Immunonutrition in the intensive care unit: a systematic review and consensus statement

CRD summary
The review assessed the effects of enteral nutrition with pharmaconutrient-enriched diets in critically ill patients. The authors concluded that enriched diets offer beneficial effects to patients requiring enteral feeding, although further research is required to identify the population who could benefit the most. The lack of individual study results, the inclusion of only published studies, and funding from the manufacturer of such diets may potentially bias the authors' conclusion.

Authors' objectives
To determine the effectiveness of enteral nutrition with pharmaconutrient-enriched diets in patients who were critically ill.

Searching
MEDLINE, EMBASE and the Cochrane CENTRAL Register were searched for articles published from 1966 to 2000. Additional studies were sought in the reference lists of retrieved articles and abstracts of proceedings of scientific meetings. Only published studies were included.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for inclusion.

Specific interventions included in the review
Studies of enteral nutrition with an immune-enhancing diet, compared with a standard diet, were eligible for inclusion. Studies that compared immune-enhancing diets with nil-by-mouth or parenteral nutrition were excluded. The interventions evaluated in the included studies were commercial diets, or diets specifically prepared for the study (glutamine-enriched, fish-oil enriched, arginine-enriched, or enriched with arginine and n-3 fatty acids). The majority of control diets in the included studies were isocaloric or isonitrogenous.

Participants included in the review
Studies of patients who were critically ill (as defined by the trialist) were eligible for inclusion. The participants in the included studies were surgical patients, trauma patients, patients receiving treatment for burns, or mixed patient groups. The mean age of the participants ranged from 7 months to 66 years.

Outcomes assessed in the review
Studies that evaluated significant clinical outcomes (e.g. mortality or infectious complications) were eligible for inclusion. Studies that evaluated surrogate outcomes (e.g. nutrition-related outcomes) were excluded. The outcomes evaluated in the included studies were the nosocomial infection rate, the incidence of adult respiratory distress syndrome (ARDS) or multiple organ dysfunctional syndrome (MODS), length of stay in the hospital, duration of mechanical ventilation, in-hospital mortality and cost.

How were decisions on the relevance of primary studies made?
Clinicians screened all citations and selected those that met the inclusion criteria. The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
The authors assigned a quality score to each study (1 being the lowest and 5 the highest), using the Jadad instrument to assess randomisation, blinding and withdrawals. The authors did not state how the papers were assessed for quality, or
how many reviewers performed the quality assessment.

Data extraction
Data were extracted from each included study in duplicate using a structured form and were checked independently for accuracy. For binary outcomes, data on the occurrence of each outcome of interest were extracted, while for continuous outcomes, data on the mean of each outcome of interest were extracted from individual studies using an intention-to-treat format.

Methods of synthesis
How were the studies combined?
The results from the individual studies were combined using a fixed-effect meta-analysis. For binary outcomes, a pooled odds ratio (OR) and 95% confidence interval (CI) were calculated separately for each outcome using the method of Peto. For continuous outcomes, a pooled difference in mean and 95% CI were calculated for each outcome. Funnel plots were used to assess publication bias, and plot asymmetry was assessed statistically.

How were differences between studies investigated?
Subgroup analyses were performed according to patient population (surgical, trauma, burn, or mixed) for those studies that reported on mortality. Statistical tests for homogeneity were performed using the Q test.

Results of the review
Twenty-six RCTs (n=2,473) were included in the review.

The authors stated that none of the included studies obtained a maximum quality score of 5 according to the Jadad scale.

Infectious complication rate: the authors stated that they were unable to find any significant effect on the rate of infectious complications, as most of the studies reported the incidence of infection at different locations instead of the overall ratio of infected individuals. No data were given in the report.

Wound infection: based on 15 RCTs, immunonutrition was associated with a significantly reduced likelihood of wound infection compared with the control (OR 0.46, 95% CI: 0.30, 0.69, P=0.003).

Intra-abdominal abscess: based on 6 RCTs, immunonutrition was associated with a significantly reduced likelihood of intra-abdominal abscess compared with the control (OR 0.26, 95% CI: 0.12, 0.58, P=0.0005).

Nosocomial pneumonia: based on 11 RCTs, immunonutrition was associated with a significantly reduced likelihood of nosocomial pneumonia compared with the control (OR 0.54, 95% CI: 0.35, 0.84, P=0.007).

Bacteraemia: based on 9 RCTs, immunonutrition was associated with a significantly reduced likelihood of bacteraemia compared with the control (OR 0.45, 95% CI: 0.29, 0.69, P=0.0002).

Urinary tract infections (UTIs): based on 10 RCTs, no statistically significant difference was shown between the immunonutrition and control groups on the occurrence of UTIs (OR 0.66, 95% CI: 0.43, 1.00, P=0.05).

Sepsis: based on 5 RCTs, no statistically significant difference was shown between the immunonutrition and control groups on the occurrence of sepsis (OR 0.45, 95% CI: 0.14, 1.45, P=0.18).

MODS and ARDS: no statistically significant difference was found between the immunonutrition and control groups on the incidence of MODS (1 RCT), while immunonutrition was associated with a significantly reduced likelihood of ARDS compared with the control (2 RCTs; OR 0.21, 95% CI: 0.09, 0.52, P=0.0007).

Mechanical ventilation duration: based on 7 RCTs, immunonutrition was associated with a significant reduction of 2.25 days (95% CI: -0.5, -3.9, P=0.009) of mechanical ventilation compared with the control.
Intensive care unit (ICU) and hospital length of stay: immunonutrition was associated with mean reductions of 1.6 days (95% CI: -1.2, -1.9, P<0.0001) and 3.4 days (95% CI: 2.7, 4.0, P<0.0001), respectively in ICU (8 RCTs) and hospital (12 RCTs) length of stay. There was evidence of statistical heterogeneity.

Mortality: based on 18 RCTs, no statistically significant difference was shown between the immunonutrition and control groups on in-hospital mortality (OR 1.1, 95% CI: 0.54, 1.42, P=0.5). A subgroup analysis according to patient population did not find a significant effect on mortality. There was no evidence of statistical heterogeneity for either the overall analysis or the subgroup analyses.

**Cost information**
The authors stated that three of the included studies calculated the added cost of the nutritional intervention to the hospital or ICU costs. Two studies found a reduction in the overall costs associated with enriched diets, while the other did not find any difference in cost.

**Authors' conclusions**
The authors stated that, given the evidence of beneficial effects and the absence of harmful effects associated with immunonutrition, its use could be recommended for patients in the ICU who require enteral feeding. However, further research is needed to identify the patient population who could benefit the most.

**CRD commentary**
The review addressed a clear research question and the inclusion criteria appeared appropriate. Several sources were searched for relevant published trials. The authors stated that publication bias was assessed but did not report the findings. In addition, it was unclear whether any language restrictions were applied to the search. Therefore, the possibility of publication and language could not be assessed. It was unclear whether the process used to select studies for inclusion was performed in duplicate, thus the possibility of selection bias could not be ruled out. However, methods were used to protect against reviewer bias and error in the data extraction process. The quality of the included studies was assessed systematically and discussed appropriately in the results.

Adequate details on the patient demographics, intervention and study design were given, which indicated clinical heterogeneity. There was no information on the results of each individual study. Furthermore, the authors stated that statistical tests of heterogeneity were performed, but the results were not reported for each outcome. This made it difficult to assess whether pooling the studies was appropriate. Consequently, the authors' conclusion and recommendation for future research appear appropriate.

**Implications of the review for practice and research**
Practice: The authors stated that there was fair evidence to recommend the use of enteral nutrition with modified diets in patients who are critically ill.

Research: The authors stated that well-conducted studies, designed according to established methodological and quality guidelines, are needed to determine the use of immunonutrition in specific sub-populations of critically ill patients.

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