Enteral Nutrition and the Risk of Mortality and Infectious Complications in Patients With Severe Acute Pancreatitis

A Meta-analysis of Randomized Trials

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Objective: To compare the effect of enteral vs parenteral nutrition in patients with severe acute pancreatitis for clinically relevant outcomes.

Data Sources: A computerized literature search was performed in the MEDLINE, EMBASE, and Cochrane databases for articles published from January 1, 1966, until December 15, 2006.

Study Selection: From 253 publications screened, 5 randomized controlled trials comparing enteral and parenteral nutrition in patients with predicted severe acute pancreatitis met the inclusion criteria.

Data Extraction: Information on study design, patient characteristics, and acute pancreatitis outcomes were independently extracted by two of us using a standardized protocol.

Data Synthesis: A meta-analysis of randomized controlled trials was performed using a random-effects model. Enteral feeding reduced the risk of infectious complications (relative risk, 0.47; 95% confidence interval, 0.28-0.77; \( P < .001 \)), pancreatic infections (0.48; 0.26-0.91; \( P = .02 \)), and mortality (0.32; 0.11-0.98; \( P = .03 \)). The risk reduction for organ failure was not statistically significant (0.67; 0.30-1.52; \( P = .34 \)).

Conclusions: Enteral nutrition results in clinically relevant and statistically significant risk reduction for infectious complications, pancreatic infections, and mortality in patients with predicted severe acute pancreatitis.


Infectious complications occur in approximately 10% of patients with acute pancreatitis and account for at least 50% of the mortality in these patients.\(^1\)\(^2\) Animal and human studies\(^4\)\(^-\)\(^6\) suggest that a loss of the gut barrier function is instrumental in the local and systemic infectious complications associated with a severe course of disease. Attempts to reduce the failure of the gut barrier, to potentially decrease the incidence of infectious complications of acute pancreatitis, have largely consisted of enteral nutrition (EN).\(^7\)\(^8\) The protective role of EN, compared with parenteral nutritional (PN), in maintaining the integrity of the gut barrier has been demonstrated in a rat model of acute pancreatitis.\(^9\) The EN group was found to have significantly less bacterial translocation and a lower blood endotoxin level than the PN group.

These experimental findings, however, have not been convincingly supported by results from randomized clinical trials (RCTs). Thereby, on the basis of previous meta-analyses\(^10\)\(^-\)\(^11\) the latest guidelines of the American College of Gastroenterology state that “it is reasonable to conclude that enteral feeding is safer and less expensive than PN, but there is not yet convincing findings that there are major improvements in morbidity and mortality of acute pancreatitis.”\(^12\)\(^{p2388}\) However, the previous meta-analyses were not stratified according to the severity of disease and included 46% to 58% patients with mild acute pancreatitis. This limits the conclusions that can be drawn because it is believed that only patients with severe acute pancreatitis need nutritional support.\(^12\)\(^-\)\(^14\) Moreover, the most comprehensive meta-analysis, by Marik and Zaloga,\(^11\) included 4 of 6 trials in which the allocation of patients to the EN or PN group either was not stated\(^15\)\(^-\)\(^16\) or was performed via quasi-randomization (medical record number\(^17\) or date of birth\(^18\)), thereby potentially leading to the selection biases. Lastly, 3 new trials have been published since then.\(^19\)\(^-\)\(^21\) In light of these issues, the pres-
ent meta-analysis aimed to provide an evidence-based appraisal of the effects of enteral feeding compared with parenteral feeding in patients with severe acute pancreatitis.

METHODS

STUDY SELECTION

The MEDLINE, EMBASE, and Cochrane databases were cross-searched for articles published from January 1, 1966, until December 15, 2006. A bibliographic search of the Cochrane database was made using the following predefined terms: acute pancreatitis AND (enteral nutrition OR enteral feeding) AND (parenteral nutrition OR parenteral feeding). Terms used for the search in EMBASE were acute pancreatitis AND (enteral nutrition OR enteral feeding) AND (parenteral nutrition OR parenteral feeding) AND [humans]/lim. Terms used for the search in MEDLINE were acute pancreatitis [title/abstract] OR pancreatitis [title/abstract] AND (enteral nutrition [title/abstract] OR enteral feeding [title/abstract]) AND (parenteral nutrition [title/abstract] OR parenteral feeding [title/abstract]). No language restrictions were applied.

Full-text articles were included in this systematic review if the title and/or abstract of the article reported (1) an RCT study design; (2) a population of patients with predicted severe acute pancreatitis (in the case of a mixed study population, i.e., patients with both mild and severe acute pancreatitis, included trials should present separate outcome data for patients with severe acute pancreatitis); (3) EN and PN interventions (EN was defined as the nasogastric or nasojejunal delivery of nutritional formula not supplemented with any immune-enhancing ingredients); and (4) at least 3 of the following outcome variables: total infectious complications, pancreatic infections, need for surgery, nonpancreatic infections, organ failure, and in-hospital mortality.

DATA EXTRACTION

Data from full-text articles were retrieved and checked for consistency by two of us (M.S.P. and H.C.V.S.) independently. Data on baseline characteristics and numbers of events for each end point were extracted. Disagreements about values were resolved by discussion between the two of us.

The methodologic quality of the studies was assessed using a previously published scoring system, with a quality scale range of 0 to 5 points.22 This quality scale incorporates method of randomization, masking, and dropouts and withdrawals. A score of 2 or less represents a low-quality study, whereas a score of at least 3 represents a high-quality study. Differences in assessment were resolved by consensus among the authors of this review.

Overall, we identified 253 publications. After initial eligibility screening, 29 potentially eligible RCTs on artificial nutrition in acute pancreatitis were retrieved (Figure 1). Twenty-four studies were subsequently excluded for the following reasons: EN was compared with no artificial nutrition,28 PN was compared with no artificial nutrition,25 fat glucose–based PN was compared with glucose-based PN,26 fructose-glucose-xylitol–based PN was compared with glucose-based PN,27 the effects of PN compared with immune-enriched PN were studied,28-30 the effects of probiotics and immune-enriched enteral nutritional formulas were studied,31-33 nasojejunal EN was compared with nasogastric EN,35,36 nasojejunal refeeding was compared with oral refeeding,37 polymeric enteral feeding formula was compared with semielemental formula,38 PN was compared with the combined use of EN and PN,39,40 or the trials considered postoperative patients only41-43 or included patients with both mild and severe acute pancreatitis without presenting data separately.15-18 Finally, 5 RCTs,19-21,44,45 in which 95 patients were randomly allocated to the EN group and 107 to the PN group, met all inclusion criteria. The characteristics of included trials are detailed in Table 1. All RCTs reached a Jadad quality score of 3. Table 2 demonstrates the feeding regimens for all RCTs. A summary of the outcome data for the included RCTs are listed in Table 3. The funnel plots for the different outcomes show no clear pattern of bias (data not presented). Table 4 summarizes the results of the meta-analysis for the respective end points reported herein.

TOTAL INFECTIOUS COMPLICATIONS

The risk of total infectious complications was reported in all 5 RCTs. Sixty-seven of 202 patients (33.2%) had infections: 21 of 95 (22.1%) in the EN group and 46 of 107 (43.0%) in the PN group. In absence of marked heterogeneity across RCTs, EN resulted in a clinically relevant and statistically significant reduction in risk for total infectious complications (relative risk [RR], 0.47; 95% confidence interval [CI], 0.28-0.77; P <.001) (Figure 2).

PANCREATIC INFECTIONS

Pancreatic infections included infected pancreatic necrosis and pancreatic abscess and were reported in all RCTs. In the absence of marked heterogeneity across stud-
ies, EN resulted in a clinically relevant and statistically significant reduction in risk of pancreatic infections (RR, 0.48; 95% CI, 0.26-0.91; P = .02).

Surgical Intervention

Pancreatic infections were an absolute indication for surgery as reported in all 5 RCTs. In the absence of marked heterogeneity across studies, EN resulted in a clinically relevant and statistically significant reduction in the need for surgery (RR, 0.37; 95% CI, 0.21-0.65; P = .001).

Nonpancreatic Infections

Nonpancreatic infections, reported in 3 RCTs, included infections of the respiratory and urinary systems. In the ab-

Table 1. Study Characteristics of the Included Trials

<table>
<thead>
<tr>
<th>Source</th>
<th>Years of Study</th>
<th>Year of Publication</th>
<th>Setting</th>
<th>Onset of Symptoms</th>
<th>Criteria of Severity</th>
<th>Severity at the Time of Inclusion in Trial (APACHE II Score), EN/PN Groups</th>
<th>Prophylactic Antibiotics, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kalfarentzos et al44</td>
<td>1990-1995</td>
<td>1997 Greece</td>
<td>Not stated</td>
<td>APACHE II score ≥ 8 and/or Imrie score ≥ 3</td>
<td>10.7 (2.6)/11.8 (1.9)</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Gupta et al45</td>
<td>1996-1998</td>
<td>2003 United Kingdom</td>
<td>Not stated</td>
<td>APACHE II score ≥ 6</td>
<td>8 [5-12]/10 [7-14]</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Louie et al19</td>
<td>1999-2001</td>
<td>2005 Canada</td>
<td>Not stated</td>
<td>Ranson score ≥ 3</td>
<td>11.8 (8.3)/12.7 (5.5)</td>
<td>79</td>
<td></td>
</tr>
<tr>
<td>Eckerwall et al20</td>
<td>2002-2004</td>
<td>2006 Sweden</td>
<td>25 (22-35) h/30 (20-35) h</td>
<td>APACHE II score ≥ 8 and/or CRP level ≥ 150 mg/L and/or peripancreatic fluid on CT</td>
<td>10 [8-13]/9 [8-10]</td>
<td>73</td>
<td></td>
</tr>
<tr>
<td>Petrov et al21</td>
<td>2002-2004</td>
<td>2006 Russia</td>
<td>&lt;.7 h</td>
<td>APACHE II score ≥ 8 and/or CRP level ≥ 150 mg/L</td>
<td>12 (10-14)/12.5 (11-16)</td>
<td>100</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; CRP, C-reactive protein; CT, computed tomography; EN, enteral nutrition; PN, parenteral nutrition.

SI conversion factor: To convert CRP to nanomoles per liters, multiply by 9.524. Data are presented as median [range] or mean (SD).

Table 2. Summary of Feeding Regimens for the Included Trials

<table>
<thead>
<tr>
<th>Source</th>
<th>Feeding Start</th>
<th>Days Receiving Feeding, EN/PN Groups</th>
<th>Parenteral Feeding Formula</th>
<th>Enteral Feeding Formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kalfarentzos et al44</td>
<td>&lt;48 h after admission</td>
<td>34.8/32.8</td>
<td>Dextrose and amino acid solutions, fat emulsion, vitamins, minerals</td>
<td>Semielemental</td>
</tr>
<tr>
<td>Gupta et al45</td>
<td>&lt;6 h after admission</td>
<td>2 [2-7]/[4-2-7]</td>
<td>Aminolyside (Synthamin 14; Baxter Nutrition Ltd, Wallingford, United Kingdom), lipid and glucose solutions, trace elements</td>
<td>Polymeric</td>
</tr>
<tr>
<td>Louie et al19</td>
<td>&gt;96 h after admission</td>
<td>13.1 (10.5)/14.6 (10.3)</td>
<td>Dextrose solution, fat emulsion</td>
<td>Semielemental</td>
</tr>
<tr>
<td>Eckerwall et al20</td>
<td>&lt;24 h after admission</td>
<td>6 [5-9]/6 [5-9]</td>
<td>Glucose, amino acid solutions and fat emulsion (Kabiven PI; Fresenius-Kabi, Uppsala, Sweden)</td>
<td>Polymeric</td>
</tr>
<tr>
<td>Petrov et al21</td>
<td>&lt;24 h after admission</td>
<td>14 [8-20]/14 [10-21]</td>
<td>Dextrose and amino acid solutions, fat emulsion</td>
<td>Semielemental</td>
</tr>
</tbody>
</table>

Abbreviations: EN, enteral nutrition; PN, parenteral nutrition. Data are presented as median [range] or mean (SD).

Table 3. Summary of Outcome Data of Trials Included in the Meta-analysis

<table>
<thead>
<tr>
<th>Source</th>
<th>No. of Patients</th>
<th>Mortality</th>
<th>Total No. of Infectious Complications</th>
<th>No. of Pancreatic Infections</th>
<th>No. of Patients With Organ Failure</th>
<th>No. of Patients Undergoing Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kalfarentzos et al44</td>
<td>18/20</td>
<td>1/2</td>
<td>5/10</td>
<td>2/4</td>
<td>Not stated</td>
<td>2/4</td>
</tr>
<tr>
<td>Gupta et al45</td>
<td>8/9</td>
<td>0/0</td>
<td>1/2</td>
<td>0/4</td>
<td>0/6</td>
<td>0 (2/0) (2) a</td>
</tr>
<tr>
<td>Louie et al19</td>
<td>10/18</td>
<td>0/3</td>
<td>1/7</td>
<td>1/4</td>
<td>7/13</td>
<td>1/4</td>
</tr>
<tr>
<td>Eckerwall et al20</td>
<td>24/26</td>
<td>1/0 b</td>
<td>3/0 b</td>
<td>1/0 b</td>
<td>3/2</td>
<td>1/0 (1) a</td>
</tr>
<tr>
<td>Petrov et al21</td>
<td>35/34</td>
<td>2/12</td>
<td>11/27</td>
<td>7/16</td>
<td>4/10</td>
<td>8/25</td>
</tr>
</tbody>
</table>

Abbreviations: EN, enteral nutrition; PN, parenteral nutrition. Number of cholecystectomies in parentheses (data were not included in meta-analysis). After exclusion of protocol violators (1 patient from each group).
sence of marked heterogeneity across studies, EN was not associated with a statistically significant reduction in risk of urinary tract infections (RR, 0.70; 95% CI, 0.21-2.36; \(P = .56\)). The same holds for the risk reduction for respiratory tract infections (RR, 0.70; 95% CI, 0.21-2.34; \(P = .56\)).

### ORGAN FAILURE

Data on organ failure were reported in 4 trials. A total of 49 patients had any type of organ failure. With a marked heterogeneity across studies, EN was not associated with a statistically significant reduction in risk of organ failure (RR, 0.67; 95% CI, 0.30-1.52; \(P = .34\)). Results of subgroup analysis of types of organ failure are presented in Table 4.

### MORTALITY

Mortality was reported in all RTCs. Twenty-one patients died, 4 of 95 (4%) in the EN group and 17 of 107 (15.9%) in the PN group. With a marginal heterogeneity across studies, EN resulted in a clinically relevant

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No. of Events, EN/PN Groups</th>
<th>Relative Risk (95% Confidence Interval)</th>
<th>(P) Value</th>
<th>Heterogeneity, (I^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infectious complication</td>
<td>21/46</td>
<td>0.47 (0.28-0.77)</td>
<td>&lt;.001</td>
<td>0.00</td>
</tr>
<tr>
<td>Death</td>
<td>4/17</td>
<td>0.32 (0.11-0.98)</td>
<td>.03</td>
<td>6.43</td>
</tr>
<tr>
<td>Surgical intervention</td>
<td>12/33</td>
<td>0.37 (0.21-0.65)</td>
<td>.001</td>
<td>0.00</td>
</tr>
<tr>
<td>Pancreatic infections</td>
<td>11/24</td>
<td>0.48 (0.26-0.91)</td>
<td>.02</td>
<td>0.00</td>
</tr>
<tr>
<td>Infected pancreatic necrosis</td>
<td>7/16</td>
<td>0.44 (0.19-1.06)</td>
<td>.05</td>
<td>0.00</td>
</tr>
<tr>
<td>Pancreatic abscess</td>
<td>4/8</td>
<td>0.62 (0.19-2.03)</td>
<td>.34</td>
<td>46.15</td>
</tr>
<tr>
<td>Organ failure</td>
<td>14/31*</td>
<td>0.67 (0.30-1.52)</td>
<td>.21</td>
<td>62.79</td>
</tr>
<tr>
<td>Renal</td>
<td>4/9</td>
<td>0.66 (0.23-1.88)</td>
<td>.44</td>
<td>0.00</td>
</tr>
<tr>
<td>Respiratory</td>
<td>7/16</td>
<td>0.78 (0.38-1.62)</td>
<td>.51</td>
<td>0.00</td>
</tr>
<tr>
<td>Shock</td>
<td>3/5</td>
<td>0.80 (0.21-3.07)</td>
<td>.75</td>
<td>0.00</td>
</tr>
</tbody>
</table>

Abbreviations: EN, enteral nutrition; PN, parenteral nutrition.

*There was 1 patient with coagulopathy.*
This meta-analysis shows that EN, compared with PN, has important beneficial effects in patients with predicted severe acute pancreatitis, notably, clinically relevant and statistically significant risk reduction in infectious complications and mortality. The present study is stronger than previous meta-analyses in its adherence to strict methodologic criteria. The quality of studies has an effect on the estimates of treatment efficacy. The trials included in the previous meta-analyses were of relatively poor quality, with 1 of 2 (50%), 4 of 7 (57%), and 4 of 6 (67%) studies having a Jadad score less than 3. Because of the nature of the treatment arms, it was essentially impossible to double blind studies. Consequently, the maximally possible Jadad score was 3. Thereby, this meta-analysis, including only trials with Jadad scores of 3, summarizes the best available evidence-based data. Another strength of this meta-analysis is that it includes a more homogeneous subgroup of patients (ie, we only included trials that reported effect estimates for patients with predicted severe acute pancreatitis). All previous meta-analyses included mixed populations, with 32 of 70 (46%), 152 of 291 (52%), and 152 of 263 (58%) predicted mild cases.

This meta-analysis has several potential weaknesses. The ability to accurately predict the course of an attack of acute pancreatitis remains a challenge as evidenced by the range (57%-92%) of positive predictive value for scoring systems. However, the selection of patients for a trial without the use of a scoring system will lead to inclusion of only 10% to 15% with a poor outcome. However, when a scoring system is used to select the patients with predicted severe acute pancreatitis, 57% to 92% of the patients will have a poor outcome. Although this is far from an ideal prediction, it will help to improve the statistical power of the study. Furthermore, there was clear heterogeneity for organ failure (I²=46.15). Different definitions of organ failure, variability in scores, and other reasons may contribute to the observed heterogeneity. In addition, there was minimal heterogeneity for mortality (I²=6.43). It is believed that mortality in acute pancreatitis has a bimodal distribution (organ failure within 1-2 weeks and infectious complications later). Taking this into account, the heterogeneity in mortality may have been influenced by differences across studies with respect to organ failure. However, the trial publications do not provide sufficient data to test for such sources of heterogeneity by meta-regression. By its relatively high weight, the trial from Russia added much information to the meta-analysis of infectious complications and mortality. In contrast to other trials included, the statistical power of this particular study was adequate for these outcomes, whereas no heterogeneity was found among trials in terms of the risk of infectious complications. Still, sensitivity analyses on the influence of different trials on the pooled outcomes did not show a clear pattern (data not shown).

Common to all meta-analyses, publication bias is a concern. Reports of trials with statistically significant results are more likely to be published than those with negative outcomes. The funnel plots show no clear pattern of such biases. Variation also occurred among the studies in terms of the location of the feeding tube. At the same time, it is unlikely that the difference between nasogastric and nasojejunal feeding would confound the results because 2 recent trials showed no difference in the outcomes between these approaches.

Despite the clear clinical benefits of EN, the exact mechanism of its favorable effect remains unclear. It is considered that EN acts to reduce the failure of the gut barrier and diminish subsequent bacterial translocation that plays a pivotal role in the development of infectious complications during severe acute pancreatitis. The clinical measurement of gut barrier function remains a challenge, and the measurement of intestinal permeability is most often performed. Apart from experimental studies, 3 clinical studies have shown that there is increased intestinal permeability to both molecules (sugar probes) and macromolecules (polyethylene glycol) in patients with severe acute pancreatitis compared with those with mild disease and healthy volunteers. The issue remains unresolved, however, because 2 trials have suggested that EN is associated with increased intestinal permeability. The trial by Powell et al, in which patients with predicted severe acute pancreatitis were randomized to receive either nasojejunal EN or no nutritional support, showed significantly increased intestinal permeability (using a differential sugar permeability test) by day 4 in patients allocated to the EN group. Another trial comparing nasogastric EN vs PN in patients with predicted severe acute pancreatitis demonstrated increased intestinal permeability (using the urinary excretion of orally administered polyethylene glycol) on day 3 in the EN group. However, both trials included a considerable number of patients with mild acute pancreatitis (11 of 27 and 26 of 48, respectively), for which it has not been shown that intestinal permeability will change considerably.

Another marker of impaired gut barrier function is the finding of endotoxemia. The serum concentration of antiendotoxin core antibodies (both IgM and IgG) can be used as an indicator of severity and an indirect marker for intestinal permeability. Results of an early trial from the United Kingdom showed that levels of serum IgM antibodies decreased significantly after 7 days of EN when compared with the PN group (P <.05). The trial by Gupta et al demonstrated that IgM antibody levels decreased significantly in the EN group (P =.03) and tended to increase in the PN group during the week of treatment. Conversely, the recent trial by Eckermann et al found decreasing levels of IgM antibodies in both the EN and PN groups without significant differences at any time point within the 10 days of follow-up. The IgG antibody may be a better marker of gut barrier failure than IgM, but, unfortunately, it was not measured in the trial from Sweden. The influence of EN on intestinal barrier function in severe acute pancreatitis merits further investigation.

A number of other issues should be addressed when considering EN in the setting of severe acute pancreati-
tis. The patients included in all 5 RCTs received prophylactic antibiotics. Theoretically, either a synergistic effect of antibiotics with EN or an antagonistic effect of antibiotics with PN cannot be ruled out. Thereby, to ascribe a decrease in the infectious complications and mortality to the enteral feeding, ultimately, a trial on EN vs EN plus antibiotics would be useful. In addition, future trials should also focus on different aspects of feeding methods, notably, the safety of nasogastric vs nasojejunal delivery of nutrients, the optimal timing for initiation of feeding, and the composition of enteral formulations.

In conclusion, since the pioneer trial by McClave et al. in 1997, the present meta-analysis of high-quality studies has summarized the decennial endeavors to define the best nutritional strategy in acute pancreatitis. This meta-analysis has demonstrated strong evidence of the benefits of enteral over parenteral feeding in patients with severe acute pancreatitis in terms of clinically relevant and statistically significant reductions in the risk of infectious complications and mortality.

Accepted for Publication: June 20, 2007.

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Author Contributions: Drs Petrov and van Santvoort had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Petrov, Windsor, and Goossen. Acquisition of data: Petrov and van Santvoort. Analysis and interpretation of data: Petrov, Besselink, van der Heijden. Drafting of the manuscript: Petrov. Critical revision of the manuscript for important intellectual content: van Santvoort, Besselink, van der Heijden, Windsor, and Goossen. Statistical analysis: Petrov and van der Heijden. Administrative, technical, or material support: Van Santvoort, Besselink, van der Heijden, and Goossen. Study supervision: Petrov, Windsor, and Goossen.

Financial Disclosure: None reported.

Previous Presentation: This study was presented in part at the 39th meeting of the European Pancreatic Club; July 2007; Newcastle upon Tyne, England, and published as an abstract in *Pancreatology*. 2007;7:254.

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