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CURRENT CONCEPTS IN CLINICAL SURGERY

Evidence-based use of enteral nutrition in acute pancreatitis

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Abstract
Purpose A systematic review was carried out to analyze current evidence-based data on the use of enteral nutrition in the management of acute pancreatitis.
Methods Literature search was performed on "Pubmed" and "Medline" databases to identify articles investigating the role and potential effect of enteral nutrition on the outcome of patients with acute pancreatitis. Relevant data were analyzed from the viewpoints of possible benefits and complications, route and timing of administration, and composition of nutrients.
Results Thirty-two prospective randomized controlled trials and 15 meta-analyses of those were identified and included in this overview. Strong evidence suggests that enteral nutrition significantly reduces mortality rate of severe acute pancreatitis. While both nasogastric and nasojejunal feeding appear to be safe in severe pancreatitis, early low-fat oral diet is possibly beneficial in patients with mild pancreatitis. Since maintenance of the gut barrier function is one of the crucial effects of enteral nutrition, enteral feeding should be commenced within the first 24 h after hospital admission, in order to prevent early bacterial translocation. However, it seems that neither immunonoenhanced nutrients nor probiotic supplementation are able to reduce mortality further, and—therefore—cannot be recommended for patients with acute pancreatitis.
Conclusion Although enteral nutrition is undoubtedly a key component of the management of acute pancreatitis, the exact role of that is needed to be defined yet. In particular, conflicting data from studies on nutrient compositions will require further clarification in the future.

Keywords Acute pancreatitis · Enteral nutrition · Immunonutrition · Bacterial translocation

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It usually takes a decade to accumulate sufficient evidence to substantially change the management of a certain condition. This is the necessary timeframe from the promising initial studies to the development of well-planned, large-scale randomized controlled trials (RCT), which can demonstrate the true value of a method in the end. Enteral nutrition (EN) in acute pancreatitis bears all of the above features without doubt.

In this paper, we systematically review 32 prospective randomized trials published on EN in acute pancreatitis as yet. Benefits, optimal technique, timing of method, composition of nutrient as well as possible complications are discussed in this overview.

Benefits of enteral nutrition

In 1997, the very first prospective randomized trial by McClave et al. demonstrated that nasojejunal feeding is a safe and beneficial method in mild and moderate pancreatitis [1]. Later on, Nakad et al. showed for the first time that nasojejunal feeding is feasible in severe acute pancreatitis (SAP), too [2].

In the following 10 years, 16 RCTs compared parenteral to enteral feeding randomizing 847 patients with acute pancreatitis altogether (Table 1) [1, 3–17]. The majority of

Table 1 RCTs comparing enteral nutrition (EN) vs parenteral nutrition (PN)

Year published	Author (ref)	Patient number	Severity of pancreatitis	Outcome of study
1997	McClave [1]	30	Mild	EN better
1997	Kalfarentzos [3]	38	Severe	EN better
1998	Windsor [4]	34	Mixed	EN better
2000	Powell [5]	27	Severe	NS difference
2001	Paraskeva [6]	23	Severe	EN better
2002	Oláh [7]	89	Mixed	EN better
2002	Abou-Assi [8]	53	Mixed	EN better
2003	Gupta [9]	17	Severe	EN better
2003	Zhao [10]	96	Severe	EN better
2005	Louie [11]	28	Severe	EN better
2006	Petrov [12]	70	Severe	EN better (even in mortality)
2006	Targarona [13]	87	Severe	EN better (even in mortality)
2007	Casas [14]	22	Severe	EN better
2007	Qin [15]	76	Mixed	EN better
2009	Doley [16]	50	Severe	NS difference
2009	Wu [17]	107	Severe	EN better (even in mortality)

studies—11 trials—investigated cases of severe or predicted SAP. While two studies failed to confirm the beneficial effect of nasojejunal feeding [5, 16], all meta-analyses have shown a statistically significant reduction of infectious complications with the use of EN [18–21]. Therefore, EN is established as a key component in the management of SAP [22]. This is further confirmed by the Guidelines of European Society of Parenteral and Enteral Nutrition on Pancreas, which claims that nasojejunal feeding is an essential component of the management of acute pancreatitis, which should be supplemented by parenteral nutrition (PN) [23]. Recently, it is common to start with a standard formula and a peptide-based formula can also be applied if the former is not tolerated. There are no specific contraindications for EN. It can be performed successfully and safely even in SAP with complications, like fistulas, ascites, or pseudocysts.

PN has no demonstrable benefit in mild or severe pancreatitis. The role of PN is limited to conditions such as serious ileus, when EN is restricted by paralysis. Nevertheless, enteral feeding with reduced amounts is suggested even in these circumstances, too, to provide the beneficial effects of that.

Since authors applied different standards for selecting approximately five-to-seven studies for inclusion in their meta-analyses, each had several limitations and the studies were relatively poor quality after all. None of them were blinded and almost all studies were based on relatively few patients, inclusion/exclusion criteria were rather variable and severity of acute pancreatitis was quite different across the papers. Furthermore, all of the meta-analyses were underpowered, and the differences were not always statistically significant. Although the meta-analyses published by Marik and Zaloga as well as McClave et al. [18, 19] demonstrated that the use of EN was associated with a significant reduction in infectious morbidity, hospital length of stay, and a trend toward reduced organ failure, these failed to confirm that enteral feeding could influence outcome in mortality. Two years later, two further meta-analyses were published independently, and the authors' intention to keep stricter methodological criteria resulted in more reliable reviews. Petrov et al. [3] included only trials with Jadad scores 3 and it involved patients with predicted SAP exclusively comparing more homogenous subgroups therefore. Altogether 202 patients were randomized in this study and the mortality rate in the EN group was 4% (4/95), while in the PN group 15.9% (17/107), which was statistically significant (RR, 0.32; 95% CI, 0.11–0.98; $p=0.03$). Cao et al. [21] analyzed six RCTs involving 224 patients and demonstrated a statistically significant decrease in mortality (OR 0.251; 95% CI, 0.095–0.666, $p=0.005$) and in multiple organ failure (MOF) (OR 0.306; 95% CI, 0.128–10.736) in patients receiving enteral feeding.

Although selection of RCTs almost always involve an element of subjective judgment, data accumulated so far demonstrate strong evidence of the benefits of enteral over parenteral nutrition in SAP in terms of statistically significant reductions in the risk of mortality. In spite of previous results, three prospective randomized trials confirmed currently that jejunal feeding can reduce mortality rate [12, 13, 17].

Complications of enteral nutrition

One of the most common complications of enteral feeding is diarrhea, which can be detected up to 20–30% of patients. Diarrhea may deteriorate volume depletion and dehydration resulting in further weakening of the general condition of patients who are very sick anyway and usually need intensive care management. Wide-spectrum antibiotics, which are frequently used in SAP, can contribute to the development of diarrhea as a significant additional factor [24]. It is possible that fiber EN formulas have some preventive effect against diarrhea though [25]. This observation was supported by a recently published study by Karakan et al. who showed that prebiotic fiber supplementation reduced complication rate in acute pancreatitis compared to standard enteral solution [26].

A meta-analysis published by Petrov and Zagainov, which was based on six RCTs comparing EN with PN, showed that enteral nutrition statistically significantly reduced the risk of hyperglycemia (RR, 0.53; 95% CI 0.29–0.98; p=0.04) as well as insulin requirement (RR, 0.41; 95% CI 0.24–0.70; p=0.001), so it is associated with better blood glucose control in SAP [27].

The facts that EN is most likely superior to parenteral nutrition in preventing septic complications of acute pancreatitis, it may also eliminate some complications of PN (catheter sepsis, pneumothorax, and thrombosis), and costs only 15% of the cost of TPN, make it an increasingly accepted treatment modality.

Route of enteral nutrition

Recently, some questioned whether nasojejunal feeding is the only proper route of enteral feeding in acute pancreatitis. The main disadvantage of nasojejunal feeding that it requires an endoscopist or radiologist to place the tube in, which may cause some delay in starting early enteral feeding. It is particularly difficult to organize nasojejunal feeding in out-of-hours, or for patients who repeatedly remove the feeding tube accidentally or intentionally. However, placement of a nasogastric tube is a simple routine procedure which can certainly facilitate to commence early enteral feeding. Taking into account the frequent rate of nasojejunal tube dislocation, nasogastric feeding seems to be the most feasible option in clinical practice. Conversely, arguments against nasogastric feeding are based on the effect of stimulating pancreatic secretion and gastric emptying problems due to paralysis.

Eatock et al. investigated this first in a prospective pilot study [28] and showed that nasogastric feeding is safe, well-tolerated, and does not cause clinical or biochemical deterioration. This was followed by two RCTs comparing nasogastric and nasojejunal feeding in 50 and 312 patients, respectively [29, 30]. Both studies concluded that nasogastric nutrition at a slow infusion was well tolerated, and there was no difference in the outcome measures (discharge, surgery, and mortality rate) between the two groups.

Furthermore, a recently published RCT compared early nasogastric feeding with total PN including 50 patients with predicted SAP [31]. In this study the authors found that total complications and pulmonary complications were significantly more frequent in EN patients, although these complications were diagnosed dominantly within the first 3 days.

Two meta-analyses were published on the three RCTs (and the first pilot study) involving altogether 131 patients [32, 33]. Neither of them showed any significant differences in mortality rate in SAP between nasogastric and conventional routes, or in length of hospital stay, infectious complication rate, and MOF. Based on these very recent studies, early nasogastric feeding appears safe and well tolerated in about 80% of the patients with predicted SAP. However, since the evidence is poor in quantity, further well-designed and large-scale RCTs required before recommendation to clinical practice.

If we accept that current evidence suggests that early enteral feeding is more beneficial than fasting in SAP, it seems reasonable to apply this hypothesis for mild pancreatitis, too. In these cases the question remains if it is necessary at all to use enteral tube feeding or just commence oral diet within 24 h.

The first pilot study about early oral feeding was published by Pupelis et al. in 2006 [34]. Twenty-nine patients with acute pancreatitis were commenced on oral diet on average of day 3 after hospital admission. This study, including 10 severe cases (APACHE II score ≥8) suggests that oral feeding could be a safe and effective alternative of enteral nutrition. Erckerwall et al. published the first RCT involving 60 patients a year later, which compared the efficacy and feasibility of immediate oral feeding and traditional fasting in patients with mild acute pancreatitis [35]. There were no signs of exacerbation of the disease process seen in terms of significant differences between treatment groups for amylase or systemic inflammatory response. This trial proved that the immediate oral feeding is feasible and safe in mild acute pancreatitis.

On the bases of the available prognostic scoring systems and biochemical markers of the first 24–48 h it is still difficult to predict with absolute certainty whether the pancreatitis is mild or severe [36]. However, two recently published RCTs suggested that it is not necessary to keep the patient on liquid diet after acute mild pancreatitis. Jacobson et al. randomized 121 patients [37] and Sathiaraj et al. randomized 101 patients [38] with mild pancreatitis to clear liquid diet or low-fat solid/soft diet. None of the studies revealed any detrimental effect applying solid diet;

moreover, solid diet was associated with shorter length of hospital stay in the latter trial.

On the grounds of the above data it is reasonable to accept that patients with proved mild acute pancreatitis should be started on a low-fat oral diet [39].

Timing of enteral nutrition

Another key issue that needs to be discussed is the time of commencement of enteral nutrition and the influence of that on disease outcome. If we accept the hypothesis that bacterial translocation can be prevented by the maintenance of intestinal barrier function with jejunal feeding, then it is reasonable to launch this mechanism as early as possible. Importantly, the so-called therapeutic window is very small: bacterial translocation and overgrowth of pathogens are already detectable in the very early phase of acute pancreatitis. Although the exact pathophysiological mechanism of bacterial infection has yet to be determined, it seems unequivocal that it is a significant risk factor for pancreatic necrosis. A multicentric study on enteral feeding published by Besselink et al. demonstrated that bacteremia can be detected as early as day 7, while infected necrosis is proved on average on day 26 after hospital admission [40]. Since the development of organ failure frequently precedes bacterial infection, the hypothesis that early bacterial invasion aggravates the SIRS making the patient even more susceptible to organ failures is sensible.

Considering the above it is evident that prophylactic strategies (either EN or antibiotic prophylaxis) aiming to prevent infectious complications should focus on early intervention [40].

A systematic review of RCTs published by Petrov et al. on EN vs. PN nutrition in patients with acute pancreatitis investigated whether timing of nutrition had an influence on the risk of development of MOF, pancreatic infectious complications, and mortality [41]. Eleven RCTs met the inclusion criteria and were analyzed. This meta-analysis showed a significant risk reduction in all the three categories with the use of EN over PN. However, these benefits were significant only if nutrition was administered within the first 48 h of admission. After 48 h it did not result in a statistically significant reduction in the risks of MOF, pancreatic infectious complications, and mortality in comparison with PN.

In summary, there are sufficient evidence-based data available which suggest that EN should begin within 24 h after hospital admission [39].

Composition of enteral nutrition

The next question relates to the optimal formulation of the EN. Composition of enteral formulas can be classified into three basic categories: polymeric, (semi)elemental, and immunoenhanced. While polymeric nutrient comprises non-hydrolyzed proteins, maltodextrins, oligofructosaccharides and long-chain triglycerides, (semi)elemental contains oligopeptides or amino-acids, maltodextrins, and medium- and long-chain triglycerides. Theoretically, semielemental nutrients stimulate pancreatic secretion in less extent, but enhance bowel absorption and those are tolerated better by patients than polymeric ones [42]. Immunoenhanced nutrients involve substrates which modulate the activity of the immune system. Various immunonutrition formulas fall in this category, such as glutamine, arginine, and omega-3 fatty acids as well as enteral nutrients supplemented by probiotics. Table 2 summarizes RCTs on enteral nutrient supplements.

Recently, a meta-analysis compared (semi)elemental and polymeric formulations indirectly, using 10 RCTs where PN was the reference treatment [43]. The authors, however, could not demonstrate statistically significant difference with regard to tolerance of feeding, infectious complications, or mortality in between two EN formulas (RR 0.62; 95% CI 0.10–3.97; $p=0.611$).

Enteral feeds with immune-enhancing ingredients such as glutamine, arginine, nucleotides, and omega-3 fatty acids that modulate the host immune and inflammatory response have recently attracted great interest [44]. There are promising experimental studies, where supplementation of enteral feed with glutamine or omega-3 fatty acids could reduce the severity of experimental acute pancreatitis models [45, 46]. An experimental study using emodin, which is a traditional Chinese purgative resin restoring intestinal mucosal function, demonstrated similar benefit in early nutrition of acute pancreatitis [47].

Unfortunately, promising animal studies could not have been reproduced in clinical settings yet. Altogether, four RCTs were published on the subject [48–51]. Although immunonutrition was shown to have some beneficial effects—shortened length of hospital stay [49], reduced gut permeability, and decreased plasma endotoxin level [51]—no significant differences were found in clinical outcome.

These published trials are too few to make any treatment recommendation, and so far the role of glutamine, arginine, and omega-3 fatty acids in acute pancreatitis are uncertain. A recently published meta-analysis [52] based on three RCTs [48–50] demonstrated clearly that immunonutrition compared with standard EN was not associated with the significantly reduced risk of total infectious complications (RR 0.82; 95% CI 0.44–1.53; $p=0.53$) and mortality (RR 0.64; 95% CI 0.20–2.07; $p=0.46$).

Adding probiotics to enteral nutrients seemed to be a promising alternative for the future. Some probiotics (living bacteria) and prebiotics (fibers) are able to stabilize the intestinal barrier and prevent bacterial translocation. Lactic-

Table 2 RCTs using supplementation of enteral nutrition

Year published	Author (ref)	Patient number	Severity of pancreatitis	Study of objectives	Outcome of study
2001	Hallay [48]	16	Mixed	EN vs EIN	NS difference
2002	Oláh [60]	45	Mixed	EN vs EN+Prob	EN+Prob better
2005	Lasztity [49]	28	Mixed	EN vs EIN	EIN: shorter LOS
2006	Pearce [50]	31	Severe	EN vs EIN	NS difference
2007	Oláh [61]	62	Severe	EN vs EN+Prob	NS difference
2007	Karakan [26]	30	Severe	EN vs EN+Preb	EN+Preb: shorter LOS
2007	Qin [15]	76	Mixed	PN vs EN+Prob	EN+Prob better
2007	Li [62]	25	Unknown	EN vs EN+Prob	EN+Prob better
2008	Huang [51]	32	Severe	EN vs EIN	NS difference
2008	Besselink [54]	296	Severe	EN vs EN+Prob	NS difference (higher mortality in study group)

EN enteral nutrition, *EIN* enteral immunonutrition, *Prob*. probiotics, *Preb*. prebiotics, *LOS* length of hospital stay

acid-producing bacteria were shown to have significant anti-infective and immunomodulatory properties. In addition, they can also prevent pathogenic bacteria to adhere on the gut mucosa via their strong affinity to enterocytes. Their complex bacteriostatic and bactericidal effects are mainly due to the production of lactic acid and antimicrobial peptides.

In a recent review, 15 clinical studies were analyzed using probiotics or synbiotics [53]. In 10 of the 15 studies, probiotics significantly reduced bacterial infection rate compared to control groups. Two studies demonstrated a clear positive trend, but no statistical significance was detected. Two further trials could not confirm the above findings at all. There was only one study which showed higher mortality rate in the probiotic group compared to control patients. This was the only multicentric study that revealed any serious side-effect of probiotics [54]. Based on RCTs published so far application of synbiotics in the perioperative period of liver, pancreas surgery, or in polytraumatized patients seems unequivocally beneficial.

The excellent results of using probiotics in experimental pancreatitis models were promising initially [55–59]. Mangiante et al. significantly reduced infected necrosis rate using *Lactobacillus plantarum* [55], and a study by van Minnen et al. from Utrecht demonstrated that probiotics reduced significantly even the late-phase mortality [58].

Six RCTs have been published on probiotic and prebiotic agents as yet. Karakan et al. investigated enteral feeding with or without prebiotics, and they found shorter length of hospital stay if patients received prebiotics, too [26]. Quin et al. investigated 76 patients with acute pancreatitis and detected significant differences and better clinical outcomes in the group of patients, where EN was supplemented with *L. plantarum*—however, control patients were fed parenterally [15].

Four RCTs were published so far comparing enteral feeding supplemented by probiotics (synbitiotics) to simple enteral feeding. In clinical studies, the effect of lactic-acid-producing bacteria in acute pancreatitis has been investigated in our department first time [60]. Based on the analysis of 45 patients with acute pancreatitis we found that the rate of pancreatic infectious complications were significantly less frequent in patients who received live *L. plantarum*. However, mortality was not significantly different between the two groups. Next, we analyzed a combination formula called "Synbiotic 2000" in a double-blind RCT in patients with predicted severe pancreatitis exclusively [61]. Altogether, 62 patients with SAP completed this study. However, the encouraging results of our previous study were not repeated on this occasion. While a decreasing trend was detected in the rate of MOF and septic complications in the study group, these differences did not reach statistical significance. In the same year, a further RCT was published on the subject, but the results of that could not be considered though due to very low patient number and poor quality of the study [62].

The first and, to date, the only surgical trial with serious adverse events of synbiotics was published by the Dutch Acute Pancreatitis Study Group [54]. In this multicenter, double-blind, placebo-controlled trial (PROPATRIA trial), altogether, 298 patients with predicted SAP were randomly assigned within 72 h of onset to receive a multispecies probiotic preparation (Ecologic 641) or placebo with fiber-enriched EN for 28 days. The rate of infectious complications was comparable in both groups, but the mortality rate was even higher in the synbiotic group (16% vs. 6%). Bowel ischemia—which was the main cause of death—occurred in 6% in the synbiotic group versus none in the placebo group. Whether there is an association between bowel ischemia and the probiotic combination is unclear.

However, this synbiotic composition should not be used in critically ill patients in the future [53].

Nevertheless, a meta-analysis of these four RCTs demonstrated that enteral feeding with probiotic could not reduce the infected necrosis [63].

It may be difficult to provide an exact explanation for the significantly worse results of the PROPATRIA study; nevertheless, there were certainly differences in etiology and patient characteristics between this one and our study. The median age of patients was 15 years older in the PROPATRIA study. Furthermore, biliary pancreatitis was a much more common etiology as well as the Imrie score of acute pancreatitis was significantly higher in this study. In addition to this, probiotics used in the PROPATRIA trial was largely different than ours, since it contained Bifidobacteria, as well, and a much higher germ count (6×10^{10}). The period of feeding was also different from our study, it lasted for 4 weeks in each patient and it was considered to be relatively aggressive when feeding was continued on pressor agents in some patients, too. Nonetheless, PROPATRIA is a remarkably well-designed study. There was no statistically significant difference found in between the two patient groups compared; however, organ failures as well as multiorgan failures were more common in the probiotic group (13.2% vs. 4.9%, and 3.0% vs. 0.7%, respectively).

A potential explanation of the higher rate of small bowel necrosis could be that splanchnic hypoperfusion, reduced nutrient absorption, fermentation, and gas production led to increased intraluminal pressure and intramural bowel ischemia [64]. Although probiotics can decrease bacterial translocation in a healthy environment, paradoxically they may be associated with an increase in enterocyte damage and bacterial translocation in a patient with organ failure [65].

However, probiotics cannot be recommended in the management of acute pancreatitis based on the available evidence-based data at present [66, 67].

In summary, current evidence unequivocally confirm that EN is beneficial in the treatment of SAP. It reduces mortality rate, infectious complications as well as MOF, possibly by maintaining the gut barrier function. Furthermore, it seems also evident that early administration of EN is advisable, which may prevent bacterial translocation from the gut that occur in the very early phase of pancreatitis. In addition to this, EN provides better glucose control than PN, it may also eliminate some complications of the latter and—last but not least—EN costs much less. As far as route of EN is concerned, nasogastric tube feeding is likely to be equally as effective as nasojejunal in SAP, although further RCTs should be carried out to confirm this in the future. However, current evidence does not support the application of immunoenhanced nutrients and probiotic supplements, and therefore none of them can be recommended in the management of acute pancreatitis at present.

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