to its severity. Approximately 75% of patients with acute pancreatitis have mild disease with a mortality rate below 1%. Mortality increases up to 20% if the disease progresses to its severe necrotizing form and, in the most severe cases, mortality can increase to 30-40%. Severe acute pancreatitis is usually accompanied by systemic inflammatory response syndrome (SIRS) which results in hypermetabolism with prominent protein catabolism. Acute malnutrition, commonly observed in patients with acute pancreatitis, is associated with immunological disturbances, septic complications and delayed healing of surgical wounds, and may lead to multiorgan dysfunction or failure syndrome (MODS or MOFS) and increased morbidity and mortality [1].

## Pathophysiological Disorders in Acute Pancreatitis

Acute pancreatitis is associated with the early activation of proteolytic enzymes (trypsinogen, chymotrypsinogen, phospho-lipase A and proelastase) inside the pancreatic

cells, resulting in self-digestion of the cellular content due to proteolysis, and extensive destruction of the pancreatic tissue. The morphological changes include edema, parenchymatous hemorrhage in the pancreas and the intestine, necrosis of the peripancreatic fat and parenchymatous necrosis of the pancreatic tissue.

Although acute pancreatitis is, at least in the beginning, a local non-specific inflammatory reaction, extensive tissue damage due to the production of hydrolytic enzymes, toxins and cytokines may cause systemic activation of inflammation, and the appearance of SIRS with hypermetabolism and negative nitrogen balance [2, 3]. The metabolic status is similar to that observed in sepsis and is characterized by a hyperdynamic condition, hypermetabolism and hypercatabolism.

The basal metabolic rate increases due to inflammatory stress and pain, leading to enhanced total energy expenditure. In severe necrotizing acute pancreatitis, 80% of all patients are catabolic, with high energy expenditure and enhanced protein catabolism. The negative nitrogen balance can be as much as 40 g/day with a deleterious effect on both nutritional status and disease progression [1, 4, 5, 6].

In a trial conducted by Sitzmann *et al*., patients with a negative nitrogen balance had a tenfold higher mortality rate than those with a normal balance [7]. An increase in resting energy expenditure (REE), measured using indirect calorimetry, was found in patients with acute pancreatitis. Dickerson *et al*. [6] reported that, in patients with acute pancreatitis, the REE measured differed by 77-139% from the one estimated using the Harris-Benedict equation. They found that, in 10% of the patients with acute pancreatitis, the REE measured was 90% of the estimated one, in 38%, it was 90-100% of the estimated and in 52%, it was greater than the estimated by 11%. The authors concluded that the Harris-Benedict equation usually under-estimates energy consumption in patients with acute pancreatitis. The development of pancreatic tissue necrosis increases energy consumption to 120% of the estimated consumption estimated by various equations [8].

Clinical studies have shown that, in patients with acute pancreatitis, protein catabolism and proteinolysis of skeletal muscles increase by 80% as compared to the control population. The plasma levels of aromatic amino acids increase and the levels of lateral chain amino acids decrease. As a result of elevated urea production, nitrogen loss in urine increases up to 20-40 g/day [8, 9].

Increased gluconeogenesis, with the parallel decrease in glucose oxidation and clearance, leads to glucose intolerance in 40-90% of patients with acute pancreatitis. As a result, about 81% of patients require extrinsic insulin administration. Di Carlo *et al*. [10] studied endocrine changes as well as amino acid status in five patients with severe lethal progressive acute pancreatitis. They found relatively low levels of lateral chain amino acids (isoleucine, leucine, and valine), but increased levels of aromatic amino acids (phenylalanine, tyrosine). Hyperglucagonemia and hyperinsulinemia, increased lipolysis and lipid oxidation and hyperlipidemia due to decreased lipid blood clearance were also reported in 12-15% of patients [10, 11].

Hypocalcemia, a frequent finding in patients with acute pancreatitis (40-60%), depends on the severity of the disease. The lowest calcium levels were observed in the first three days after the onset of the disease. The etiology of hypocalcaemia is multifactorial and is attributed to the saponification of the calcium with free fatty acids, hypo-albuminemia and hypomagnesemia as well as to the increased calcitonin release and decreased parathormone secretion. Finally, the deficiency of micronutrients such as thiamine, folic acid and zinc contributes to metabolic disturbances in patients with acute pancreatitis, especially in alcoholic patients [12, 13].

## The Role of 'Pancreatic Rest'

In the treatment of patients with acute pancreatitis, it is of great importance to obtain 'pancreatic rest' in order to reduce the exocrine secretion of the pancreas.

'Pancreatic rest' is an important factor in the remission of inflammatory activity of the gland. In the past few years, it has become clear what exactly 'pancreatic rest' means. A decrease in the secretion of proteinic enzymes seems to be the most important factor in the reduction of the inflammatory activity in the pancreas. It has been proven that a decrease only in the secretion of proteinic enzymes, without a simultaneous decrease of the total volume of the pancreatic fluid and its concentration in bicarbonates, is enough to ensure 'pancreatic rest' and to contribute to the remission of inflammatory activity of the pancreas [14]. In addition, the reduction of proteinic enzyme secretion is not necessarily required to reach levels below the basic excretion level for the recovery of the pancreas. Finally, the early infusion of oligopeptide solutions for enteral nutrition, distally to the first jejunal helix, has been shown to ensure adequate 'pancreatic rest'.

The administration of nutrition in the more distal portion of the intestinal tract causes less stimulation of the pancreatic secretion. The administration of nutrition distally to the first helix of the jejunum stimulates the secretion of multiple inhibitory factors. These factors include the inhibitory polypeptide, the polypeptide YY, somatostatin, various intra-luminal proteases, and even biliary salt. All these substances inhibit or drastically reduce pancreatic secretion [15]. It has been found that the special features and the complexity of the digestion procedure of various nutritive substances significantly affect pancreatic secretion [15, 16].

From the three main nutritional agents (proteins, lipids, carbohydrates), lipids more intensively stimulate pancreatic secretion while carbohydrates have the weakest stimulatory effect. Long chain fatty acids are also more stimulating than medium chain fatty acids. Whole proteins stimulate pancreatic secretion more than simple amino acids while oligopeptides (dipeptides and tripeptides) seem to have even less stimulating action. Finally, solutions of high osmolarity are more stimulating than solutions of low osmolarity [16, 17].

Although 'pancreatic rest' is widely practiced, it remains theoretical and inadequately tested. There are no randomized studies which demonstrate that 'pancreatic rest' hastens recovery in acute pancreatitis.

## The Role of Intestinal Mucosal Barrier Integrity

In the treatment of patients with severe acute pancreatitis, achieving 'pancreatic rest' seems to be as important as the assurance of functional and anatomical integrity of the intestinal mucosal barrier. The gastrointestinal tract is the biggest immunological organ of the human body. It constitutes 65% of the total immunological tissue and 80% of the immunoglobulin-producing tissue [18, 19]. Consequently, normal gastrointestinal tract function controls the systemic immunological response to a significant degree and contributes to the progress of severely ill patients in a positive way [20].

In the fed state, strong intercellular conjunctions ensure the total functional integrity of the gastrointestinal tract. Normal motility of the bowel maintains the microbial flora, and the secretion of biliary salts and immunoglobulins against the intraluminal antigens protects from the adhesion of bacteria to the intestinal wall and prevents bacterial translocation [21, 22, 23, 24].

In cases of even short functional inactivity of the bowel, the integrity of the intestinal tract is disturbed. The physiological motility decreases, the intestinal villus atrophy, the intestinal wall blood flow is reduced, especially at the mucosa, and the strong intercellular and endothelial conjunctions are destroyed. The consequences of these disturbances are the overgrowth of intra-luminal bacteria [19] and the migration of bacteria to the mesenteric lymph nodes and the systemic circulation [24]. Furthermore, the local secretion of immunoglobulins and the production of biliary salts are reduced due to nutrient deficiency. the adhesion of bacteria to the intestinal wall increases, and translocation of bacteria and bacterial products (endotoxins) is enhanced [21]. The final results are the loss of intraluminal

antigen activity, and lymphoid tissue decomposition, even in distal organs. The explanation of these pathophysiological mechanisms is based mainly on animal studies. Although animal studies have suggested mechanisms by which lack of enteral stimulation can have a negative impact, and review articles have made a case for this gut-connection in TPN complications, there is little experimental data in humans with acute pancreatitis to support the idea that the lack of gut stimulation is the primary source of complications in humans with acute pancreatitis receiving TPN.

Another serious consequence of the reduced intestinal wall blood flow is the appearance of ischemia-reperfusion injury [25]. The results of this event are the production of free oxygen radicals in the intestinal lumen and the activation of local macrophages. These macrophages migrate to the systemic circulation, and trigger free oxygen radical production [26] and the activation of the arachidonic acid cascade in different organs, such as the liver, the kidney and the lungs [26, 27]. In conclusion, the activated macrophages link the disruption of the intestinal mucosal barrier, caused by the functional inactivity of the intestine, with the systemic manifestations of the acute pancreatitis which negatively affect its course. In patients supported by total parenteral nutrition (TPN), the functional inactivity of the bowel results in generalized, non-specific SIRS and MOFS [25, 26, 27, 28]. Review articles have made a case for ischemia-reperfusion injury in severe shock, but there is little data to support that this routinely occurs in acute pancreatitis while receiving TPN.

## The Role of Artificial Nutrition in Acute Pancreatitis

The effect of the disease on the nutritional status of the patient depends on its severity. The majority of the patients (80%) have mild acute pancreatitis (less than 3 Ranson criteria) and are managed by ‘functional rest’ of the intestine for a short period, intravenous hydration and analgesia [29]. On the contrary, patients with severe acute pancreatitis (greater than 3 Ranson criteria) need long hospitalization and have increased complications and mortality rates. In these patients, nutritional support is expected to positively affect the course of the disease and improves the outcome [1].

Until recently, enteral nutrition either orally or by feeding tube, was believed to have a negative impact on the progression of the disease due to the stimulation of exocrine pancreatic secretion and the consequent worsening of the autodigestive process of the pancreas. Even though nutritional deficits are frequent in severe acute pancreatitis, nutrition, as a part of the therapy, was neglected for a long time.

## Enteral *versus* Parenteral Nutrition

Despite fears that enteral nutrition may exacerbate acute pancreatitis because of the known stimulatory effect of luminal nutrients on trypsinogen synthesis, several randomized clinical trials have shown that the outcome is better and the cost is lower if enteral nutrition is used instead of TPN [20, 30, 31]. There is accumulating clinical evidence that enteral nutrition can improve survival and reduce the complications accompanying the severe acute pancreatitis.

The explanations are complex and related to the fact that:

- enteral nutrition avoids TPN complications;
- luminal nutrition maintains intestinal health;
- enteral amino acids are more effective in supporting splanchnic protein synthesis;
- enteral nutrition may prevent the progression of multiple organ failure.

Topical nutrients are the most potent stimulators of mucosal regeneration through their stimulation of the release of growth factors and of mucosal blood flow, probably due to the presence of the amino acid arginine which is a precursor of nitric oxide and growth factors. In addition to its mucosal protective and immunomodulatory effects, enteral nutrition is the most effective way of supporting the intestinal metabolism. By

down-regulating splanchnic cytokine production and modulating the acute phase response, enteral nutrition reduces catabolism and preserves protein [32]. In addition, enteral nutrition with a diet enriched with glutamine has a beneficial effect on the recovery of IgG and IgM-proteins with a trend to shorter disease duration [33].

Vu *et al*. [34] studied the activation of pancreatic secretion in eight healthy volunteers in response to proximal or more distal jejunal delivery of nutrients into the small intestine. Duodenal outputs of pancreatic enzymes were measured by aspiration using a recovery marker. The distal opening was used for the continuous administration of a mixed liquid meal and was located at either the ligament of Treitz or 60 cm further distally. They reported that during proximal jejunal feeding, pancreatic enzyme output increased significantly over basal levels while no significant increase over basal levels was observed during distal jejunal feeding. The authors concluded that continuous feeding in the distal jejunum does not stimulate exocrine pancreatic secretion.

Kaushik *et al*. [35] studied pancreatic secretory responses to feeding in 36 healthy volunteers by standard double-lumen duodenal perfusion/aspiration techniques over 6 hours. Subjects were assigned to no feeding (n=7), duodenal feeding with a polymeric diet (n=7) or low-fat elemental diet (n=6), mid-distal jejunal feeding (n=11) or intravenous feeding (n=5). All diets provided 40 kcal/kg ideal body weight/day and 1.5 g protein/kg ideal body weight/day. They found that, in comparison to basal fasting trypsin secretion rates, duodenal feeding with the polymeric and elemental formulae stimulated trypsin secretion whereas intravenous feeding and mid-distal jejunal did not. The authors suggested that enteral feeding can be administered without stimulating pancreatic trypsin secretion provided it is delivered into the mid-distal jejunum. The mechanism may involve activation of the ileal brake mechanism.

O'Keefe *et al*. [36] studied 27 healthy volunteers while they were receiving either oral drinks or duodenal infusions of a complex formula diet, duodenal or intravenous infusions of elemental (protein as free amino acids, low fat) formulas or saline, and measured the pancreaticobiliary secretory responses while monitoring blood hormone and nutrient levels. Diets were matched for protein and energy. They found that, compared with the placebo, all oroenteral diets stimulated amylase, lipase, trypsin and bile acid secretion, and increased plasma concentrations of gastrin and cholecystokinin whereas intravenous feeding did not. The complex formula produced a similar response whether given as drinks or duodenal infusions. Changing the duodenal formula to an elemental formula reduced enzyme secretion by 50%, independently of cholecystokinin. Higher increases in plasma insulin, glucose, and amino acids were noted with intravenous feeding. The authors concluded that delivering food directly to the intestine by a feeding tube does not reduce pancreaticobiliary secretion. Enteral 'elemental' formulae diminish, but only intravenous feeding avoids pancreatic stimulation. Intravenous administration impairs metabolic clearance.

In another study by O'Keefe *et al*. [37] the stimulatory effects of enteral and parenteral feeding on the synthesis and turnover of trypsin was measured. Intravenous infusions were labeled with 1-$^{13}$C-leucine and enterals were labeled with $^{2}$H-leucine. Isotope enrichment of plasma, secreted trypsin, and duodenal mucosal proteins were measured over 6 h by duodenal perfusion/aspiration and endoscopic biopsy. Thirty healthy volunteers were studied during fasting (n=7), intravenous feeding (n=6), or postpyloric enteral feeding (duodenal polymeric (n=6), elemental duodenal (n=6), and jejunal elemental (n=5)). The results demonstrated that, compared to fasting, enteral feeding increased the rate of appearance and secretion of newly labeled trypsin and expanded zymogen stores. These differences persisted whether the feedings were polymeric or elemental, duodenal, or jejunal. In contrast, intravenous feeding had no effect on basal rates. The authors

concluded that all common forms of enteral feeding stimulate the synthesis and secretion of pancreatic trypsin, and only parenteral nutrition avoids it.

In a prospective, but not controlled, study, Nakad *et al*. [38] administered oligopeptide enteral solutions by nasojejunal tube to 21 patients with severe acute pancreatitis 3 days after their admission to the hospital. The nasojejunal tube was placed by endoscopy. Twenty out of 21 patients (95%) tolerated the entire estimated energy load well, without any specific problems of reflux and aspiration. Progressive improvement of the clinical condition was observed without recurrence of the disease or a fatal course. In another non-controlled clinical study, Voitk *et al*. [39] administrated a monomeric enteral solution by jejunostomy in six patients who had undergone surgery for the management of complications of acute pancreatitis. Five of these patients showed progressive improvement and one of them died from corrosion of the splenic artery by a large pancreatic pseudocyst. Kudsk *et al*. [40] administered an elemental solution by jejunostomy to 11 patients who had undergone laparotomy, because of hemorrhagic or septic complications of acute pancreatitis. Five of these patients had undergone surgery within 48 hours from the onset of the disease and were fed immediately postoperatively. No complications were observed which could be attributed to enteral nutrition, and the clinical condition of these patients had not deteriorated. O'Keefe *et al*. [41] studied the stimulation of pancreatic secretion, after the intraduodenal infusion of a monomeric nutritional solution, in three patients with moderate acute pancreatitis and compared it to that of four healthy volunteers. They found that the secretion of pancreatic enzymes, especially trypsin and lipase, was significantly lower in the patients with acute pancreatitis. The writers suggested that, in acute pancreatitis, the stimulating action of food is noticeably decreased. Eatock *et al*. [42] administered an oligopeptide enteral solution with a low fat concentration to 26 patients with severe acute pancreatitis. All patients had 3 or more Glasgow criteria, more than 6 criteria of the APACHE II score, and the Balthazar severity index was at least five. The administration of a nutritional solution started 48 hours after hospital admission, with an initial rate of 20-30 ml/hour which progressively increased to 100 ml/hour. The jejunal administration of enteral nutrition was well tolerated by 22 patients (88%), without any signs of clinical deterioration. Finally, Eatock *et al*. [43] compared the administration of nasogastric and nasojejunal nutrition in 27 and 22 patients with the same severity criteria, respectively. They did not find any differences in morbidity and mortality in these two groups of patients.

Several trials have now proven that TPN should be avoided in the management of patients with acute pancreatitis. In the early trial by Sax *et al*., no difference in mortality or complication rates between TPN and enteral nutrition could be demonstrated [44].In a prospective randomized controlled study, McClave *et al.* compared early enteral nutrition (within 48 h of admission) via a jejunal tube to TPN in patients with mild to moderate acute pancreatitis (average Ranson criteria 1.3) [20]. The main finding was that enteral nutrition was much cheaper. The average cost per patient for TPN was $3,294 compared to an cost of enteral nutrition of only $761 ($P<0.02$).

Abou-Assi *et al*. studied 156 patients with acute pancreatitis in a prospective randomized comparative trial between jejunal elemental formula feeding and bowel rest with TPN [30]. Seventy-five percent of the patients improved during the 48 h observation and were discharged within 4 days, eating normally. Of the 53 remaining patients (average Ranson criteria 3), 26 were randomized to jejunal elemental diet feeding (mainly radiological placement) and 27 to TPN. Duration of the feeding was significantly shorter with enteral nutrition (6.7 *vs*. 10.8 days; $P<0.05$), and metabolic ($P<0.003$) and septic complications ($P=0.01$) were significantly higher in TPN-fed patients as were hospital costs. TPN was more effective in meeting estimated nutritional

requirements (80% *vs*. 54%; P<0.0001). This study supports the view that preservation of the gut function with even hypocaloric quantities of nutrients may be beneficial. Kalfarentzos *et al*. [31] randomized 38 patients with severe necrotizing acute pancreatitis to TPN or a semi elemental diet administered distally to the ligament of Treitz by using a radiologically placed tube. The total number of days on nutritional support was similar (35 days in the enteral nutrition group; 33 days in the TPN group) as was the quality of nutrients delivered (1.4 g protein, 24 kcal energy/kg/day). Seven patients in the TPN group developed pancreatic complications in comparison to only 2 in the enteral nutrition group, and the incidence of total septic events and total complications were significantly more common in the TPN group (P<0.01 and 0.05, respectively). Again, the cost of enteral nutrition was one-third that of TPN.

Focusing on the inflammatory response to feeding, Windsor *et al*. randomized 34 patients to TPN or enteral nutrition for 7 days [32]. All clinical outcome parameters improved in the enteral nutrition group, but not in the TPN group: SIRS presented in 11 enteral nutrition patients prior to feeding and only in 2 after the 7 days (P<0.05) while, in the TPN group, SIRS presented in 12 prior to feeding and 10 after. Furthermore, in the enteral nutrition group, the APACHE II score decreased significantly from 8 to 6 (P<0.0001) and the CRP from 156 to 84 mg/L (P<0.005) with no significant change in the TPN group. The reduction in inflammatory response with enteral nutrition could be ascribed to the suppression of bacterial overgrowth rather than to the reduction in pancreatic injury. This observation was supported by the finding of a) no increase in screen endotoxin antibodies in the enteral nutrition group as compared to an increase in the TPN group (P<0.05); and b) no difference in CT evaluation of the pancreatic injury after enteral nutrition or TPN. To test the effectiveness of early feeding (within 6 hours of the diagnosis of predicted severe acute pancreatitis, APACHE II score greater than 5), Gupta *et al*. randomized 17 patients to receive enteral nutrition or TPN [8]. Markers of systemic inflammation and oxidative stress were compared between the two groups. Three patients in the TPN group developed respiratory failure and 3 developed non-respiratory single organ failure. None in the enteral nutrition group developed such complications. Hospital stay was shorter in the enteral nutrition group (7 *vs*. 10 days). Although limited by a small sample size, this trial demonstrates the importance of starting enteral nutrition early in the clinical outcome of severe acute pancreatitis.

Marik and Zaloga have recently published a meta-analysis of randomized controlled clinical trials comparing enteral nutrition to TPN in acute pancreatitis [45]. They concluded that enteral nutrition should be the preferred route of nutritional support in patients with acute pancreatitis because it was associated with a significantly lower incidence of infection and a reduced length of hospital stay. There were no significant differences in mortality and non-infectious complications.

Although tube feeding results in fewer complications than parenteral nutrition, there are no randomized studies demonstrating an improved prognosis with early enteral nutrition as compared to no feeding nor are there any randomized studies which compare tube feeding to oral nutrition. There is also a need to study the best time to begin nutritional support in severe acute pancreatitis.

## What is the Preferred Route of Enteral Feeding?

Tube feeding is possible in the majority of patients with acute pancreatitis but may need to be supplemented by the parenteral route. Enteral nutrition delivered into the jejunum distally to the ligament of Treitz is commonly recommended to minimize pancreatic stimulation [4] but this can present several technical and logistical challenges. The placement of the jejunal feeding tubes, accidental removal and proximal migration of

the tube can contribute to reduction or delay in providing adequate nutrition.

In a recent randomized controlled trial, Eatock *et al*. questioned whether or not early nasogastric feeding was as effective and safe as nasojejunal feeding in patients with severe acute pancreatitis [43]. Forty-nine consecutive patients with objectively graded severe acute pancreatitis, were randomized to receive either nasogastric (27 patients) or nasojejunal (23 patients) feeding. The results showed that nasogastric feeding was safe, with no differences in pain score, analgesic requirement, serum C-reactive protein concentrations or clinical outcome. Naso-gastric feeding was equally well tolerated and the outcome was no different from nasojejunal feeding. They concluded that, when compared to nasojejunal feeding, nasogastric feeding is considered simpler, cheaper and easier to use, and is as good as nasojejunal feeding in patients with severe acute pancreatitis.

In a study of Kumar *et al*. [46],early nasojejunal feeding was compared to nasogastric feeding. A total of 31 patients with severe acute pancreatitis were randomized to receive feeding by either nasogastric (15 patients) or nasojejunal (16 patients). The authors reported no difference in the outcome measures (discharge, surgery, death) and satisfactory toleration of enteral nutrition by both nasojejunal and nasogastric routes. Neither nasojejunal nor nasogastric feeding led to recurrence or worsening of pain in acute pancreatitis.

Eckerwall *et al*. [47] randomized 50 patients to receive TPN or enteral nutrition groups in order to compare the efficacy and safety of early nasogastric enteral nutrition with TPN. They reported that, in predicted severe acute pancreatitis, early nasogastric enteral nutrition was feasible and resulted in a better control of blood glucose levels, although the overall complication rate was higher in the enteral nutrition group. No beneficial effects on the intestinal permeability or on the inflammatory response were seen by enteral nutrition treatment.

In a recent study, Merola *et al*. [48] reported that more patients having a nasogastric tube had infected necrosis and needed to switch to parenteral nutrition. The hospital stay also seemed longer in the patients with a nasogastric tube. However, this was a single centre study with a small sample size.

Further multicenter randomized trial studies are needed to confirm whether nasogastric feeding is a practical and effective form of management for patients with severe acute pancreatitis.

Patients with severe necrotizing disease usually have gastric outlet obstruction, and feeding into the stomach will be ineffective and possibly hazardous. In a study by Oleinikov *et al*., it seems that enteral nutrition was not possible in the majority of patients with severe acute pancreatitis having a mean APACHE II score of 17.2 and a mean Ranson score of 4.3 on admission [49]. This was probably due to the development of a severe retroperitoneal inflammatory process.

Recognizing patients who are at risk of developing necrotic pancreatitis and who will require ‘offensive’ early nutritional nasojejunal support is often difficult. For the determination of the severity of acute pancreatitis, and in an attempt to predict morbidity and mortality, the use of the APACHE II grading system was proven more accurate than clinical evaluation of the patient at the time of admission. In two prospective randomized comparative studies, the sensitivity of the clinical evaluation in predicting the development of severe acute pancreatitis was 34-44% while the sensitivity of the APACHE II grading system was 63-82% (severe acute pancreatitis; APACHE II score greater than 9). Even greater was the sensitivity of the predictive ability (75-89%) with the combination of APACHE II (score greater than 9) and the Ranson criteria (more than 2 criteria) [13, 50].

Therefore, according to these criteria, patients with an APACHE II score greater than 9 and more than 2 Ranson criteria in the first 48 hours from their admission, make up 20% of the patients with acute pancreatitis. These

patients usually have pancreatic necrosis in more than 30% of the organ, mortality is about 19% and morbidity about 38%, and it is usually not feasible to feed them normally *per os* for a period of 7-10 days from the onset of the disease. Contrarily, patients with an APACHE II score equal to, or less than, 9 and less than 2 Ranson criteria have zero mortality, present complications in 6% and the vast majority (81%) will be fed normally *per os* in less than a week [44, 50, 51, 52].

Using these diagnostic parameters, the clinician has the ability of predicting, immediately from the first 48 hours, which patients are at risk of developing severe pancreatitis and, therefore, need early enteral nutrition by the nasojejunal tube in order to minimize the disruption of the functional integrity of the intestinal mucosal barrier, limit bacterial translocation and reduce the intensity of systemic inflammatory reaction.

## Do the Complications of Acute Pancreatitis Constitute Contra-Indications for the Administration of Enteral Nutrition?

Pancreatic ascites, pancreatic fistulas and pancreatic pseudocysts are complications in the normal course of patients with severe acute pancreatitis. There are a large number of retrospective studies, with small numbers of patients, from which it has been shown that the administration of enteral nutrition is a safe and efficient way of supporting the nutrition of patients with complications of acute pancreatitis [17, 39, 53].

In these patients, although the acute phase of pancreatitis has passed, hospitalization is still needed and their energy requirements should be supported by enteral nutrition with a nasojejunal tube or by the oral administration of a monomeric or oligopeptide, usually, immunomodulative solution for enteral nutrition. This treatment is followed only by minor diarrhea which is usually managed by making adjustments to the solutions administered and with the administration of antidiarrhoic drugs, and the cessation of the enteral nutrition is rarely necessary [15, 17, 31, 53]. Surgeryfor the management of hemorrhage or pancreatic abscess gives the opportunity of carrying out a jejunostomy for the nutrition of the patients [40, 54].

In two prospective studies by Hernandez-Aranda *et al*. [55] and by Bodoky *et al*. [56], patients who have undergone surgery for acute pancreatitis were postoperatively randomly divided to be fed by TPN or enteral nutrition by jejunostomy. The authors observed that there was no reported difference between the two groups regarding the volume and the composition of the pancreatic secretion or the course of the disease [55, 56].

In patients with severe acute pancreatitis, who are candidates to be supported by enteral nutrition, a special silicone nasojejunal tube should be placed immediately by endoscopy or radiological control. The end of the tube should be at a distance of 25-30 cm after the Treitz ligament. The administration of the nutritive solution should start at a rate of 25 mL/h and gradually increase until the desired quantity (25 kcal/kg/day) in 24-48 hours [15].

With the nasojejunal tube placed correctly, almost any type of enteral nutritional solution can ensure satisfactory secretory ‘pancreatic rest’. However, to achieve the maximum inhibition of the secretion of pancreatic enzymes, an elemental diet or an oligopeptide diet should be administered [36, 57]. With the administration of a fat-free elemental diet minimum stimulation of the pancreatic secretion is ensured while oligopeptide diets in which 70% of the contained fat is in the form of moderate chain triglycerides are better absorbed in the intestine, although they cause relatively greater stimulation of the pancreatic secretion. However, this is still theoretical and is not based on randomized controlled trials.

The appearance of signs of mild paralytic ileus does not necessarily require the cessation of nutritional support, and it is possible that deceleration of the administration rate of the nutritional solution is sufficient. Oral refeeding can usually be a problem (pancreatitis from refeeding). Usually, food *per os* is given after 3-4 days after the patient last complained about pain, and the levels or serum amylase and lipase have returned to almost normal. Prognostic

criteria for the possibility of early oral refeeding are: a) the initial extent of the pancreatic necrosis (less than 1/3 of the pancreas), b) the duration of pain (less than 6 days), and c) the maximum serum level of pancreatic lipase (less than the triple of normal lipase level) [58].

## When Should Parenteral Nutrition Be Used?

Based on the idea that the stimulation of exocrine pancreatic secretion will worsen the disease because of increased secretion of pancreatic enzymes and maximization of self digestion of the organ, TPN was, for many years, the only method of nutritional support for patients with acute pancreatitis. However, the majority of the studies were non-randomized and retrospective, with a limited number of patients and relatively few data regarding the consequences of artificial nutrition on the final outcome of the disease. In one of the first non-randomized, non-controlled studies conducted from 1966 to 1972, Feller *et al*. [59] found that the patients with acute pancreatitis who received TPN showed decreased morbidity and mortality. Thus, they recommended the use of intravenous nutritional support for all patients with acute pancreatitis. In 1976, after retrospectively studying 46 patients with acute pancreatitis who were receiving TPN, Goodgame and Fisher [60] did not find any beneficial effect on total morbidity and mortality whereas they found a 17% increase in infectious complications which were related to the intravenous feeding catheter. In 1984, Grand *et al*. [33] reviewed their experience with the usage of TPN in 121 patients with acute (73 patients) and chronic (48 patients) pancreatitis. They did not observe any significant positive effect on the course of the disease. On the contrary, they found an increase in infectious complications from the catheter in 14.8% of patients with acute pancreatitis and in 17.4% of patients with chronic pancreatitis. A significant problem was hyperglycemia in 82% of patients with acute disease and 78% of patients with chronic disease, requiring the administration of 87 IU/day and 54 IU/day of insulin, respectively. One year later, Kirby and Graig [61] concluded that the overall effect of TPN on the progress of acute pancreatitis had not yet been established. They also stated that TPN may have some beneficial results in patients with complications which prolong the course of the disease, such as fistulas or pancreatic ascites. In a prospective, non-controlled study in patients with acute pancreatitis who received TPN, Sitzmann *et al*. [7] found an almost tenfold mortality rate in patients who did not manage to achieve a positive nitrogen balance in a two week period from the beginning of artificial nutrition (21.4% *vs*. 2.5%; $P<0.01$). They also observed a correlation between mortality and the composition of the TPN solution. Patients with glucose intolerance and whose energy requirements were supplied mainly by fat, had a 15% mortality rate, almost threefold the mortality of patients who received a nutritional solution with a normal proportion of non-proteinic calories (60-70% carbonates; 20-30% fat). The maximum mortality (33%) rate was reported in patients with fat intolerance and coverage of energy requirements exclusively by carbonates.

Until now, in the only prospective randomized study by Sax *et al*. [44] made in 54 patients with relatively mild acute pancreatitis (less than 3 Ranson criteria), it was observed that the patients who received TPN as compared to the patients who received conventional treatment (intravenous administration of crystalloid solutions, gastric decongestion, analgesia), experienced longer hospitalization periods (16 *vs*. 10 days) and a higher rate of septic complications from the catheter (10.5% *vs*. 1.5%; $P=0.03$).

In patients with acute pancreatitis who receive TPN, except for the infectious complications related to the intravenous catheter, common causes of complications are atrophy and disturbance of the functional integrity of the intestine. These abnormalities lead to immunosuppression and to an increase in the severity and duration of systemic inflammatory response syndrome. Atrophy of the mucous membrane of the intestine can

promote bacterial translocation, and increased rates of hospital infections, sepsis and organ failure [41, 56, 62, 63, 64].

In a clinical study by Fong *et al*. [65], healthy volunteers were randomly divided into two groups; one was administered nasogastric nutrition and the other was administered TPN for seven days each. *Escherichia coli* endotoxin was then intravenously administered. The people who received TPN had higher levels of glycogen, epinephrine, C-reactive protein and tumor necrosis factor (TNFa). In addition, they presented a greater loss of amino acids and lactic acid from the skeletal muscles. The study proved that TPN can weaken the metabolic response to infection and sepsis by a non-controlled hormonal response and increased systemic and splanchnic production of cytokines which promote the inflammatory process [65].

A number of studies have concluded that enteral nutrition is at least as effective and may be more effective than TPN in providing nutritional support in patients with acute pancreatitis.iIn a recent meta-analysis of all the prospective randomized controlled studies comparing enteral nutrition and TPN in patients with acute pancreatitis, Marik and Zaloga [45]conclude that:

1. the effort to assure functional rest of the gastrointestinal tract with or without parenteral nutrition currentlyremains the rule;
2. in patients with functional integrity of the gastrointestinal tract, enteral nutrition must be the practice therapy of choice for nutritional support;
3. TPN seems to cause immunosuppression as well as promoting systemic inflammatory response; from this point of view, TPN could prove harmful;
4. TPN significantly increases the risk for infection and the possibility of surgery when compared to enteral nutrition;
5. the early administration of enteral nutrition must be the standard therapeutic approach in patients with severe acute pancreatitis; TPN is only required in a few patients.

**Glutamine Supplementation, Probiotics**

De Beaux *et al*. randomized 14 patients with severe acute pancreatitis to receive standard parenteral feeding or isocaloric, isonitrogenous, glutamine-enriched parenteral feeding [66]. Thirteen patients completed the study protocol and there was a trend for the glutamine fed group to show improved lymphocyte proliferation, increased T-cell DNA synthesis and decreased release of the proinflammatory cytokine IL-8. In a recent study, Halley *et al*. reported the beneficial effect of a glutamine rich multifibre diet as compared to a standard fibre diet on the time trend of IgG and IgM, with shorter disease duration [67].

In a double-blinded trial by Olah *et al*., patients with acute pancreatitis were randomized into two groups: the treatment group (n=22) received a preparation containing live *Lactobacillus plantarum* together with a substrate of oat fiber (a probiotic) for one week by nasojejunal tube [68] and the control group received heat-inactivated *Lactobacillus* strain preparation (n=23). Infected pancreatic necrosis and abscesses occurred in 4% of patients in the treatment group as compared to 30% in the control group (P=0.023). The mean length of hospital stay was shorter in the treatment group (P<0.05).

The use of probiotics is controversial in patients with acute pancreatitis. In the recent multicenter double-blind, placebo-controlled trial of Besselink *et al*. [69], involving patients with predicted severe acute pancreatitis, probiotic prophylaxis did not reduce the risk of infectious complications and was associated with an increased risk of mortality. A possible explanation could be that the administration of probiotics might increase the local oxygen demand in the small bowel mucosa and that the presence of probiotics caused local inflammation at the level of the mucosa. The authors concluded that the administration of probiotics must be regarded as unsafe especially in patients at risk for non-occlusive mesenteric ischemia.

In the study of Kuklinski *et al*., reduction of the levels of selenium in the plasma of

patients with acute pancreatitis was observed, and positive results after the addition of selenium into the intestinal diet of these patients was reported [70].
Despite the limited number of reports on this subject, European Society of Parenteral and Enteral Nutrition (ESPEN) Guidelines recommend the use of enteral nutrition with selenium in patients with acute pancreatitis [4].
Larger clinical randomized trials are needed to confirm the effectiveness of antioxidants and immunomodulatory components of nutritional support in this category of patients.

**ESPEN Recommendations for Nutritional Support of Patients with Acute Pancreatitis**

Not all patients with acute pancreatitis need specific nutritional support. There is no evidence that nutritional support (enteral or parenteral) has a beneficial effect on the clinical outcome in patients with mild acute pancreatitis. In mild acute pancreatitis, the clinical course is usually uncomplicated and patients can consume a low-fat oral diet within 3-7 days. The disease does not have a major impact on nutritional status, energy or substrate metabolism. It is not clear whether this is true in cases with pre-existing malnutrition. It is crucial for patients with signs of malnutrition that their requirements are met by providing artificial nutrition.
The ESPEN Guidelines recommend three steps for the nutritional support of patients with mild acute pancreatitis, if they can consume an oral diet within 5-7 days:

- in the first 2-5 days fasting, analgesia, i.v. fluids and electrolyte replacement is the treatment of choice;
- if the pain is controlled and enzyme levels are decreased, a diet rich in carbohydrates and moderate in protein and fat can be started;
- normally, these patients can be discharged from the hospital after 4-7 days with a normal diet.

In severe acute pancreatitis, early enteral nutrition by a jejunal tube is recommended as the first step. There is substantial experimental evidence, not only from randomized controlled trials, to support the opinion that enteral nutrition in severe acute pancreatitis has some benefits: a) it down-regulates the systemic inflammatory response, and b) it prevents the colonization of the intestine by pathogenic bacteria and reduces bacterial translocation in the intestinal wall with the reduction of superinfection of the pancreatic necrosis [9, 31, 34, 42, 43]. Experts advise that enteral nutrition should always be tried if an adequate intake of normal food is not possible [4]. For these reasons, a low volume of enteral nutrition (10-30 mL/h) should be started and, if necessary, given in parallel with parenteral nutrition. If upper gastric intolerance occurs, small bowel feeding should be preferred.
In patients with severe acute pancreatitis who have complications or who need surgery, the ESPEN Guidelines recommend the following:

- begin early, with continuous enteral feeding using a jejunal tube as soon as the clinical signs predict severe acute pancreatitis;
- an elemental diet is used most often, but standard enteral or immune-enhancing formulation can be given;
- if enteral nutrition is insufficient, parenteral nutrition should be added;
- the administration of fat can be regarded as safe;
- hyperglycemia (more than 10 mmol/L) and hypertriglyceridemia (more than 12 mmol/L) should be avoided.

Patients on enteral nutrition or TPN should receive 25-35 kcal/kg body weight/day depending on the severity of the disease. The optimal goal for supplying protein is to administer between 1.2 and 1.5 g/kg body weight/day. A higher protein intake should only be given to patients with a severe negative nitrogen balance. A lower protein intake is sometimes necessary in patients with severe renal or hepatic failure. Fat can be given safely up to 2 g/kg body weight/day but triglyceride levels must be monitored carefully and should be kept within normal ranges. Enteral intake by continuous feeding regimen is recommended.
Oral refeeding can be started if the patient is stable, gastric outlet obstruction has been resolved, pain has ceased and amylase and

lipase values are decreasing. Oral refeeding with a diet rich in carbohydrates and moderate in proteins and fat is recommended. If the diet is well-tolerated, oral nutrition can be increased continuously. The nutrient requirements depend on the severity of the disease. Patients with severe acute pancreatitis are hypermetabolic. If the disease is complicated by sepsis or MODS/MOFS, the resting energy expenditure is significantly increased.

## Conclusions

Severe acute pancreatitis interferes with nutrient digestion and absorption and is associated with protein catabolism, metabolic instability and increased nutritional requirement. Several studies have demonstrated that enteral nutrition via nasogastric or nasojejunal tubes is possible and beneficial in patients with severe acute pancreatitis. Further multicenter randomized trials studies are needed to confirm whether nasogastric feeding, as compared to nasojejunal feeding, is a practical and effective form of management for patients with severe acute pancreatitis. Nutritional support has shown no beneficial effect in mild acute pancreatitis. Parenteral nutrition increases complications due to uncontrolled hyperglycemia and infection, and is more expensive than enteral nutrition. Parenteral nutrition should be reserved for patients with severe pancreatitis who cannot tolerate enteral nutrition, who have an exacerbation of their disease with enteral feeding, and for those before undergoing pancreatic surgery if they have severe signs of malnutrition. Not enough information is available to make specific recommendations for the use of specific supplements of enteral nutrition. The use of probiotics is controversial in patients with acute pancreatitis. Whether any nutritional therapy for patients admitted for severe acute pancreatitis is better than no artificial nutrition support, is difficult to answer according to the limited studies available.

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**Keywords** Enteral Nutrition; Parenteral Nutrition, Total; pathophysiology

**Abbreviations** ESPEN: European Society of Parenteral and Enteral Nutrition; MODS: multiorgan dysfunction syndrome; MOFS: multiorgan failure syndrome; REE: resting energy expenditure; SIRS: systemic inflammatory response syndrome; TPN: total parenteral nutrition

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