

Enteral Nutrition in Severe Acute Pancreatitis: Future Development

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Acute pancreatitis is a disease with a wide spectrum of clinical courses, ranging from the mild form, with minimum morbidity and almost zero mortality, to the severe form with a high percentage of complications and a high risk for a lethal outcome.

In about 80% of patients, the inflammatory process is self-limiting, involving only the pancreas and peripancreatic tissues, and resolves spontaneously within less than a week. These mild cases require only a short period of fasting, intravenous hydration, electrolytes and analgesia. Patients can usually start an oral low fat diet within 3-7 days after the onset of their pain, resulting in minor and usually easily reversible nutritional defects.

Severe acute pancreatitis is characterized by various degree of necrosis of pancreatic parenchyma together with local and systemic complications such as systemic inflammatory response syndrome (SIRS) and multiple organ failure (MOF). This latter form of the disease represents a typical hypermetabolic septic model with increased resting energy requirements, and considerable protein catabolism which leads to severe malnutrition.

As a result, nutritional support in acute pancreatitis should be one of the main therapeutic aims, and nutritional management should depend on the underlying pancreatic disease form.

Furthermore, contamination of pancreatic necrosis and consequent sepsis is the main cause of late death in severe acute pancreatitis [1]. The organisms responsible for secondary pancreatic infection are usually gram negative

bacteria of the same type that colonize the gastrointestinal tract. This suggests gut barrier dysfunction, increased intestinal permeability and subsequent bacterial translocation through the gut wall. Intestinal permeability changes were proven to occur in acute pancreatitis and were directly related to the severity of the disease. Patients with severe acute pancreatitis had increased intestinal permeability as compared to healthy controls [2] or those with mild attacks, and patients who developed MOF had even greater changes as compared to those with severe disease, and a more favorable outcome. Overall, the maintenance of the intestinal structure and function is a multifactorial process which requires adequate delivery of energy and oxygen supply. Enterocytes use glutamine and short chain fatty acids as primary fuel. The presence of these nutrients in the lumen stimulates the proliferation of mucosal cells and enhances gut integrity. Fasting leads to mucosal atrophy, an increased rate of enterocyte apoptosis, decreased glutamine and arginine transport and altered mucin composition of goblet cells. Attempts to favorably modulate the immune and inflammatory responses of severely ill patients have led to the enrichment of nutrition with various immune-enhancing nutrients. This has become known as immunonutrition. Of the various nutrients that have been suggested as beneficial, glutamine, arginine, omega-3 fatty acids and nucleotides [3] have been introduced in clinical use, in the form of several standard formulas, often in combined preparations. There are a number of reports, mainly in severely injured patients,

dealing with the role of immune-enhanced enteral diets in these cases. A meta-analysis [4] which included 1,009 patients from 11 trials showed that immune-modulated regimens resulted in a significant reduction of infection complications and length of hospital stay, but had no effect on survival. Only one study dealt with the use of glutamine in acute pancreatitis, as a supplement in standard TPN. They found that glutamine improves leukocyte activity and reduces proinflammatory cytokine release in acute pancreatitis. No conclusions can be drawn from these studies, although it seems possible that immune-enriched diets could play a role; however, further studies are needed to clarify this issue.

Total parenteral nutrition has failed to show any clinical benefits for the patient, as it cannot protect the gut mucosa [5].

On the contrary, enteral feeding repairs the mucosal damage of fasting and given very early, it preserves epithelial integrity, and bacterial ecology, thereby helping to maintain gut barrier function.

Recently, the role of the gut in acute pancreatitis has been expanded beyond the bacterial and endotoxin translocation phenomenon, as emerging evidence has indicated that the gut may be a source of cytokines and a site of neutrophil priming. It appears that intestinal ischemia and reperfusion injury results in the overactivation of gut macrophages and gut-associated lymphoid tissue, which in turn excessively release cytokines and other mediators. The release of cytokines contributes to SIRS and MOF.

Based on the above, efforts were made to find a more natural way of delivering nutrients to patients with pancreatitis. Despite concerns for a possible stimulatory effect of oral feeding on pancreatic secretion and fear of disease exacerbation, several experimental and clinical trials [6, 7] have shown that the delivery of nutrients into the jejunum does not increase pancreatic secretion and is well-tolerated with no increase in complications. More specifically, although the administration of lipids in the duodenum is a strong

stimulatory factor for pancreatic exocrine secretion, jejunal delivery of the same amount of lipids causes minimal pancreatic reaction. Similarly, intravenous lipid infusion has little effect as has been shown in human studies. Gastric or duodenal protein or carbohydrate administration is also a strong stimulus for pancreatic secretion while, as expected, jejunal delivery of the same nutrients is harmless to the pancreas.

Additionally, it was confirmed that enteral feeding is technically feasible and clinically safe even in critically ill patients with severe disease and provides efficient nutritional support. Severe paralytic ileum is not a contraindication to nasojejunal feeding, but, in rare cases, it may prevent adequate caloric intake. From the practical point of view, enteral feeding is achieved by the insertion of a nasojejunal feeding tube, placed for the most part, endoscopically or under radiological screening, distal to the ligament of Treitz. Occasionally, correct feeding tube location and maintenance of its patency may be troublesome. Recently, the Glasgow group reported results from gastric delivery of the enteral feeding regimens. They concluded that early nasogastric feeding is usually possible and well-tolerated in patients with severe acute pancreatitis

Up to now five randomized controlled studies have been published comparing enteral feeding with TPN. Four of them [8, 9, 10, 11] agree that a significant reduction in total - including septic - complications were observed in the enteral feeding group. The cost was three times lower in the enteral nutrition (EN) group than in the TPN group and they recommended the use of EN in all patients with severe disease. Powel *et al.* [12] published the only randomized controlled study comparing EN with no nutritional support and studied the effect of early EN on markers of the inflammatory response in predicted severe pancreatitis. Serum interleukin 6, tumor necrosis factor receptor 1 and CRP were used as inflammatory markers. Despite previous findings, the authors stated that early EN did not ameliorate the inflammatory response in patients with severe

acute pancreatitis as compared to no nutritional intervention. Finally, a randomized study is underway by our group; we are trying to identify the role of early EN, as compared to standard TPN, in reducing the need for surgery in patients with predicted severe acute pancreatitis. We reported preliminary results in which we showed that early EN seemed to reduce surgical interventions in the EN group by reducing the incidence of sepsis (9% vs. 33%) [13].

Although we have seen sporadic reports of the effective use of different probiotics in acute pancreatitis, Olah *et al.* [14] published the first randomized study which attempted to identify the role of lactobacillus as a supplement to enteral feeding. They concluded that supplementary *Lactobacillus plantarum* 299 is effective in reducing both, pancreatic sepsis and the number of surgical interventions.

Inasmuch as, until now, the published studies have encountered a number of methodological problems (most studies are retrospective with heterogeneous groups of patients, in none of the randomized controlled studies is a primary endpoint identified or a sample size and power calculation performed, the number of patients was small and, in most of them, patients with mild acute pancreatitis were also included), future randomized controlled trials are needed. These studies should respond to some important open issues such as:

- Does the routine use of nutritional support in severe acute pancreatitis have any benefit in terms of clinical outcome?
- Do we have enough evidence to conclude that enteral nutrition is better than TPN as the trends have shown in well-designed but not important studies? Which route is better?
- Is there any role for immunomodulated diets and any other related supplements?
- What about new factors targeting the maintenance of gut integrity (e.g. trophic factors) [15].

Keywords Adjuvants, Immunologic; Biological Response Modifiers; Enteral Nutrition; Immunologic and Biological Factors; Immunologic Factors; Pancreatitis; Pancreatitis, Acute Necrotizing; Parenteral Nutrition; Probiotics

Abbreviations EN: enteral nutrition

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