Abstract
Enteral nutrition has been strongly recommended by major scientific societies for the nutritional management of patients with acute pancreatitis. Providing severe acute pancreatitis patients with enteral nutrition within the first 24-48 h of hospital admission can help improve outcomes compared to parenteral nutrition and no feeding. New research is focusing in on when and what to feed to best improve outcomes for acute pancreatitis patients. Early enteral nutrition have the potential to modulate the immune responses. Despite this consistent evidence of early enteral nutrition in patients with acute pancreatitis, clinical practice continues to vary due to individual clinician preference. Achieving the immune modulating effects of enteral nutrition heavily depend on proper placement of the feeding tube and managing any tube feeding associated complications. The current article reviews the immune modulating effects of enteral nutrition and pro- and prebiotics and suggests some practical tools that help improve the patient adherence and tolerance to the tube feeding. Proper selection of the type of the tube, close monitoring of the tube for its placement, patency and securing its proper placement and routine checking the gastric residual volume could all help improve the outcome. Using peptide-based and high medium chain triglycerides feeding formulas help improving feeding tolerance.

Hegazi RA, DeWitt T. Enteral nutrition and immune modulation of acute pancreatitis. World J Gastroenterol 2014; 20(43): 16101-16105 Available from: URL: http://www.wjgnet.com/1007-9327/full/v20/i43/16101.htm DOI: http://dx.doi.org/10.3748/wjg.v20.i43.16101

INTRODUCTION
The majority of acute pancreatitis (AP) episodes are considered mild or moderate. However, up to a third of patients with AP present with either severe acute pancreatitis (SAP) (defined as either infected (peri)pancreatic necrosis or persistent organ failure) or critical AP (defined as both infected (peri)pancreatic necrosis and persistent organ failure) according to a newly published consensus...
classification of the severity of AP\(^5\). SAP is a common cause of systemic inflammatory response syndrome (SIRS), a serious complication that is associated with multi-organ failure, increased risk of infections and mortality and mediated by increased expression of pro-inflammatory cytokines and chemokines\(^5\). In addition to this inflammatory and catabolic stress, the gastrointestinal symptoms patients with AP present with (abdominal pain, vomiting and diarrhea) pose an even more increased risk of malnutrition. Enteral nutrition (EN) exerts immune modulating effects in patients with AP beyond meeting the caloric and protein requirements. The current article reviews the nutritional issues of patients with AP and explores the potential immune modulating role of EN and nutrients.

**IMMUNE MODULATING EFFECTS OF ENTERAL NUTRITION**

Compared to parenteral nutrition (PN), the use of enteral nutrition in patients with SAP has been shown to improve clinical outcomes, decrease infective complications and reduce the incidence of multiple organ failure in patients with SIRS\(^5\). The exact mechanism of these beneficial effects of enteral nutrition in patients with SIRS remains to be determined. Previous studies to explain these effects suggest immunomodulatory effects of enteral nutrition on both the systemic and intestinal mucosal immune systems. The integrity of the intestinal epithelial and immune cells of the gut-associated lymphoid tissue and the intestinal barrier plays an important role in maintaining intestinal homeostasis and preventing bacterial translocation\(^6\). The intestinal epithelial cells (IEC)-derived cytokine secretion plays a major role not only in maintaining intestinal mucosal functions but also in the maturation and optimum functions of lymphocytes. Enteral nutrients play a major role in maintaining the integrity of IEC. For instance, duodenal infusion of the amino acid glutamine induced the expression of the major cytoprotective enzyme, heme-oxygenase-1 (HO-1).

HO-1 is an important enzyme for immune homeostasis and exerts anti-inflammatory effects in animal models of intestinal inflammation\(^5\).

The literature has consistently shown that EN is preferred to PN in patients with SAP and therefore EN was recommended by major gastroenterology, critical care and nutrition societies (Table 1). Consistently, Wu et al\(^6\) (2010) conducted a randomized trial to determine the effects of EN compared to PN in preventing pancreatic necrotic infection in patients with SAP. EN patients experienced significantly less (\(P < 0.05\)) necrosis, surgery related complications and mortality compared to the PN group\(^6\). The most common cause of mortality (27%) was multiple organ failure from sepsis impacting 43% of patients on PN and 11% on EN (\(P < 0.05\))\(^6\).

The beneficial immune, hormonal and endocrine effects of EN on the intestinal mucosa make it superior to long-term starving patients with mild and moderate acute pancreatitis. Consistently, a recent randomized controlled trial showed that patients receiving EN within 24 h of hospital admission had significantly reduced intensity and duration of abdominal pain, need for opiates, and risk of oral food intolerance as compared to the no-feeding group, with no difference in hospital length of stay\(^7\).

For EN to exert its immune and other beneficial effects, the patient’s tolerance to the fed formula is key. Tube feeding associated intolerance is common, occurring in approximately 50% of tube-fed patients. Due to the associated exocrine pancreatic insufficiency, patients with SAP are at even higher risk of feeding intolerance. The nutrient composition of EN formulas may help enhance the tolerance to the formula and increase the likelihood of adherence for patients to achieve their goal feeding. Consistently, major clinical and scientific societies recommend feeding patients with SAP with peptide based and high medium chain triglycerides formulas (Table 1). Interestingly, medium chain triglycerides have been shown to exert anti-inflammatory effects in animal models of inflammatory bowel diseases\(^8\).

| Association | Recommendation for nutritional care of SAP (Grade) |
|-------------|-------------------------------------------------|
| International Consensus Guideline Committee\(^[28]\) | EN is generally preferred over PN, or at least EN should, if feasible, be initiated first. (Grade A: Platinum) For EN, consider small peptide-based, medium chain triglyceride oil formula to improve tolerance. (Grade B: Gold) |
| European Society of Parenteral and Enteral Nutrition\(^[29]\) | In severe necrotizing pancreatitis, EN is indicated if possible (A) Peptide-based formula can be used safely in AP (A) Standard formula can be tried if they are tolerated (C) |
| ASPEN/SCCM 2009 Critical Care Guidelines\(^[30]\) | Patients with severe acute pancreatitis may be fed enterally by the gastric or jejunal route. (Grade: C) Tolerance to EN in patients with severe acute pancreatitis may be enhanced by the following measures: Changing the content of the EN delivered from intact protein to small peptides, and long-chain fatty acids to medium-chain triglycerides of a nearly fat-free elemental formulation. (Grade: E) |
| American College of Gastroenterology\(^[31]\) | In severe AP, EN is recommended to prevent infectious complications Parenteral nutrition should be avoided unless the enteral route is not available, not tolerated or not meeting caloric requirements (strong recommendation, high quality of evidence) |

SAP: Severe acute pancreatitis; EN: Enteral nutrition.
EARLY VS DELAYED ENTERAL NUTRITION

We previously reported that early initiation of jejunal feeding (within 24 h of consulting) and reaching early goal tube feeding were associated with less duration of stay in the intensive care unit independent of the APACHE II scores. Consistently, a retrospective analysis of predicted SAP patients early EN (< 48 h) was superior to delayed EN (> 48 h) in the prevention of infected necrosis and mortality. Akin to SAP, early EN is preferred to late EN in critically ill and surgical patients. Recently, Sun et al. investigated the impact of early EN on the immune function and clinical outcomes. The single-center, prospective, randomized controlled trial analyzed 60 patients with SAP. One group (n = 30) received EN within 48 h of admission and the second group received TPN days 1-7 and then started EN on day 8. At day 7, difference were seen in the immune parameters between the two groups with the early EN group having significant differences in CD4+ T-lymphocyte percentage, CRP levels, HLS-DR expression and IgG levels (P < 0.05). No significant differences were seen in CD4+/CD8+, CD8+ T-lymphocyte percentage, IgM or IgA. The authors suggest that early EN in SAP patients may play a role in moderating the excessive immune response that is seen in the early stages of SAP. Significant decreases in ICU stay, pancreatic infections, MODS and SIRS were seen in the early EN group. There was no difference seen in hospital mortality or surgical operations between the two groups. While this study reported on early EN compared to delayed EN, the data reported is comparing early EN to exclusive TPN in days 1-7 of hospital stay.

While research continues to support early EN in SAP patients, there is an ongoing discussion on the optimal tube type selection that allows patients to reach goal feeding rates while minimizing stimulating the exocrine pancreatic secretions. In 2012, Singh et al. conducted a randomized, parallel-group, active controlled trial to determine if there was a difference in clinical outcomes for patients fed nasogastric (NG) vs nasojejunal (NJ). A pilot study had previously suggested that there were no differences in clinical outcomes and this larger study further supports those findings. There was no significant difference seen between NG and NJ groups in pain in mortality, refeeding, length of hospital stay or intestinal permeability. The NG group did experience significantly higher rates of any one infectious complication compared to the NJ group (95% CI). Tube placement either NG or NJ in AP patients can positively impact the patient. We have previously shown that a double-lumen nasogastric decompression and jejunal feeding tube system (NGJ) is a safe conservative management for patients with gastric outlet obstruction reducing the need for surgery and PN.

Interestingly, despite the prevailing evidence of the clinical outcome benefits of EN in patients with AP, physician preference for PN is still a reality leading to many unnecessary PN orders. A study in Australia and New Zealand by Davies et al. in 2011 determined that the most common reasons patients received PN were preference of the treating intensivist (38%) or surgeon (22%). In this prospective observational multicenter study, 42% of the patients received PN and that PN was more frequently the initial therapy compared to EN. Some myths and fears of initiating tube feeding in patients with SAP may have contributed to these observations. Having the technical capabilities of not only placing the enteral tubes but more importantly managing them is key to implementing a successful tube feeding strategy at any certain setting. For instance, tube displacement, a complication that could lead to the risk of aspiration, should be managed by radiographic confirmation of the position of the tip of tube and routine follow up by a dedicated nutrition therapy team. We have previously shown that devices like nasal bridle devices could help maintaining the tubes in place. Certain types of tubes like the NGJ tube system is another tool that can help address the problems of monitoring and managing the gastric residual volume while maintaining enteral feeding.

IMMUNE MODULATING EFFECTS OF PREBIOTICS AND PROBIOTICS

The intestinal luminal micro biota plays an important role in the pathogenesis of SAP-associated infections. It was hypothesized that the gut is the “undrained abscess” in patients with SAP. Microbial analysis of peri-pancreatic fluid collections reveal that the source of these microbial translocation is likely the intestinal lumen. Therefore, modulating the milieu of the intestinal microbes into the more beneficial strains had been the target of years of research. Prebiotics are the exogenous microbes that when given orally exerts some benefits to the host. Prebiotics are non-digestible dietary carbohydrates fermented by the intestinal microbes the byproducts of which stimulate the proliferation of the beneficial intestinal microbes or enhance their metabolic activities. Pre and probiotics have been hypothesized to possibly play a role in AP by modulating the gut micro biota to decrease bacterial translocation and reduce the associated infections. Prebiotics have been previously reported to be beneficial to the care of SAP patients by normalizing APACHE II and CRP levels. However, the study by Besselink et al. (2008) casted some doubt on the beneficial role of probiotics. To summarize, Besselink et al. randomized 298 patients with predicted SAP into two groups. The intervention group received a probiotics mix of probiotics strains and was compared to a placebo group. Both groups received enteral feeding. The primary endpoint of the study, infectious complications, was not significantly different between the two groups and mortality was higher in the probiotics group. However, this study has some limitations that were previously discussed in detail. For instance, questions were raised regarding the lack of clinical studies demonstrating the safety of the specific probiotics mix and doses used in the study. At baseline, gut ischemia was
more common in the probiotics group raising a concern of selection bias. Moreover, both study groups received a prebiotics-supplemented enteral formula. It could be questioned whether the bifidogenic effects of these probiotics had resulted in “iatrogenic bacterial overgrowth” in the probiotics group or that the outcome of the study could have been affected by a more favorable effect in the control group. Sharma et al[23] looked at the role of probiotics on gut permeability and endotoxemia to prevent infectious complications in AP patients. The investigators enrolled 50 patients into a double-blind, randomized placebo controlled trial. Due to results of the aforementioned study by Sharma et al[23] was abandoned the study after only enrolling 50 patients. The analysis of the 50 patients did not show any effects of probiotics in helping maintain gut integrity to prevent infectious complications. The authors suggest that probiotic use is inappropriate in the routine management of AP.

Research continues in the area of probiotics in SAP patients to help better understand which strains of probiotics may prove to possess clinical benefits. One interesting concept is to combine probiotics with EN. In 2013, Wang et al[24] studied the effects of ecoinmunonutrition (adding combined live Bacillus subtilis and Enterococcus faecium enteric-coated probiotics to EN) on gastric motility and cytokine production in patients with SAP. The study included 183 patients who were randomized to receive TPN, EN or ecoinmunonutrition. Compared to TPN, EN and ecoinmunonutrition significantly decreased plasma TNF-α and IL-6 levels ($P<0.05$) with the ecoinmunonutrition group seeing even further decreases at days 7 and 14 compared to the EN group ($P<0.05$). At days 7 and 14, the anti-inflammatory cytokine IL-10 levels were significantly increased in both EN and ecoinmunonutrition groups compared to the TPN group ($P<0.05$) with the ecoinmunonutrition group again showing greater increases compared to the EN group ($P<0.05$). The study was also able to detect significant differences in the occurrence of pancreatic sepsis, MODS and mortality among the three groups. The EN and the ecoinmunonutrition group had significantly less rate of sepsis, MODS and mortality compared to TPN ($P<0.005$) and the ecoinmunonutrition group had significantly less levels of markers of inflammation compared to the EN group.

Akin to the ecoinmunonutrition is the symbiotics approach of combining probiotics and prebiotics. Studies of the effects of symbiotics in the management of patients with acute pancreatitis have been previously investigated and showed promising results. Olah and colleagues randomized 45 patients with acute pancreatitis into two groups[25]. Both groups received jejunal feeding of isoaloric feeding formulas supplemented with 10 grams of oat fiber. The treatment group (22 patients) received live lactobacillus plantarum 299, and the control group (23 patients) received a similar dose of heat-inactivated lactobacillus plantarum 299. The rate of pancreatic infection was significantly lower in the symbiotics group than the control group ($30\% \text{ vs } 5\%, P < 0.05$). Moreover, patients required significantly less surgical interventions in the symbiotics group as compared to the control group ($22\% \text{ vs } 5\%, P < 0.05$)[26]. The same investigators also studied the effectiveness of another group of symbiotics (a mix of 4 different lactobacillus genera and 4 plant fibers)-supplemented jejunal feeding in patients with severe acute pancreatitis[26,27]. Consistently, the study showed that septic complications (infected pancreatic necrosis or abscesses) were significantly lower in the symbiotics group. The inherent composition of individual patient’s intestinal micro biota could play a role in determining the effects of the different strains of probiotics and type of prebiotics. Identifying these profiles of intestinal micro biota could help selecting the right combination of probiotics and/or prebiotics for the right patient, an interesting area for future research.

CONCLUSION

Patients with acute pancreatitis are at increased risk of malnutrition due to both decreased food intake and increased requirements as a result of the associated inflammatory disease. In addition to meeting calorie and protein requirements, enteral nutrition exerts an immune modulating effect on the intestinal and systemic immune responses. Enteral nutrients, prebiotics and probiotics are important for the optimal function of the intestinal epithelial cells and maintaining the intestinal micro biota homeostasis. Achieving the beneficial effects of enteral nutrition requires proper selection, placement and management of the feeding tubes and proper selection of the feeding formula.

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**P-Reviewer:** Neri V, Ruckert F  **S-Editor:** QI Y  **L-Editor:** A  **E-Editor:** Wang CH
