Early enteral nutrition, provided within 24 h of injury or intensive care unit admission, significantly reduces mortality in critically ill patients: a meta-analysis of randomised controlled trials

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CRD summary
This review concluded that early enteral nutrition reduced mortality and pneumonia in critically ill patients, but further research was needed to confirm the findings and their generalisability. Given the poor quality of the evidence, the authors' cautious conclusion for further research appears reasonable.

Authors' objectives
To assess the effectiveness of early standard enteral nutrition for treatment of critically ill patients.

Searching
MEDLINE and EMBASE were searched without language restrictions through to October 2008. The full search strategy was available from the authors on request. Reference lists of relevant reviews and guidelines were searched manually. Experts in the field were contacted.

Study selection
Randomised controlled trials (RCTs) were eligible for inclusion if they compared early enteral nutrition (defined as standard enteral nutrition formula through any feeding tube route within 24 hours of initial injury or intensive care unit admission) with any form of standard care provided later than 24 hours after injury or intensive care unit admission in critically ill patients.

Eligible studies were required to report clinically meaningful patient-orientated outcomes (mortality, quality of life and physical function) as the primary outcome. Secondary outcomes of interest included complications and major intensive care unit infections (vomiting/regurgitation, pneumonia, bacteraemia, sepsis and multiple organ dysfunction syndrome). RCTs with methodological flaws, defined a priori as pseudo-randomisation (clear failure to maintain allocation concealment) and excessive (>10%) loss to follow-up were excluded. Studies based on subgroups of patients from larger trials were not eligible for inclusion if the larger trial was already included.

Included studies were conducted in ventilated medical and surgical intensive care unit patients, burn patients, patients with severe pancreatitis and/or peritonitis and trauma patients. Where Acute Physiology and Chronic Health Evaluation (APACHE) scores were reported, patients’ mean APACHE II scores ranged from 11.3 to 22.4. Most RCTs administered early enteral nutrition via nasogastric tube with starting concentrations between 20mL/h and 50mL/h that increased over time to to achieve set goals (as reported in the review). Most RCTs used the same early enteral nutrition protocol as the intervention, but administered at least 24 hours after admission. Mortality was measured on intensive care unit discharge or at 28-day follow-up.

At least three reviewers independently assessed papers for inclusion. Discrepancies were resolved by majority consensus.

Assessment of study quality
At least three reviewers independently assessed the quality of the included studies. Assessment included criteria on allocation concealment, blinding and completeness of patient follow-up. Discrepancies were resolved by majority consensus.

Data extraction
At least three reviewers extracted outcome data to calculate odds ratios (ORs) and their 95% confidence intervals (CIs). Discrepancies were resolved by majority consensus.
Methods of synthesis
A fixed-effect model was used to combine odds ratios and their 95% CIs. Statistical heterogeneity was assessed using the $X^2$ test and $I^2$ statistic. Where statistical heterogeneity was present, the following potential sources of heterogeneity (identified a priori) were investigated: study quality; disease groupings; intervention timing and dose; cointerventions and comparison intervention received; and outcome measurement and timing. Where sources of heterogeneity could not be identified, studies were presented as a narrative synthesis.

A sensitivity analysis was conducted to include RCTs that were identified during study selection and excluded due to methodological flaws.

Publication bias was reported to have been assessed through inspection of a funnel plot.

Results of the review
Six RCTs (n=234) were included in the review. Sample sizes ranged from 20 to 60 patients. RCTs were of poor quality. No studies reported sufficient detail on the method of randomisation and it was unclear whether allocation concealment was maintained. None reported type of blinding. All six RCTs reported complete follow-up for all patients. Forest plots indicated that analyses were conducted on an intention-to-treat basis.

Early standard enteral nutrition showed a statistically significant reduction in mortality compared to control (OR 0.34, 95% CI 0.14 to 0.85). There was no evidence of statistical heterogeneity ($I^2=0\%$). Sensitivity analysis did not significantly alter the results. None of the RCTs reported quality of life or direct measures of physical function.

Two RCTs showed a statistically significant reduction in pneumonia in patients who received early enteral nutrition (OR 0.31, 95% CI 0.12 to 0.78), with no evidence of statistical heterogeneity ($I^2=0\%$).

None of the RCTs reported on sepsis. No statistical differences were found between groups for other complications or major intensive care unit infections. Sensitivity analysis that included two trials with methodological flaws supported the significant reduction in mortality using early enteral nutrition.

Funnel plots to assess publication bias were not presented in the review.

Authors' conclusions
Standard enteral nutrition provided within 24 hours of injury or intensive care unit admission reduced mortality and pneumonia in critically ill patients, but further research was needed to confirm the findings and their generalisability.

CRD commentary
The review question was clear and was supported by clearly defined inclusion criteria. The literature search was limited to two electronic databases. Attempts were made to locate unpublished material. The authors reported that there was no evidence of publication bias, but data were not presented in the review. The search was not restricted by language, which reduced potential for language bias. Each stage of the review process was described and undertaken by multiple independent reviewers, which reduced potential for reviewer error and bias. Study quality was assessed and was generally poor (acknowledged by the authors). Appropriate statistical analyses were considered a priori to investigate any statistical heterogeneity; there was no evidence of statistical heterogeneity. The authors highlighted clinical and methodological heterogeneity with studies that used different patient groups and varied study methods. They also acknowledged the small number of studies included for each outcome measurement and small sample sizes, which can affect the robustness of findings. This was a generally well-conducted piece of research. Given the poor quality of the evidence, the authors' cautious conclusion for further research appears reasonable.

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Implications of the review for practice and research
Practice: The authors stated that well-advised clinical judgement should be used when applying the findings to clinical
practice as they may not generalisable to all patient groups.

Research: The authors stated that a large-scale multicentre clinical trial that included diverse groups of critically ill patients was needed.

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