Should immunonutrition become routine in critically ill patients: a systematic review of the evidence

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Authors' objectives
To evaluate the effect of enteral immunonutrients in critically ill patients.

Searching
MEDLINE, EMBASE, BIOSIS Previews, CINAHL and the Cochrane Controlled Trials Register were searched from 1990 to 2000 for English and non-English language studies (the search terms were reported). The major manufacturers of immune-enhanced formulas were contacted. The bibliographies of review and original articles were examined and personal files and abstract proceedings of recent scientific meetings were searched. Three studies were excluded because they were only available as abstracts.

Study selection
Study designs of evaluations included in the review
Only randomised controlled trials (RCTs) were included.

Specific interventions included in the review
Studies of enteral nutrition supplemented with any combination (at least two) of arginine, glutamine, omega-3 fatty acids, or nucleotides compared with standard enteral nutrition were included. Eighteen trials used high arginine content formulas (Impact or Immun-Aid), while four used a formula consisting of L-arginine and omega-3 fatty acids which contained less arginine than Impact or Immun-Aid.

Participants included in the review
Studies of critically ill patients (i.e. those being routinely cared for in a critical care setting) or elective surgical patients were included. The participants were elective surgical patients (9 studies), critically ill patients with severe trauma (6 studies), critically ill patients in an intensive care unit (ICU; 6 studies) and critically ill patients with severe burns (1 study).

Outcomes assessed in the review
Studies assessing clinically important outcomes such as mortality, infectious complications and length of hospital stay were included. Studies reporting nutritional or immunological outcomes only were excluded. The primary outcomes of interest were mortality in the ICU and hospital, and the number of patients with new infectious complications including pneumonia, intra-abdominal abscess, sepsis, line sepsis, wound infection and urinary tract infection.

How were decisions on the relevance of primary studies made?
Two reviewers independently assessed the identified articles.

Assessment of study quality
The studies were assessed for randomisation, intention-to-treat analysis, blinding, patient selection, baseline comparability of the groups, extent of follow-up, description of the treatment protocol, description of cointerventions and definition of outcomes. The studies were scored out of 14 points. Two reviewers independently assessed each study and any disagreements were resolved by consensus.

Data extraction
The data extraction was carried out in duplicate with any discrepancies resolved by consensus. For mortality and infectious complications, the percentage of patients who had the outcome in the treatment and control group was...
extracted. The mean (with standard deviation, SD) length of hospital stay and mean (SD) duration of mechanical ventilation were also extracted for the intervention and control groups. Risk ratios (relative risk, RR) were calculated for all the outcome variables except length of stay, for which an effect size (ES) was calculated.

Methods of synthesis
How were the studies combined?
The authors used maximum likelihood methods of combining RRs across the included studies. The studies were pooled using a random-effects model to estimate the overall RR. The Mantel-Haenszel method was used to test the significance of the treatment effect.

How were differences between studies investigated?
Statistical tests were carried out to investigate heterogeneity (method not stated). Pre-specified subgroup analyses were carried out based on study quality, arginine content and patient group.

Results of the review
Twenty-two RCTs (n=2,419) were included.

Mortality was not reduced by enteral immunonutrition compared with standard formulas (22 studies; RR 1.10, 95% confidence interval, CI: 0.93, 1.31). Although the statistical test for heterogeneity was non significant (p=0.54), the authors stated that a visual inspection suggested heterogeneous treatment effects. A subgroup analysis showed no difference in mortality for high arginine content formulas compared with standard formulas (RR 1.05, 95% CI: 0.88, 1.25), but studies using formulas other than high arginine formula were associated with higher mortality (RR 2.13, 95% CI: 1.08, 4.21), (p=0.06 for the between-subgroup comparison). Mortality was not reduced by immunonutrition in both the critically ill (RR 1.18, 95% CI: 0.88, 1.58) and elective surgical (RR 0.99, 95% CI: 0.42, 2.34) patient groups (p=0.70 for the between-subgroup comparison). The higher quality studies (a score of 8 or more points) showed a trend towards higher mortality (RR 1.19, 95% CI: 0.99, 1.43) for immunonutrition compared with standard formula, whereas the lower quality studies showed a trend towards lower mortality (RR 0.74, 95% CI: 0.49, 1.14), (p=0.06 for the between-subgroup comparison).

In comparison with standard formulas, immunonutrition was associated with fewer patients with infectious complications (18 studies; RR 0.66, 95% CI: 0.54, 0.80). There was statistically-significant heterogeneity (p<0.001). A subgroup analysis showed there was a lower rate of infectious complications in studies with high arginine content formula compared with standard formula (RR 0.55, 95% CI: 0.46, 0.67), but not for the studies using other formulas (RR 1.27, 95% CI: 0.74, 2.22), (p=0.01 for the between-subgroup comparison). Immunonutrition had no effect on the rate of infectious complications in studies of critically ill patients (RR 0.96, 95% CI: 0.77, 1.20), but was associated with a lower rate of complications in studies of elective surgical patients (RR 0.53, 95% CI: 0.42, 0.68), (p=0.002 for the between-subgroup comparison). The higher quality studies showed a lower rate of infectious complications (RR 0.53, 95% CI: 0.42, 0.68) for immunonutrition compared with standard formula, whereas there was no difference for the lower quality studies (RR 1.01, 95% CI: 0.68, 1.50), (p=0.01 for the between-subgroup comparison).

Compared with standard formulas, immunonutrition was associated with a shorter hospital stay (17 studies; effect size, ES -0.63, 95% CI: -0.94, -0.32). There was statistically-significant heterogeneity (p<0.001). A subgroup analysis showed that the high arginine content formula was associated with a shorter hospital stay (ES -0.77, 95% CI: -1.09, -0.45) whereas the other formulas were associated with longer hospital stays in comparison with standard formulas (ES 0.37, 95% CI: -0.09, 0.83), (p=0.008 for the between-subgroup comparison). Immunonutrition was associated with a shorter hospital stay in both critically ill (ES -0.47, 95% CI: -0.93, -0.01) and elective surgical patients (ES -0.76, 95% CI: -1.14, -0.37), (p=0.95 for the between-subgroup comparison). The higher quality studies showed that immunonutrition was associated with shorter hospital stays in (ES -0.67, 95% CI: -1.00, -0.35), whereas the lower quality studies showed no effect on length of hospital stay (ES -0.37, 95% CI: -1.56, 0.82), (p=0.30 for the between-subgroup comparison).

Further subgroup analyses in relation to the critically ill patient group only were also reported.
Authors' conclusions
Immunonutrition does not improve mortality in comparison with standard formulas, though it may decrease the rate of infectious complications. However, the effectiveness of immunonutrition is variable depending upon the type of formula, the patient population and study quality.

CRD commentary
The review question was clear in terms of the intervention, participants, outcomes and study design. A number of relevant electronic databases were searched and the subject headings used in the search strategy were given. Unpublished data were sought and language restrictions were not applied. The study selection, data extraction and quality assessment processes were carried out in duplicate, which helps to reduce errors and bias. Relevant details were provided on individual studies, although the only information provided on the participants was whether they were critically ill or elective surgical patients. More information on the disease-related characteristics and age of the patients would have been useful in assessing potential sources of heterogeneity. The authors assessed statistical heterogeneity after pooling had been carried out. Heterogeneity was identified and possible sources, specified a priori, were investigated. Given the heterogeneity identified, the pooled measures of effect need to be treated with caution.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors state that research is required to identify the mechanism which may lead to immunonutrition being harmful, and to identify which patient groups benefit most and the most effective formulas.

Bibliographic details

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Other publications of related interest
This additional published commentary may also be of interest. Oltermann MH, Smith S. Immunonutrition does not decrease mortality in critically ill patients, but may reduce infectious complications and hospital stay for elective surgery patients. Evidence-based Healthcare 2002;6:20-1.

Indexing Status
Subject indexing assigned by NLM

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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.