World Journal of Gastroenterology

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.3748/wjg.v20.i43.16101

World J Gastroenterol 2014 November 21; 20(43): 16101-16105
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

TOPIC HIGHLIGHT

WJG 20th Anniversary Special Issues (18): Pancreatitis

Enteral nutrition and immune modulation of acute pancreatitis

Refaat A Hegazi, Tiffany DeWitt

Refaat A Hegazi, Tiffany DeWitt, Research and development division, Abbott Nutrition, Columbus, OH 43219, United States
Author contributions: Hegazi RA and DeWitt T have been equally involved in reviewing the literature and writing the manuscript.
Correspondence to: Refaat A Hegazi, MD, PhD, MPH, MS, Medical Director Research and Development, Abbott Nutrition, 3300 Stelzer Rd, Columbus, OH 43219, United States. refaat.hegazi@abbott.com
Telephone: +1-614-6247811 Fax: +1-614-7277811
Received: March 1, 2014 Revised: May 9, 2014
Accepted: June 12, 2014
Published online: November 21, 2014

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.

Key words: Enteral nutrition; Acute pancreatitis; Immune modulating

Core tip: Due to the decreased food intake and increased nutrient requirements, patients with acute pancreatitis are at increased risk of malnutrition. Beyond meeting calorie and protein requirements, enteral nutrition exerts an immune modulating effect on the intestinal and systemic immune responses. Achieving the beneficial effects of enteral nutrition requires proper selection, placement and management of the feeding tubes and proper selection of the feeding formula. This review highlights new research of the immune effects of enteral nutrition, probiotics and prebiotics and suggests tools to help improve the patient adherence and tolerance to tube feeding.

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

Table 1 Current nutrition practice guidelines of enteral nutrition in patients with severe acute pancreatitis

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.

classification of the severity of AP[1]. 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[2]. 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[3]. 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[4]. 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].

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[9]. 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[10]. Akin to SAP, early EN is preferred to late EN in critically ill and surgical patients[11]. Recently, Sun *et al*[12] 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 of 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*[13] 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[14] and this larger study further supports those findings[13]. There was no significant difference seen between NG and NJ groups in pain in mortality, refeeding, length of hospital stay or intestinal permeability[13]. The NG group did experience significantly higher rates of any one infectious complication compared to the NJ group (95%CI)[13]. 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[15].

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*[16] 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[16]. 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 bridles could help maintaining the tubes in place[17]. 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[18]. Microbial analysis of peri-pancreatic fluid collections reveal that the source of these microbial translocation is likely the intestinal lumen[18]. Therefore, modulating the milieu of the intestinal microbes into the more beneficial strains had been the target of years of research. Probiotics 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[19]. However, the study by Besselink *et al*[20] (2008) casted some doubt on the beneficial role of probiotics. To summarize, Besselink *et al*[20] 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[21,22]. 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 prebiotics 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 ecoimmunonutrition (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 ecoimmunonutrition. Compared to TPN, EN and ecoimmunonutrition significantly decreased plasma TNF-α and IL-6 levels ($P < 0.05$) with the ecoimmunonutrition 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 ecoimmunonutrition groups compared to the TPN group ($P < 0.05$) with the ecoimmunonutrition 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 ecoimmunonutrition group had significantly less rate of sepsis, MODS and mortality compared to TPN ($P < 0.005$) and the ecoimmunonutrition group had significantly less levels of markers of inflammation compared to the EN group.

Akin to the ecoimmunonutrition is the synbiotics approach of combining probiotics and prebiotics. Studies of the effects of synbiotics 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 isocaloric 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 synbiotics group than the control group (30% *vs* 5 %, $P < 0.05$). Moreover, patients required significantly less surgical interventions in the synbiotics group as compared to the control group (22% *vs* 5%, $P < 0.05$)[25]. The same investigators also studied the effectiveness of another group of synbiotics (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 synbiotics 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.

REFERENCES

1 **Dellinger EP**, Forsmark CE, Layer P, Lévy P, Maraví-Poma E, Petrov MS, Shimosegawa T, Siriwardena AK, Uomo G, Whitcomb DC, Windsor JA. Determinant-based classification of acute pancreatitis severity: an international multidisciplinary consultation. *Ann Surg* 2012; **256**: 875-880 [PMID: 22735715 DOI: 10.1097/SLA.0b013e318256f778]

2 **Dambrauskas Z**, Giese N, Gulbinas A, Giese T, Berberat PO, Pundzius J, Barauskas G, Friess H. Different profiles of cytokine expression during mild and severe acute pancreatitis. *World J Gastroenterol* 2010; **16**: 1845-1853 [PMID: 20397261]

3 **McClave SA**. Drivers of oxidative stress in acute pancreatitis: the role of nutrition therapy. *JPEN J Parenter Enteral Nutr* 2012; **36**: 24-35 [PMID: 22235106 DOI: 10.1177/0148607111424410]

4 **Capurso G**, Zerboni G, Signoretti M, Valente R, Stigliano S, Piciucchi M, Delle Fave G. Role of the gut barrier in acute pancreatitis. *J Clin Gastroenterol* 2012; **46** Suppl: S46-S51 [PMID: 22955357 DOI: 10.1097/MCG.0b013e3182652096]

5 **Hegazi RA**, Rao KN, Mayle A, Sepulveda AR, Otterbein LE, Plevy SE. Carbon monoxide ameliorates chronic murine colitis through a heme oxygenase 1-dependent pathway. *J Exp Med* 2005; **202**: 1703-1713 [PMID: 16365149 DOI: 10.1084/jem.20051047]

6 **Wu XM**, Ji KQ, Wang HY, Li GF, Zang B, Chen WM. Total enteral nutrition in prevention of pancreatic necrotic infection in severe acute pancreatitis. *Pancreas* 2010; **39**: 248-251

[PMID: 19910834 DOI: 10.1097/MPA.0b013e3181bd6370]
7 **Petrov MS**, McIlroy K, Grayson L, Phillips AR, Windsor JA. Early nasogastric tube feeding versus nil per os in mild to moderate acute pancreatitis: a randomized controlled trial. *Clin Nutr* 2013; **32**: 697-703 [PMID: 23340042 DOI: 10.1016/j.clnu.2012.12.011]
8 **Bertevello PL**, De Nardi L, Torrinhas RS, Logullo AF, Waitzberg DL. Partial replacement of ω-6 fatty acids with medium-chain triglycerides, but not olive oil, improves colon cytokine response and damage in experimental colitis. *JPEN J Parenter Enteral Nutr* 2012; **36**: 442-448 [PMID: 22269895 DOI: 10.1177/0148607111421788]
9 **Hegazi R**, Raina A, Graham T, Rolniak S, Centa P, Kandil H, O'Keefe SJ. Early jejunal feeding initiation and clinical outcomes in patients with severe acute pancreatitis. *JPEN J Parenter Enteral Nutr* 2011; **35**: 91-96 [PMID: 21224435 DOI: 10.1177/0148607110376196]
10 **Wereszczynska-Siemiatkowska U**, Swidnicka-Siergiejko A, Siemiatkowski A, Dabrowski A. Early enteral nutrition is superior to delayed enteral nutrition for the prevention of infected necrosis and mortality in acute pancreatitis. *Pancreas* 2013; **42**: 640-646 [PMID: 23508012 DOI: 10.1097/MPA.0b013e318271bb61]
11 **Marik PE**, Zaloga GP. Early enteral nutrition in acutely ill patients: a systematic review. *Crit Care Med* 2001; **29**: 2264-2270 [PMID: 11801821]
12 **Sun JK**, Mu XW, Li WQ, Tong ZH, Li J, Zheng SY. Effects of early enteral nutrition on immune function of severe acute pancreatitis patients. *World J Gastroenterol* 2013; **19**: 917-922 [PMID: 23431120 DOI: 10.3748/wjg.v19.i6.917]
13 **Singh N**, Sharma B, Sharma M, Sachdev V, Bhardwaj P, Mani K, Joshi YK, Saraya A. Evaluation of early enteral feeding through nasogastric and nasojejunal tube in severe acute pancreatitis: a noninferiority randomized controlled trial. *Pancreas* 2012; **41**: 153-159 [PMID: 21775915 DOI: 10.1097/MPA.0b013e318221c4a8]
14 **Kumar A**, Singh N, Prakash S, Saraya A, Joshi YK. Early enteral nutrition in severe acute pancreatitis: a prospective randomized controlled trial comparing nasojejunal and nasogastric routes. *J Clin Gastroenterol* 2006; **40**: 431-434 [PMID: 16721226]
15 **O'Keefe S**, Rolniak S, Raina A, Graham T, Hegazi R, Centa-Wagner P. Enteral feeding patients with gastric outlet obstruction. *Nutr Clin Pract* 2012; **27**: 76-81 [PMID: 22307492 DOI: 10.1177/0884533611432935]
16 **Davies AR**, Morrison SS, Ridley EJ, Bailey M, Banks MD, Cooper DJ, Hardy G, McIlroy K, Thomson A. Nutritional therapy in patients with acute pancreatitis requiring critical care unit management: a prospective observational study in Australia and New Zealand. *Crit Care Med* 2011; **39**: 462-468 [PMID: 21221003 DOI: 10.1097/CCM.0b013e318205df6d]
17 **Hegazi R**, Rolniak S, Centa P. Effect of a nasal tube retention device (AMT Bridle) on frequency of nasojejunal feeding tube displacement. *Nutr Clin Pract* 2008; **23**: 19
18 **Marshall JC**, Charbonney E, Gonzalez PD. The immune system in critical illness. *Clin Chest Med* 2008; **29**: 605-616, vii [PMID: 18954696 DOI: 10.1016/j.ccm.2008.08.001]
19 **Karakan T**, Ergun M, Dogan I, Cindoruk M, Unal S. Comparison of early enteral nutrition in severe acute pancreatitis with prebiotic fiber supplementation versus standard enteral solution: a prospective randomized double-blind study. *World J Gastroenterol* 2007; **13**: 2733-2737 [PMID: 17569144]
20 **Besselink MG**, van Santvoort HC, Buskens E, Boermeester MA, van Goor H, Timmerman HM, Nieuwenhuijs VB, Bollen TL, van Ramshorst B, Witteman BJ, Rosman C, Ploeg RJ, Brink MA, Schaapherder AF, Dejong CH, Wahab PJ, van Laarhoven CJ, van der Harst E, van Eijck CH, Cuesta MA, Akkermans LM, Gooszen HG. Probiotic prophylaxis in predicted severe acute pancreatitis: a randomised, double-blind, placebo-controlled trial. *Lancet* 2008; **371**: 651-659 [PMID: 18279948 DOI: 10.1016/S0140-6736(08)60207-X]
21 **Hegazi R**. Prebiotics in Immuno-modulation for Treatment of Acute Pancreatitis . In: Watson R ZS, Preedy V, editors. Dietary Components and Immune Function. New York, NY: Humana Press, 2012: 611-624
22 **Reid G**, Gibson G, Sanders ME, Guarner F, Versalovic J. Probiotic prophylaxis in predicted severe acute pancreatitis. *Lancet* 2008; **372**: 112-113; author reply 114 [PMID: 18620940 DOI: 10.1016/S0140-6736(08)61024-7]
23 **Sharma B**, Srivastava S, Singh N, Sachdev V, Kapur S, Saraya A. Role of probiotics on gut permeability and endotoxemia in patients with acute pancreatitis: a double-blind randomized controlled trial. *J Clin Gastroenterol* 2011; **45**: 442-448 [PMID: 21135704 DOI: 10.1097/MCG.0b013e318201f9e2]
24 **Wang G**, Wen J, Xu L, Zhou S, Gong M, Wen P, Xiao X. Effect of enteral nutrition and ecoimmunonutrition on bacterial translocation and cytokine production in patients with severe acute pancreatitis. *J Surg Res* 2013; **183**: 592-597 [PMID: 23726433 DOI: 10.1016/j.jss.2012.12.010]
25 **Oláh A**, Belágyi T, Issekutz A, Gamal ME, Bengmark S. Randomized clinical trial of specific lactobacillus and fibre supplement to early enteral nutrition in patients with acute pancreatitis. *Br J Surg* 2002; **89**: 1103-1107 [PMID: 12190674]
26 **Oláh A**, Belágyi T, Issekutz A, Olgyai G. [Combination of early nasojejunal feeding with modern synbiotic therapy in the treatment of severe acute pancreatitis (prospective, randomized, double-blind study)]. *Magy Seb* 2005; **58**: 173-178 [PMID: 16167471]
27 **Oláh A**, Belágyi T, Pótó L, Romics L, Bengmark S. Synbiotic control of inflammation and infection in severe acute pancreatitis: a prospective, randomized, double blind study. *Hepatogastroenterology* 2007; **54**: 590-594 [PMID: 17523328]
28 **Mirtallo JM**, Forbes A, McClave SA, Jensen GL, Waitzberg DL, Davies AR. International consensus guidelines for nutrition therapy in pancreatitis. *JPEN J Parenter Enteral Nutr* 2012; **36**: 284-291 [PMID: 22457421 DOI: 10.1177/0148607112440823]
29 **Meier R**, Ockenga J, Pertkiewicz M, Pap A, Milinic N, Macfie J, Löser C, Keim V. ESPEN Guidelines on Enteral Nutrition: Pancreas. *Clin Nutr* 2006; **25**: 275-284 [PMID: 16678943 DOI: 10.1016/j.clnu.2006.01.019]
30 **McClave SA**, Martindale RG, Vanek VW, McCarthy M, Roberts P, Taylor B, Ochoa JB, Napolitano L, Cresci G. Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.). *JPEN J Parenter Enteral Nutr* 2009; **33**: 277-316 [PMID: 19398613 DOI: 10.1177/0148607109335234]
31 **Tenner S**, Baillie J, DeWitt J, Vege SS. American College of Gastroenterology guideline: management of acute pancreatitis. *Am J Gastroenterol* 2013; **108**: 1400-1415; 1416 [PMID: 23896955 DOI: 10.1038/ajg.2013.218]

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

Published by **Baishideng Publishing Group Inc**
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com

ISSN 1007-9327