Systematic review and meta-analysis of enteral nutrition formulations in acute pancreatitis

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CRD summary
This review of enteral nutrition formulations in patients with acute pancreatitis concluded that there was no significant difference between polymeric and semi-elemental formulations for feeding intolerance, infectious complications or mortality. There was no sound clinical evidence to justify the use of immunonutrition or probiotics formulations. Limitations of the evidence and review process make the reliability of the conclusions unclear.

Authors' objectives
To compare the tolerance and safety of enteral nutrition formulations in patients with acute pancreatitis.

Searching
MEDLINE, Scopus and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched, from inception to 1st January 2009, for publications in any language; search terms were reported. Bibliographies of each retrieved article and conference proceedings of selected scientific meetings (Digestive Disease Week, United European Gastroenterology Week, International Association of Pancreatology, American Pancreatic Association and European Pancreatic Club from 2004 to 2008) were handsearched. All types of publication were considered.

Study selection
Randomised controlled trials (RCTs) of patients with acute pancreatitis that compared two different feeding regimes, at least one of which had to include enteral tube feeding, were eligible for inclusion; the type of formulation used had to be clearly described. Trials of the tolerance of oral re-feeding, or combined enteral and parenteral nutrition, or postoperative nutrition were excluded.

The primary outcomes were feeding intolerance (defined as an episode of temporary reduction, stoppage or withdrawal of feeding) and total infectious complications and/or in-hospital mortality.

The enteral formulations used in the included trials (in decreasing order of use) were semi-elemental, polymeric, fibre-enriched, supplemented with probiotics, and immunonutrition (glutamine, arginine and omega-3 fatty acids) formulations. In over half of the trials, patients had severe acute pancreatitis; the remaining trials were of patients with both mild and severe acute pancreatitis (77% severe acute and 23% mild). All trials (except one) were single-centre trials. All the included trials were published in peer-reviewed journals. Two trials comparing nasogastric and naso-jejunal routes of enteral nutrition were excluded.

Two independent reviewers performed the selection.

Assessment of study quality
Methodological quality was assessed using five quality criteria of the Cochrane Collaboration: method of randomisation, allocation concealment, blinding, incomplete outcome data, and selective outcome reporting.

Two reviewers performed the quality assessment.

Data extraction
The numbers of events for each outcome were extracted in order to calculate weighted averages and relative risk (RR) with 95% confidence intervals (CIs). Authors were contacted for missing data.

Two reviewers performed the extraction.

Methods of synthesis
Relative risks were pooled using a random-effects model, since the formulation contents varied from manufacturer to manufacturer. Between trial heterogeneity was determined using the Q statistic and $I^2$ test. Where only one RCT compared two different formulations, an adjusted indirect meta-analysis was applied (Glenny et al 2005) in order to preserve the within-trial randomisation of the originally assigned comparative groups.

Sensitivity analyses were performed for trials of patients with severe acute pancreatitis.

Funnel plots were used to visually assess publication bias.

**Results of the review**

Twenty RCTs were identified (n=1,070 patients, range 17 to 296). Trial quality was heterogeneous: three RCTS met all five quality criteria; six met four quality criteria; eight met two quality criteria; and three only met one criterion. Seven trials were blinded. Nine trials clearly had concealed randomisation.

None of the meta-analyses for feeding intolerance, total infectious complications or mortality showed significant differences between groups.

**Semi-elemental versus polymeric formulation** (ten RCTs): An indirect adjusted meta-analysis using parenteral nutrition as a reference treatment was used for the comparison. For both mild and severe acute pancreatitis patients, there was no significant difference in the risk of total infectious complications (RR 0.48, 95% CI 0.06 to 3.76), mortality (RR 0.63, 95% CI 0.04 to 9.86) or feeding intolerance (RR 0.62, 95% CI 0.10 to 3.97). The results of indirect meta-analysis for the severe acute pancreatitis patients alone were also not significant.

**Fibre-enriched supplemented with probiotic versus fibre-enriched formulation** (three RCTs): A direct meta-analysis found no significant difference in the risk of total infectious complications (RR 0.71, 95% CI 0.40 to 1.27), mortality (RR 0.85, 95% CI 0.18 to 4.14), or feeding intolerance (RR 0.69, 95% CI 0.43 to 1.09). Results were also not significant for severe acute pancreatitis patients alone.

**Fibre-enriched supplemented with immunonutrition versus fibre-enriched formulation** (two RCTs): A direct meta-analysis for severe acute pancreatitis patients alone found no significant difference for total infectious complications (RR 0.93, 95% CI 0.36 to 2.4), mortality (RR 0.60, 95% CI 0.10 to 3.55), or feeding intolerance (RR 1.60, 95% CI 0.31 to 8.29).

**Trials not included in the meta-analyses:** One RCT found a significantly reduced rate of infectious complications (p=0.008), with no difference in mortality, for semi-elemental plus probiotic formulation versus parenteral nutrition. Another RCT that compared fibre-enriched versus fibre-free formulations found no significant difference for infectious complications or mortality, but an increased intolerance with the fibre-free formulation (it was not possible to calculate the statistical significance). The two other RCTs, that compared polymeric formulation versus no nutrition, and polymeric formulation plus n-3 polyunsaturated fatty acids versus polymeric formulation alone, both found no significant difference for infectious complications or mortality.

Funnel plots showed no evidence of publication bias.

**Authors' conclusions**
The use of polymeric compared with semi-elemental enteral nutrition formulations did not lead to a significantly higher risk of feeding intolerance, infectious complications or death in patients with acute pancreatitis. The supplementation of enteral nutrition with probiotics or the use of immunonutrition did not significantly improve clinical outcomes.

**CRD commentary**
The review addressed a well-defined question in terms of participants, interventions, study design and relevant outcomes. Relevant databases were searched in any language and unpublished studies were considered. Publication bias was assessed and no evidence found. Efforts were made to reduce error and bias in study selection, but it was not clear whether two reviewers performed the quality assessment and study extraction independently.
Trial quality was assessed using suitable criteria. It appeared that more than half of the included trials were of relatively low quality. Some relevant trial details were reported, but there were no details of length of follow-up, loss to follow-up, or the gender and age of patients. Statistical heterogeneity was assessed but no relevant details were reported. The main conclusion of the review was based on an indirect meta-analysis, which may not have the same degree of validity as a direct meta-analysis. Sensitivity analyses were performed when possible. The sample sizes of most of the included trials were small. There were some potential limitations arising from the review process.

The authors’ main conclusion appeared to reflect the evidence, but there was limited evidence supporting the other conclusions. Given this, and limitations in the review process, the overall reliability of the authors’ conclusions is unclear.

**Implications of the review for practice and research**

**Practice:** The authors recommended the use of semi-elemental and polymeric formulations, but did not recommend the use of fibre-enriched, probiotic or immunonutrition formulations in acute pancreatitis.

**Research:** The authors identified a need for further basic science research on probiotic and immunonutrition formulations, including research on the interactions between probiotics and gut microflora in acute pancreatitis. They recommended RCTs with sufficient power comparing fibre-enriched and fibre-free formulations in acute pancreatitis. They did not recommend further studies on semi-elemental or polymeric formulations since adequately powered studies to assess mortality, for example, would require large sample sizes (approximately 2,000 patients per study arm).

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