The use of an inflammation-modulating diet in patients with acute lung injury or acute respiratory distress syndrome: a meta-analysis of outcome data

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CRD summary
This review found that a diet enriched with eicosapentaenoic acid and γ-linolenic acid in mechanically ventilated patients with acute lung injury/acute respiratory distress syndrome was associated with a significant reduction in mortality risk, and improved oxygenation and ventilation, compared with standard diet. Several possible sources of bias in this review make the reliability of these conclusions unclear.

Authors' objectives
To evaluate the effectiveness of an inflammation-modulating diet enriched with eicosapentaenoic acid (EPA) and γ-linolenic acid (GLA) in mechanically ventilated patients with acute lung injury/acute respiratory distress syndrome (ARDS).

Searching
MEDLINE via PubMed (1950-2006), EMBASE (1974-2006), Cochrane Central Register of Controlled Trials (CENTRAL) (fourth quarter, 2006) and ClinicalTrials.gov were searched. Search terms were reported. Journals (unspecified) and Index Medicus were handsearched. Only published peer-reviewed studies were included.

Study selection
Randomised controlled trials (RCTs) of critically ill patients with respiratory failure requiring mechanical ventilation due to a lung inflammatory process (such as acute lung injury or ARDS) were eligible for inclusion. Critically ill patients were defined as patients recruited in an intensive care unit. Patients had to receive either a diet with EPA and GLA (without any L-arginine, L-glutamine and/or nucleotide supplementation) or a standard control diet with none of the aforementioned substances. Studies had to include at least one severity of illness score and include 28-day all-cause mortality as an endpoint.

Primary outcomes assessed were 28-day in-hospital all-cause mortality, 28-day ventilator-free and intensive care unit-free days and development of new organ failures. A number of additional clinical parameters were assessed. Studies included participants with ARDs, acute lung injury and severe sepsis/septic shock. Mean intake of EPA was 4.9g/day to 6.9g/day, docosahexaenoic acid (DHA) was 2.2g/day to 2.9g/day and GLA was 4.6g/day to 5.8g/day. Elevated antioxidants were also given. Control diets were isocaloric and isonitrogenous with equal amounts of lipid to intervention.

The authors stated neither how papers were selected nor how many reviewers performed study selection.

Assessment of study quality
Methodological quality was assessed in terms of allocation concealment and adequacy of randomisation. The authors did not state how many reviewers performed the validity assessment.

Data extraction
For categorical outcomes, odds ratios (ORs) were calculated, with their associated 95% confidence intervals (CIs). Relative risks were used to confirm the odds ratios. For continuous outcomes, standardised mean differences (SMD) and 95% CIs were used. Intention to treat data were extracted where possible. Study authors were contacted if further information was required.

The authors did not state how many reviewers performed the data extraction.

Methods of synthesis
Odds ratios or standardised mean differences and their 95% CIs were pooled in a fixed-effect meta-analysis. Statistical heterogeneity was assessed using the $I^2$ statistic, the $X^2$ test and a funnel plot (also was used to investigate publication bias). Intention to treat analysis was undertaken for 28-day in-hospital all-cause mortality (the only outcome for which this data was available in all studies).

**Results of the review**

Three RCTs were included in the review (n= 411, 296 evaluable patients). Sample size varied from 100 to 165. Randomisation was detailed in all studies and appropriate methods of allocation concealment were used by each study. Two studies were double-blind.

**Clinical outcomes:** The inflammation-modulating diet was associated with a reduction in 28-day in-hospital all-cause mortality (OR 0.40, 95% CI 0.24 to 0.68, p=0.001; n=296), an increase in ventilator free days (SMD 0.56, 95% CI 0.32 to 0.79, p<0.0001; n=296), an increase in intensive care unit-free days (SMD 0.51, 95% CI 0.27 to 0.74, p<0.0001; n=296) and reduction in risk of development of new organ dysfunction (OR 0.17, 95% CI 0.08 to 0.34, p<0.0001; n=201). Results where relative risks and intention-to-treat analyses were used. No significant heterogeneity was detected in any of these analyses except ventilator-free days ($X^2$ p=0.06, $I^2$=64.7%).

Improvements in a number of ventilation parameters were reported (further details in the paper).

**Authors’ conclusions**

There was a significant reduction in mortality risk (as well as improvements in oxygenation and ventilation and other clinical outcomes) in patients with acute lung injury/ARDS given EPA and GLA compared with standard diet.

**CRD commentary**

The research question was supported by inclusion criteria for participants, intervention outcomes and study design. The search was restricted to published studies, which increased the possibility of publication bias. As only three studies were included, the funnel plot may not have been useful in detecting publication bias. The authors did not detail whether searches were restricted by language, so it was unknown whether language bias was possible. The review process was not reported, so it was not known whether steps were taken to minimise bias and error in study selection, data extraction or validity assessment (such as by performing these in duplicate). The authors reported that the effect of additional antioxidant supplementation in the intervention group was unclear. A limited validity assessment of primary studies was conducted and statistical heterogeneity was assessed. Little statistical heterogeneity was detected, but few study details were presented so clinical heterogeneity could not be assessed. As there were several possible sources of bias in this review, the reliability of the authors’ conclusions is not clear.

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

**Practice:** The authors did not state any implications for practice.

**Research:** The authors stated that further study was needed to determine whether diet can play a role in the early stages of sepsis and prevention of development of severe sepsis or septic shock.

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