Immunonutrition in the critically ill: a systematic review of clinical outcome

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Authors' objectives
To perform a meta-analysis addressing whether enteral nutrition with immune-enhancing feeds benefits critically ill patients after trauma, sepsis, or major surgery.

Searching
Studies were identified by a MEDLINE search (from 1967 to January 1998) for original articles in English using the search terms 'human', 'enteral nutrition', 'arginine', 'nucleotides', 'omega-3 fatty acids', 'immunonutrition', 'IMPACT', and 'Immun-Aid'. The authors of studies and the manufacturers of the feeds were contacted for additional published and unpublished information. Access to the original databases was obtained for the three largest studies.

Study selection
Study designs of evaluations included in the review
Randomised trials. Only trials with institutional review board approval and appropriate informed consent were considered for the meta-analysis.

Specific interventions included in the review
Two commercially available enteral feeding preparations enriched with 'immunonutrients' (including arginine, glutamine, omega-3 fatty acids, and nucleotides) were the interventions included in the review. These were IMPACT (Novartis Nutrition, Bern, Switzerland) and Immun-aid (McGaw, Irvin, CA). Control feeds (standard enteral feed preparations) included Osmolite, Vivonex, Trauma-cal, Promote with Casec, Fresubin, and isocaloric and isonitrogenous feeds.

Participants included in the review
Critically ill patients requiring enteral nutrition via a tube (nasoenteric or jejunostomy). Patients were subdivided according to whether primary diagnosis was medical, surgical or trauma based.

Outcomes assessed in the review
Main outcome measures were mortality, infection rate, days of mechanical ventilation, intensive care unit (ICU) length of stay (LOS), hospital LOS, and days with diarrhoea.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the reviewers performed the selection.

Assessment of study quality
Methodologic quality was graded using the clinical trial grading system of Chalmers et al (see Other Publications of Related Interest no.1). Two reviewers graded each of the articles for methodologic quality. It is unclear whether reviewers were blinded to source, or how discrepancies were resolved.

Data extraction
Two reviewers extracted data from the articles. Where clinical trial data came directly from the authors, a single reviewer extracted the data for the required variables. Data extraction differences were resolved by consensus between the two reviewers. Data were extracted on: number of patients randomised, number of patients treated, trial feed, control feed, total parenteral nutrition, blinding, number of deaths, patient type (medical, surgical, trauma), calorie intake (kcal/kg/day), nitrogen intake(g/kg/day), and results. Infection and mortality were treated as binary variables and relative risks (RRs) for the treatment group versus the control group. Other outcomes were treated as continuous.
variables and the mean difference comparing treatment minus control results was calculated.

**Methods of synthesis**

How were the studies combined?
A meta-analysis was performed on an intention-to-treat basis. Studies were weighted by the inverse of their variance. Numerical data presented in tables were derived from a random-effects model, but results from both fixed-effect and random-effects models were displayed in forest plots. The authors report that funnel plots were developed for this study, but these were not presented in the article.

How were differences between studies investigated?
The authors state that ‘standard heterogeneity tests were conducted’, but the specific tests are not mentioned.

**Results of the review**

Twelve studies (n=1557) were included in the meta-analysis. 1482 patients were included in an intention-to-treat analysis. 434 were medical, 601 were surgical, and 447 were trauma patients.

Quality scores for the included trials ranged from 0.41 to 0.77.

There was no overall effect of immunonutrition on mortality (relative risk (RR) = 1.05 (95% CI: 0.78, 1.41, p=0.76)), reduction in ICU LOS (-1.4 days (95% CI: -0.7, 3.5, p=0.20)), or days with diarrhoea (0.0 (95% CI: -0.3, 0.2, p=0.78). There were significant overall reductions in infection rate (RR = 0.60 (95% CI: 0.42, 0.86, p=0.005)), ventilator days (-2.6 days (95% CI: -5.1, -0.1, p=0.04)) and hospital LOS (-2.9 days (95% CI: -4.4, -1.4, p=0.0002)).

Subgroup analysis showed significant reductions in the relative risk of infection (0.48 (95% CI: 0.28, 0.83, p=0.01)) and hospital LOS (2.3 days (95% CI: 0.6, 4.0, p=0.007) in surgical patients. Immunonutrition significantly reduced ventilator days in trauma patients (4.0 (95% CI: 0.6, 7.5, p=0.02)). These findings remained significant after censoring for mortality.

The authors report that there was no heterogeneity between trials for any of the main comparisons in the meta-analysis.

The authors report that funnel plots showed no obvious biases as a function of study size, but these were not presented in the article.

**Authors’ conclusions**

The benefits of enteral immunonutrition were most pronounced in surgical patients, although they were present in all groups. The reduction in hospital length of stay and infections has resource implications.

**CRD commentary**

On the whole, this is a methodologically sound review. The inclusion criteria were appropriate to the review question, validity assessment was carried out by two reviewers using predefined criteria, and relevant study details were presented in tables. The meta-analysis was appropriate and heterogeneity was assessed visually and statistically. Funnel plots were not presented, making publication bias difficult to assess, although the authors do state that there were no obvious biases as a function of study size. It is possible that the authors failed to identify all the relevant research, as only MEDLINE was searched, and only English language articles were included. Also, the relative risk and confidence intervals for infection rate reported in the abstract appear to differ from those given in the text and tables of the review. The authors’ conclusions follow from the results presented but should be interpreted with some degree of caution due to the methodological limitations highlighted.

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

Practice: The authors state that the benefits were most marked in the surgical group, and they recommend that immunonutrition be used in these patients. They also state that, although the results in the other patient subgroups are
less clear, there were overall benefits for infection rate, hospital LOS and ventilator days, suggesting that any critically ill patient suitable for enteral feeding may potentially benefit from immune-enhancing enteral feeds.

Research: The authors state that a large, double-blind, multicentre, randomised controlled trial of immunonutrition is now required.

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**Other publications of related interest**


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**Record Status**
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.