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Advanced enteral therapy in acute pancreatitis: Is there a room for immunonutrition? A meta-analysis

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ABSTRACT

Background: It is believed that certain nutrients such as glutamine, arginine and omega-3 fatty acids may play a significant role in metabolic, inflammatory, and immune processes in acute pancreatitis. The present systematic review aimed to define whether the addition of these substances to enteral nutrition provides any clinical benefit over standard enteral formulas in patients with acute pancreatitis.

Methods: A computerized search on electronic databases (Cochrane Central Register of Controlled Trials, EMBASE and MEDLINE) and manual search of the abstracts of major gastroenterological meetings (UEGW, DDW) were undertaken. The studied outcomes were total infectious complication, in-hospital mortality and length of hospital stay. The data were meta-analyzed using a random-effects model.

Results: A total of three randomized controlled trials satisfied the inclusion criteria. When compared with standard enteral nutrition, immunonutrition was not associated with the significantly reduced risk of total infectious complications (risk ratio 0.82; 95% confidence interval 0.44–1.53; $P = 0.53$) and death (risk ratio 0.64; 95% confidence interval 0.20–2.07; $P = 0.46$). Mean difference in length of hospital stay between two groups was not significant ($P = 0.80$).

Conclusions: There is no evidence that enteral nutrition supplemented with glutamine, arginine and/or omega-3 fatty acids, in comparison with standard enteral nutrition, has any beneficial effect on infectious complications, mortality or length of hospital stay in acute pancreatitis. The pursuit of new compositions of enteral formulations in this category of patients may be advocated.

1. Introduction

During the last decade, advancements in the nutritional management of patients with acute pancreatitis have established enteral feeding as an essential element of the treatment.[1–3] Because the gastrointestinal tract is the largest immune organ in the body, containing around 65% of immune tissue overall, the use of immune-enhanced enteral formulations may further amplify the beneficial effect of intra-luminal therapy in acute pancreatitis.[4,5] Of the various nutrients that thought to have immune-enhancing properties, glutamine, arginine, omega-3 fatty acids and nucleotides have been advocated for use both separately and in combined preparations.[6,7] The feeding formulas on the basis of these substances had positive effects on the rate of infectious complications in different experimental settings, including acute pancreatitis.[8,9]

There was also a number of clinical studies, which suggested that immunonutrition may have a potential to modify the inflammatory response. The results of randomized controlled trials (RCTs) that compared the use of immune-enhanced

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and standard enteral formulas were statistically aggregated in three meta-analyses.[10–12] The most recent and comprehensive systematic review of 2419 patients from 22 RCTs found that the effect of immune-enhancing enteral nutrition may depend on the subset of the analyzed patients.[12] In particular, there was no effect of immunonutrition on the risk of infectious complications or death within the subgroup of critically ill patients only. At the same time, administration of high-arginine-content formulas (12–15 g/L) in a combined group of critically ill and elective surgery patients were associated with a statistically significant reduction in infectious complications and a trend to a lower mortality in comparison with other immune-enhancing diets. In its turn, the use of high- and low-arginine-content formulas was associated with a significantly lower risk of infectious complications in elective surgery patients when compared with critically ill patients.

However, due to the fact that patients with acute pancreatitis may be referred to both the critically ill group and the elective surgery group, the real clinical applicability of ''immunoactive'' enteral formulations in patients with acute pancreatitis is still unknown. Thereby, our aim is to define a clinical effect of immunonutrition in the setting of acute pancreatitis on the basis of reviewing of all RCTs on immune-enhanced versus standard enteral nutrition.

2. Methods

2.1. Study identification

A computerized literature search on three databases (MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials) from January 1, 1990 to December 1, 2007 was performed. The search strategy for MEDLINE was ''acute pancreatitis'' [Title/Abstract] AND (''enteral nutrition'' [Title/Abstract] OR ''enteral feeding'' [Title/Abstract]) OR (''glutamine'' [Title/Abstract] OR ''arginine'' [Title/Abstract] OR ''omega-3 fatty acids'' [Title/Abstract]) OR (''nucleotides'' [Title/Abstract]) OR (''immunonutrition'' [Title/Abstract]). The search strategy for EMBASE was ''acute pancreatitis'' AND (''immunonutrition'' OR ''immune-enhanced formulas'') AND [humans]/lim. The search strategy in Cochrane library was ''acute pancreatitis'' AND (''enteral nutrition'' OR ''enteral feeding'') AND (''immunonutrition'' OR ''immune-enhanced formulas'').

An additional search was done using the references of the original articles and abstracts of major gastroenterological meetings (DDW, UEGW) from 2001 to 2007. No language restrictions were applied.

2.2. Study selection criteria

The criteria for trial inclusion were as follows:

(1) The target population consisted of patients with acute pancreatitis.
(2) RCT was included if the intervention arm received enterally a feed supplemented with glutamine and/or arginine and/or omega-3 fatty acids and/or nucleotides (immunonutrition); the control arm had to receive an enteral feeding without above-mentioned supplements (standard enteral nutrition).
(3) Clinical outcome measures were total infectious complication, in-hospital mortality and/or length of hospital stay.

2.3. Data acquisition and quality assessment

Two authors independently applied the inclusion criteria to the relevant publications and abstracted the data from the articles. Methodological quality of included studies was assessed using a previously published quality score.[12] It consists of nine parameters (randomization, analysis, blinding, patient selection, comparability of groups at baseline, extent of follow-up, treatment protocol, cointerventions and outcomes) with quality score range from 0 to 14 points.

2.4. Statistical analysis

The data analysis was performed using the meta-analysis software (Bax L., Yu L.M., Ikeda N., Tsuruta N., Moons K.G.M. MIX: Comprehensive Free Software for Meta-analysis of Causal Research Data – Version 1.51. 2006). Data on infectious complication and mortality were combined to determine risk ratio (RR), with its 95% confidence interval (CI). The continuous outcomes of hospital stay were combined using the mean difference method. The presence of heterogeneity was assessed using I^2 measure, with $I^2 > 0.2$ indicating significant heterogeneity. Irrespective of the degree of heterogeneity of effect among the included trials, a random-effects model was used. Possible biases were explored by funnel plots.

3. Results

A total of 208 publications were initially retrieved, from which 27 RCTs concerning enteral nutrition in acute pancreatitis were identified Fig. 1. Twenty-four trials were excluded for the following reasons:

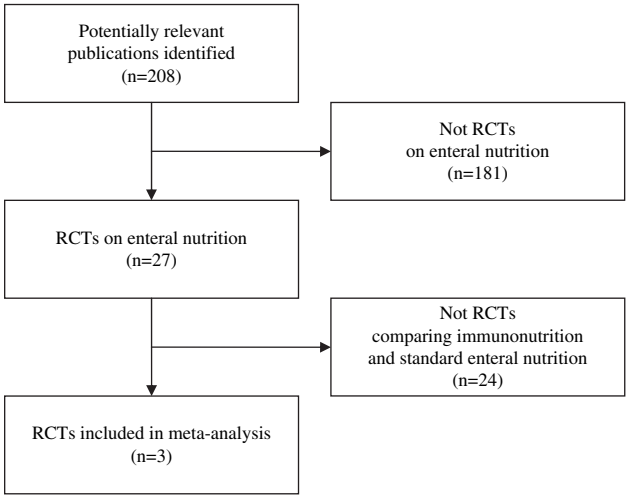

Fig. 1 – Identification of eligible randomized controlled trials.

Table 1 – Summary of study characteristics for the included trials

Study	Methodological quality of studies[a]	Severity (score)[b]	Mild:severe acute pancreatitis, patients[b]	Supplemented nutrients	Sitting of tube	Feeding start	Duration of nutrition, days
Hallay et al.[37]	6	3.6 (3–5)/3.9 (3–6) (Ranson)	0:11/0:8	Glutamine, arginine	Endoscopic	<24 h of admission	5
Lasztity et al.[38]	8	8 (5–12)/7.6 (5–13) (APACHE II)	11:3/11:3	Omega-3 fatty acids	Endoscopic	<24 h of admission	10.6 ± 6.7/ 17.6 ± 10.5[b]
Pearce et al.[39]	11	9 (8–19)/9.5 (8–16) (APACHE II)	0:15/0:16	Glutamine, arginine, omega-3 fatty acids	Blind (Bengmark's tube)[c]	<72 h after onset	3–15

a The range of the quality score is 0–14.
b Immunonutrition/standard enteral nutrition.
c Three patients had endoscopic placement of a nasojejunal tube and one had a needle jejunostomy at laparotomy.

Table 2 – Summary of clinical outcomes for the included trials

Study	Number of patients[a]	Mortality[a]	Total infectious complications[a]	Length of stay, days[a]
Hallay et al.[37]	11/8	3/2	2/3	Not stated
Lasztity et al.[38]	14/14	1/2	5/7	13.0 ± 7.7/19.3 ± 7.2
Pearce et al.[39]	15/16	0/3	5/4	19.1 ± 14.4/13.4 ± 11.1

a Immunonutrition/standard enteral nutrition.

(1) nasojejunal feeding was compared with nasogastric[13,14];
(2) oral feeding was compared with nasojejunal[15];
(3) polymeric and semi-elemental enteral formulas were compared[16];
(4) effect of prebiotics and probiotics was evaluated[17–19];
(5) enteral nutrition was compared with parenteral nutrition[20–33] and nil-per-os regimen[34];
(6) combination of enteral and parenteral nutrition was compared with parenteral nutrition.[35,36]

Eventually, three RCTs met all the inclusion criteria.[37–39] Overall, 78 patients were enrolled in the studies, of which 40 were allocated to the immunonutrition group, whereas 38 were randomized to standard enteral nutrition. Table 1 presents the study characteristics for the included trials. Formal assessment of the funnel plot did not yield any evidence of a publication bias.

All RCTs reported the number of total infectious complications (Table 2). A total of 26 patients suffered any infectious complication, 12 of 40 (30%) in the immunonutrition group and 14 of 38 (37%) in the standard enteral nutrition group. As it is depicted on Fig. 2, the use of immuno-enriched nutritional formula was not associated with a significant reduction in the risk of infectious complications (RR 0.82; 95% CI 0.44 to 1.53; $P = 0.53$). The I^2 measure for heterogeneity was 0.

Eleven of 78 (14%) patients died, four in the immunonutrition group and seven in the standard enteral nutrition group (Table 2). When the three included trials presenting data on mortality were aggregated, no statistically significant mortality benefit was evident for the use of immunonutrition (RR 0.64; 95% CI 0.20–2.07; $P = 0.46$; Fig. 3). There was no significant heterogeneity between trials ($I^2 = 0$).

Two studies reported on length of hospital stay (Table 2). Administration of immunonutrition was not associated with

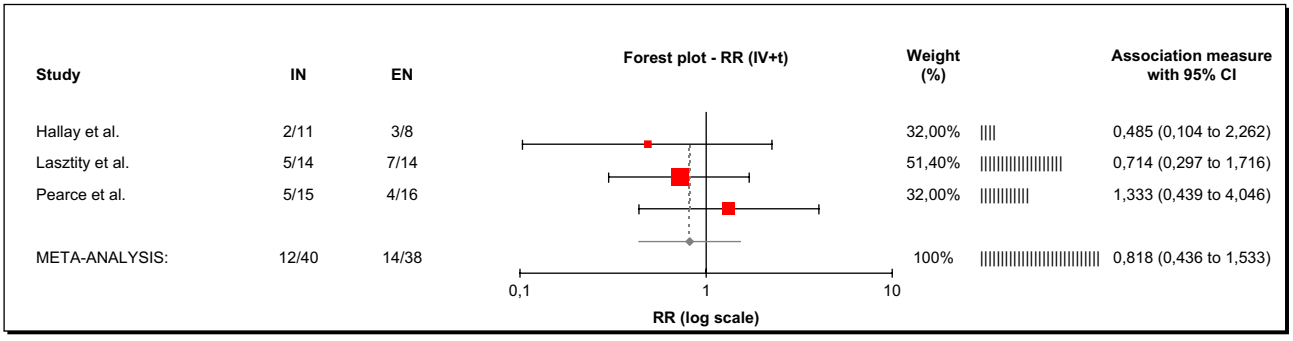

Fig. 2 – Random-effects model of relative risk of infectious complications associated with immunonutrition in comparison with standard enteral nutrition.

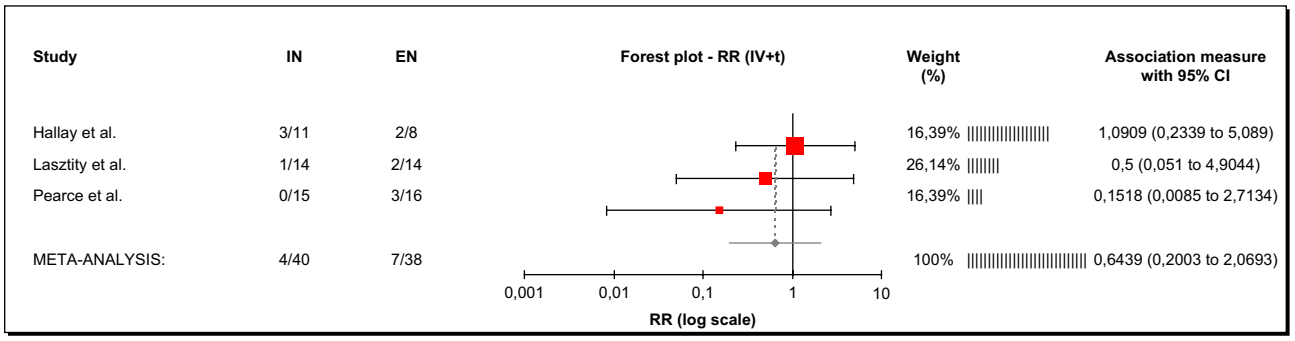

Fig. 3 – Random-effects model of relative risk of death associated with immunonutrition in comparison with standard enteral nutrition.

a significant reduction in length of hospital stay (mean difference −0.87; 95% CI −12.57 to 10.84; $P = 0.80$). There was a significant heterogeneity between studies ($I^2 = 57.2$).

4. Discussion

This systematic review failed to show any clinical beneficial effect of enteral nutrition supplemented with glutamine, arginine and/or omega-3 fatty acids, when compared with standard enteral nutrition, in patients with acute pancreatitis.

On the surface, as the sample size of the present meta-analysis is fairly small, it seems that no definitive conclusions can be drawn from it. Nevertheless, a conducted meta-analysis of critically ill and elective surgery patients,[12] which was greater in terms of study population, found a statistically significant benefit of immunonutrition (reduced risk of infectious complications) only in the subgroup of patients who received high-arginine-content formulas. However, excessive supplementing of arginine could potentially lead to a pancreas damaging effect,[38,40] probably due to the excessive production of nitric oxide.[41,42] It is also known that administration of omega-3 fatty acids decreases antioxidant capacity.[43] Nevertheless, the relevance of these experimental observations is difficult to evaluate in clinical setting because immunonutrition is usually administered in a compound and it is hard to ascribe a beneficial or harmful effect of immunonutritional formulation to any single immune-enhancing agent. Moreover, it was shown that a single ''immunoactive'' substance (such as arginine or omega-3 fatty acids) can be associated with opposite effects on systemic inflammation.[44]

Influence of nutrition on markers of systemic inflammatory response syndrome (SIRS) in acute pancreatitis was investigated in a number of RCTs. By demonstrating a significant reduction in serum C-reactive protein (CRP) concentration and number of patients with SIRS before and after nutrition in the enterally fed over parenterally fed patients with severe acute pancreatitis, the early RCT from the UK[23] raised an optimism regarding the expeditious influence of enteral nutrients on the inflammatory cascade and immune defense mechanisms in acute pancreatitis. However, the subsequent RCTs showed that enteral nutrition did not significantly change CRP level in comparison both with parenteral nutrition[29,30,32,33] and with nil-per-os regimen.[34] Moreover, CRP concentration was significantly lower by day 3 of feeding in the standard enteral nutrition group when compared to the immunonutrition group.[39] Similarly, enteral over parenteral nutrition,[33] enteral feeding over fasting,[34] immunonutrition over standard enteral feeding[39] did not affect the level of cytokines. In part, it might be due to the fact that enteral nutrition increases mesenteric lymph flow, permitting toxic factors in mesenteric lymph to maintain an inflammatory response while bypassing the portal circulation and liver.[45]

It should be also realized that immunonutrition has an intrinsic limitation in the clinical setting because enteral feeding usually requires a progressive increase of the infusion rate during the first 2–3 days to be tolerated while reaching the target rate. Thereby, the amount of immune-enhancing substrates given in the first days might be insufficient to produce a prompt modulation of the host response. At the same time, it is known that the first 48–72 h period after the onset of acute pancreatitis (so-called ''therapeutic window'') is the best period for prevention/attenuation of the inflammatory response and applying treatment modalities.[46] Another marked drawback is the cost-effectiveness of ''immunoactive'' formulas, which is substantially higher than that of a standard enteral diet.[47] All things considered, even though a formal interpretation of the results of our systematic review may require a new large-scale RCT on immunonutrition, a prudent insight would recommend to investigate another substances which may modify a standard enteral feed and potentially have a beneficial clinical implication in acute pancreatitis.

In conclusion, it seems that the addition of glutamine, arginine and/or omega-3 fatty acids to the enteral feed has no beneficial impact on the course of acute pancreatitis. At the same time, the continued refinement of intra-luminal therapy may potentially have an exciting clinical implication in acute pancreatitis through preserving the innate gut barrier function and boosting the immune system.

Conflict of interest
All authors have no conflict of interests.

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Ethical approval
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