



Nutrition Support in Acute Pancreatitis

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Abstract

Acute pancreatitis (AP) is a lethal disease with no specific treatment. It promotes a systemic inflammatory response syndrome that results in a highly catabolic stress state. The early phase of AP is based on mitochondrial damage, adenosine triphosphate (ATP) depletion and subsequent necrosis in pancreatic cells. A lack of enteral feeding predisposes the increase of intestinal wall permeability and translocation of bacteria that is related to the development of pancreatic infection. Nutritional support is a subject of discussion and plays an important role when AP is diagnosed. The concept of “bowel rest” has evolved over the years. Up to now, current evidence-based guidelines for the initial management of AP prefer enteral nutrition (EN) over parenteral nutrition (PN) as a primary therapy. It decreases mortality rate, reduces risk of multiple organ failure, infectious complications and operative interventions. Also, EN is associated with shorter length of hospital stay (LOS), when compared to PN. EN initiated after 48 h of admission has no statistically significant differences in the risk of multiple organ failure, infectious complications or mortality, when compared with PN. Parenteral feeding initiated early (within 24 h of admission) can worsen the outcomes, compared to standard therapy (no artificial nutrition support). Both of nasogastric (NG) and nasojejunal (NJ) routes are equally beneficial in patients with predicted severe or necrotizing pancreatitis requiring enteral tube feeding. NG feeding, compared to NJ feeding, has no statistical significant differences in the incidence of mortality, tracheal aspiration, diarrhea and pain exacerbation. It is being discussed what is the right time to start nutrition support in patients with AP. Early (within 24 h of admission) enteral feeding is highly recommended in order to preserve gut-mucosal barrier function and reduce bacterial translocation. In summary, current guidelines and recent analyses confirm that EN is considered as a “gold standard” in the management in patients with severe AP and should be administered within 24 h of admission.

Keywords: acute pancreatitis; nutrition support; enteral nutrition; nasogastric feeding; nasojejunal feeding

Introduction

Acute pancreatitis (AP) is a potentially lethal disease with increasing incidence and no specific treatment. AP promotes a systemic inflammatory response syndrome [1]. One of the most severe complication of AP is the infection of pancreas, which can lead to mortality rate up to 80%. The occurrence of pancreatic infection is mostly related to the translocation of microorganisms from the intestinal tract. In addition, same enteric pathogens can cause sepsis [2–4]. A lack of enteral feeding predisposes to the increase of intestinal wall permeability and translocation of bacteria due to an atrophy of mucous layer in the intestinal tract [5,6].

The collaboration of the International Association of Pancreatology (IAP) and the American Pancreatic Association (APA) revised acute pancreatitis management guidelines (2002) and updated them in 2012. The guidelines came in 12 topics: a) diagnosis and etiology of AP, b) prognosis and severity prediction, c) imaging, d) fluid therapy, e) intensive care management, f) preventing infectious complications, g) nutritional support, h) biliary tract management, i) indications for intervention in necrotizing pancreatitis, j) timing of intervention, k) intervention strategies and l) timing of cholecystectomy. As mentioned, nutritional support is the subject of discussion and plays an important role when AP is diagnosed. These guidelines suggest that in patients with predicted mild AP oral feeding can be restarted once abdominal pain decreases and inflammatory markers improve (GRADE 2B, strong agreement). Every case of severe AP requires nutritional support. In addition, enteral tube (nasojejunal (NJ) or nasogastric

(NG) route) should be inserted as a primary therapy (GRADE 1B, strong agreement). Both of elemental and polymeric enteral nutrition (EN) formulations are suggested (GRADE 2B, strong agreement). EN is preferred over parenteral nutrition (PN), which should be considered as a second-line therapy, mainly in cases when NJ tube feeding is not tolerated [7,8].

Pathogenic mechanisms of acute pancreatitis

Physiologically AP is characterized by reduction of adenosine triphosphate (ATP) and calcium ions overload in pancreatic acinar cells. In this way intracellular zymogen is activated, which is followed by auto-digestion. Despite the type of initial etiological factor (bile acids, ethanol and fatty acids) of AP, the early phase of AP at cellular level is similar and based on mitochondrial damage, ATP depletion in pancreatic ductal and acinar cells. Calcium overload in the mitochondrial matrix induces opening of the non-specific inner mitochondrial membrane channel called mitochondrial permeability transition pore (MPTP) [9]. It results in mitochondrial depolarization and impaired ATP production. What is more, MPTP opening causes activation of phosphoglycerate mutase family member 5 (PGAM5) which is a mitochondrial executor of necrosis as shown in a figure. Later this process leads to pancreatic necrosis [10–12]. Vervliet with co-authors conducted a research, which showed that galactose feeding can reduce AP markers via restoring ATP levels and calcium ions homeostasis [13]. Theoretically, carbohydrates can improve the status of patient with AP.

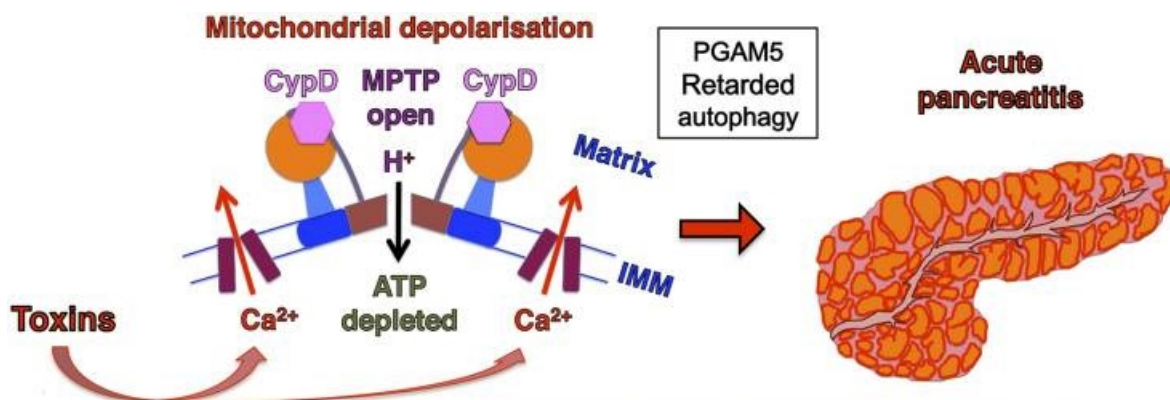


Figure. The role of mitochondrial permeability transition pore in the development of acute pancreatitis [9]. MPTP opening across the IMM causes mitochondrial depolarization and impaired ATP production. It induces PGAM5 activation and subsequent necrosis. ATP – adenosine triphosphate, Ca^{2+} – calcium ions, CypD – cyclophilin D, IMM – inner mitochondrial membrane, MPTP – mitochondrial permeability transition pore, PGAM5 – phosphoglycerate mutase family member 5.

Significance of nutritional management in acute pancreatitis

Patients with AP have been traditionally treated with “bowel rest” for a long time in an effort to avoid the stimulation of inflamed pancreas. It was believed that nutritional therapy has a negative effect on the progression of the AP. However, many current studies showed the benefit of initial enteral feeding.

According to Guideline on Initial Management of AP (2018) by American Gastroenterological Association (AGA) Institute, early oral feeding (within 24 h of admission) is strongly recommended as tolerated, rather than keeping the patient nothing by mouth (NPO) [14]. Results of 11 randomized control trials showed that delayed feeding was associated with 2.5-fold higher risk of interventions for necrosis than early feeding (odds ratio (OR), 2.47; 95% confidence interval (CI), 1.41 - 4.35).

Moreover, multiple organ failure was more common in patients with delayed feeding (OR, 2.00; 95% CI, 0.49 - 8.22) [15]. In meta-analysis based on data of 165 patients, infected pancreatic necrosis was observed in 45% of patients, who received EN after 24 h of admission, and in 19% of those, who received EN within 24 h of admission, while organ failure was diagnosed in 42% and in 16% of cases respectively. The conclusion was that early start of EN (within 24 h of admission) could reduce complications of AP [17]. Recent study of prospectively collected data of 600 patients with AP showed that the mortality rate is 27% in patients with EN and 57% in group of patients without EN [16]. Enteral feeding should be recommended within 24 h of admission in order to preserve gut-mucosal barrier function and reduce bacterial translocation [18].

AGA suggests either NG or NJ route in patients with predicted severe or necrotizing pancreatitis requiring enteral tube feeding [14]. The approach of enteral feeding was revised in Singh with co-authors research: the infectious complications in NG group occurred in 23.1% of cases, in NJ group – 35.9%. Authors came up with conclusion, that early NG feeding was not inferior to NJ feeding in patients with severe AP while pain in refeeding, intestinal permeability and endotoxemia were comparable in both groups [17]. Kumar concluded that EN at a slow infusion was well tolerated through both of NJ and NG routes. Recurrence of pain and outcome measures (hospital discharge, surgery, death) can not be associated neither

with NJ, nor with NG feeding [18]. According to Eatock and co-authors, NG feeding has no disadvantages compared to NJ feeding regarding APACHE II scores, C-reactive protein (CRP) measurement, visual analogue score (VAS) or analgesic medications requirements. Mortality rates are also similar [19]. NG tube is as safe method for feeding purposes as NJ tube. Both of these feeding methods are relevant to use as delayed and especially as early enteral feeding [20]. Chang with colleagues also found, that NG feeding, compared to NJ feeding, had no statistical significant differences in the incidence of mortality, tracheal aspiration, diarrhea, pain exacerbation ($p > 0.05$) [21].

Enteral versus parenteral nutrition

AGA strongly recommends EN rather than PN in patients with AP and inability to feed orally [14]. An adequate nutrition is important in terms of recovery. In patients with AP, EN significantly reduces mortality (relative risk (RR) = 0.5), risk of multiple organ failure (RR = 0.55), systemic infections (RR = 0.39), operative interventions (RR = 0.44), when compared to the patients who receive total PN, especially in cases of severe AP [22,23]. Also, EN reduces length of hospital stay (LOS) by 2.37 days, when compared to total PN [22]. Marik and Zaloga performed a research in which they concluded that there is a lower incidence of infections ($p = 0.004$), less surgical interventions ($p = 0.05$) and reduced LOS (2.9 days) in patients with EN, when compared to patients with PN. On the other hand, there was no statistical significant difference between EN and PN considering mortality and non-infectious complications [24]. Petrov and co-authors performed a systematic review concerning the controversy between EN, PN and no supplementary nutrition in treating AP. It was found, that the frequency of infectious complications was similar between EN and no supplementary nutrition groups, but the EN group was associated with lower mortality rates ($p = 0.01$). Mortality rate was also significantly

lower in PN group than in no supplementary nutrition group ($p = 0.04$). Risk of infectious complications was significantly lower in EN group, when compared with PN group ($p < 0,001$), although there was no significant change in mortality [25]. In other systematic review, Petrov with colleagues determined that EN started within 48 h of admission resulted in significantly lower risk of multiple organ failure (RR = 0.44), pancreatic infectious complications (RR = 0.46) and mortality (RR = 0.46), when compared to PN. On the other hand, EN started after 48 h of admission had no statistically significant differences in the risk of multiple organ failure, infectious complications or mortality, when compared with PN [26]. Early feeding in patients with mild to moderately severe AP also reduces the mean LOS, but measuring patients by this aspect brings more heterogeneity [27]. PN initiated early (within 24 h of admission) can worsen the outcomes, compared to standard therapy (no artificial nutrition support). The supply of PN with parenteral glutamine adjunct can improve the outcomes: it reduces duration of nutrition therapy and decreases LOS, when compared with PN alone [28]. However, unnecessary use of PN is related to increased harm to patients with AP. EN is more preferable feeding method in patients with AP.

Conclusions

AP is a life-threatening disease with a purely symptomatic treatment. Current guidelines and studies confirm that EN is a beneficial and considered as a “gold standard” in the management in patients with severe AP. EN reduces the risk of mortality, multiple organ failure and infectious complications. Both NG and NJ feeding are equally effective and safe enough. Early administration of EN (within 24 h of admission) is highly recommended to decrease the severity of disease and reduce overall complications.

References

1. Poropat G, Giljaca V, Hauser G, Štimac D. Enteral nutrition formulations for acute pancreatitis. *Cochrane Database Syst Rev*. 2015 Mar 23;(3):CD010605.
2. Renner IG, Savage WT, Pantoja JL, Renner VJ. Death due to acute pancreatitis. A retrospective analysis of 405 autopsy cases. *Dig Dis Sci*. 1985 Oct;30(10):1005–18.
3. Medich DS, Lee TK, Melhem MF, Rowe MI, Schraut WH, Lee KK. Pathogenesis of pancreatic sepsis. *Am J Surg*. 1993 Jan;165(1):46–50; discussion 51-2.
4. Runkel NS, Moody FG, Smith GS, Rodriguez LF, LaRocco MT, Miller TA. The role of the gut in the development of sepsis in acute pancreatitis. *J Surg Res*. 1991 Jul;51(1):18–23.
5. Hadfield RJ, Sinclair DG, Houldsworth PE, Evans TW. Effects of enteral and parenteral nutrition on gut mucosal permeability in the critically ill. *Am J Respir Crit Care Med*. 1995 Nov;152(5):1545–8.
6. Deitch EA, Winterton J, Li MA, Berg R. The Gut as a Portal of Entry for Bacteremia Role of Protein Malnutrition. *Ann Surg*. 1987 Jun;205(6):681–92.
7. Working Group IAP/APA Acute Pancreatitis Guidelines. IAP/APA evidence-based guidelines for the management of acute pancreatitis. *Pancreatol*. 2013 Jul;13(4 Suppl 2):e1-15.
8. Mirtallo JM, Forbes A, McClave SA, Jensen GL, Waitzberg DL, Davies AR, et al. International consensus guidelines for nutrition therapy in pancreatitis. *JPEN J Parenter Enteral Nutr*. 2012 May 28;36(3):284–91.
9. Mukherjee R, Mareninova OA, Odinokova I V, Huang W, Murphy J, Chvanov M, et al. Original article: Mechanism of mitochondrial permeability transition pore induction and damage in the pancreas: inhibition prevents acute pancreatitis by protecting production of ATP. *Gut*. 2016;65(8):1333.
10. Hegyi P, Petersen OH. The Exocrine Pancreas: The Acinar-Ductal Tango in Physiology and Pathophysiology. In: *Reviews of physiology, biochemistry and pharmacology*. 2013. p. 1–30.
11. Gukovskaya AS, Pandol SJ, Gukovsky I. New insights into the pathways initiating and driving pancreatitis. *Curr Opin Gastroenterol*. 2016 Sep;32(5):429–35.
12. Huang W, Cash N, Wen L, Szatmary P, Mukherjee R, Armstrong J, et al. Effects of the Mitochondria-Targeted Antioxidant Mitoquinone in Murine Acute Pancreatitis. *Mediators Inflamm*. 2015;2015:1–13.
13. Vervliet T, Yule DI, Bultynck G. Carbohydrate Loading to Combat Acute Pancreatitis. *Trends Biochem Sci*. 2018 Oct;43(10):741–4.
14. Crockett SD, Wani S, Gardner TB, Falck-Ytter Y, Barkun AN, Crockett S, et al. American Gastroenterological Association Institute Guideline on Initial Management of Acute Pancreatitis. *Gastroenterology*. 2018 Mar;154(4):1096–101.
15. Lankisch PG, Apte M, Banks PA. Acute pancreatitis. *Lancet*. 2015 Jul;386(9988):85–96.
16. Párniczky A, Kui B, Szentesi A, Balázs A, Szűcs Á, Mosztbacher D, et al. Prospective, Multicentre, Nationwide Clinical Data from 600 Cases of Acute Pancreatitis. *Einwächter H, editor. PLoS One*. 2016 Oct 31;11(10):e0165309.
17. Singh N, Sharma B, Sharma M, Sachdev V, Bhardwaj P, Mani K, et al. Evaluation of Early Enteral Feeding Through Nasogastric and Nasojejunal Tube in Severe Acute Pancreatitis. *Pancreas*. 2012 Jan;41(1):153–9.
18. 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(5):431–4.
19. Eatock FC, Chong P, Menezes N, Murray L, McKay CJ, Carter CR, et al. A randomized study of early nasogastric versus nasojejunal feeding in severe acute pancreatitis. *Am J Gastroenterol*. 2005 Feb;100(2):432–9.
20. Oláh A, Jr LR. Enteral nutrition in acute pancreatitis: A review of the current evidence. *World J Gastroenterol*. 2014 Nov

- 21;20(43):16123.
21. Chang Y, Fu H, Xiao Y, Liu J. Nasogastric or nasojejunal feeding in predicted severe acute pancreatitis: a meta-analysis. *Crit Care*. 2013 Jun 20;17(3):R118.
22. Al-Omran M, Albalawi ZH, Tashkandi MF, Al-Ansary LA. Enteral versus parenteral nutrition for acute pancreatitis. *Cochrane database Syst Rev*. 2010 Jan 27;20;(1):CD002837.
23. Petrov MS, van Santvoort HC, Besselink MGH, van der Heijden GJMG, Windsor JA, Gooszen HG. Enteral Nutrition and the Risk of Mortality and Infectious Complications in Patients With Severe Acute Pancreatitis. *Arch Surg*. 2008 Nov 17;143(11):1111.
24. Marik PE, Zaloga GP. Meta-analysis of parenteral nutrition versus enteral nutrition in patients with acute pancreatitis. *BMJ*. 2004 Jun 12;328(7453):1407.
25. Petrov MS, Pylypchuk RD, Emelyanov N V. Systematic review: nutritional support in acute pancreatitis. *Aliment Pharmacol Ther*. 2008 Sep 15;28(6):704–12.
26. Petrov MS, Pylypchuk RD, Uchugina AF. A systematic review on the timing of artificial nutrition in acute pancreatitis. *Br J Nutr*. 2008 Nov 19;101(6):787–93.
- Vaughn VM, Shuster D, Rogers MAM, Mann J, Conte ML, Saint S, et al. Early Versus Delayed Feeding in Patients With Acute Pancreatitis: A Systematic Review. *Ann Intern Med*. 2017 Jun 20;166(12):883–92.
- McClave SA, Chang W-K, Dhaliwal R, Heyland DK. Nutrition support in acute pancreatitis: a systematic review of the literature. *JPEN J Parenter Enteral Nutr*. 2006 Mar 5;30(2):143–56.