CRD summary
The review found that immunonutrition decreased morbidity and hospital stay, but not mortality, after major gastrointestinal elective surgery; tolerance of enteral feeding with immunonutrition was similar to that with standard formula. Given the potential for bias and error in some parts of the review process, this conclusion should be interpreted cautiously.

Authors' objectives
To evaluate the effect of immunonutrition on postoperative complications, tolerance, length of hospital stay and mortality in patients undergoing gastrointestinal surgery.

Searching
MEDLINE, EMBASE, the Cochrane Database of Systematic Reviews and the Cochrane Central Register of Controlled Trials were searched for studies published between January 1985 and September 2009. Search terms were reported. No language restrictions were applied. Electronic links to related articles and references of selected articles were searched. Six trial registers were screened for unpublished studies; the principal investigators of these studies were contacted. Manufacturers of immunonutrition formulas were contacted for ongoing relevant studies.

Study selection
Randomised controlled trials (RCTs) that compared the effect of perioperative enteral immunonutrition with standard enteral nutrition in patients undergoing major gastrointestinal elective surgery were eligible for inclusion. Trials of immunonutrition given either before, after or both before and after surgery were eligible. Trials that compared one immunonutrition regimen with another, or that compared immunonutrition with parenteral nutrition were excluded. At least one of the main outcome measures had to be reported; these were overall complications, infectious complications, in-hospital mortality, and length of hospital stay. Immunonutrition was defined as enteral nutrition composed of at least two of the three main components of amino acids (arginine and/or glutamine), omega-3 fatty acids, and/or RNAs.

The included trials were conducted in Europe, USA, or Asia. Trials included patients with upper and lower gastrointestinal surgery, mainly for cancer; one trial included laparoscopic surgery. Preoperative nutritional therapy ranged from five to seven days, most commonly administered at 1000mL/day. Postoperative nutritional therapy was started within the first 24 hours in all trials; treatment ranged from three to over 10 days, with nutritional infusion rates increasing up to 25kcal/kg/day by day three. Tolerance was measured and defined as the absence of any intolerance event (vomiting, nausea, displacement of nasogastric tube, abdominal cramping or bloating).

Two reviewers independently performed the study selection, and discrepancies were resolved by discussion with the whole research team.

Assessment of study quality
Trial quality was assessed using the Jadad score, which assigned a score based on randomisation, allocation concealment, adequate blinding, and an adequate description of completeness of follow-up. A score of 3 or more points was considered high quality; a score of 1 or 2 was considered low quality.

The authors did not state how many reviewers performed the validity assessment.

Data extraction
Relevant data were extracted to enable to presentation of odds ratios (OR) or mean differences (MD) and associated 95% confidence intervals (CI). Authors of multiple studies were contacted in order to avoid inclusion of duplicate data.

The authors did not state how many reviewers performed the data extraction.
Methods of synthesis
Meta-analysis was used to calculate pooled odds ratios or mean differences and 95% confidence intervals using fixed-effect (with inverse-variance weighting) and random-effects models. Heterogeneity was assessed $\chi^2$ and $I^2$. Subgroup analyses were performed including only high quality trials.

Funnel plots were drawn to evaluate possible publication bias.

Results of the review
Twenty-one RCTs (2,730 participants) were included in the review. In three multiple-arm trials, two intervention groups were compared with one control group, so the results were based on a total of 24 comparisons from the 21 studies. Twelve trials were considered to be of high quality. Eleven trials used an intention-to-treat analysis.

Immunonutrition significantly reduced overall postoperative complications, irrespective of whether it was given before surgery (OR 0.48, 95% CI 0.34 to 0.69; six RCTs), both before and after surgery (OR 0.39, 95% CI 0.28 to 0.54; five RCTs) or only after surgery (OR 0.46, 95% CI 0.25 to 0.84; eight RCTs).

Immunonutrition significantly reduced postoperative infection when given before surgery (OR 0.36, 95% CI 0.24 to 0.56), both before and after surgery (OR 0.41, 95% CI 0.28 to 0.58) or only after surgery (OR 0.53, 95% CI 0.40 to 0.71). Although all trials provided data on postoperative infection, it was not clear how many provided data for each timing of intervention.

No significant heterogeneity between trials was found for overall complications or postoperative infection.

Immunonutrition led to a shorter hospital stay (MD $-2.12$ days, 95% CI $-2.97$ to $-1.26$), based on 21 comparisons (2,279 participants), but there was substantial heterogeneity between the trials ($I^2=81\%$). Mean differences of similar magnitude were found for all three timings of intervention.

The beneficial effects of immunonutrition were confirmed when low-quality trials were excluded. Perioperative immunonutrition had no influence on mortality. Six trials that assessed tolerance found no difference in the risk of an intolerance event between the intervention and control groups.

There was no evidence of publication bias for postoperative infectious complications and mortality. Funnel plots for overall complications showed minor asymmetry ($I^2=27\%$); hospital stay showed major asymmetry ($I^2=81\%$).

Cost information
Cost-effectiveness analyses in three trials (462 patients) found the difference in mean cost for immunonutrition compared with the control group was 1,426 Euro (per patient), 2,281 Euro (per patient) and 23,248 Euro (total cost) in favour of immunonutrition. This corresponded to mean savings of 52%, 13% and 18%. The higher direct costs of immunonutrition were outweighed by the lower overall complication rates and shorter hospital stay associated with its use.

Authors' conclusions
Perioperative enteral immunonutrition after major gastrointestinal surgery decreased morbidity and hospital stay, but not mortality. Tolerance of enteral feeding with immunonutrition was similar to that with standard formula.

CRD commentary
The review question was clear. Study design, participant, intervention and outcome inclusion criteria were clearly stated. The search strategy included relevant major data sources. As attempts were made to identify unpublished as well as published data, and no language restriction was applied to the search, the chances of publication and language bias were reduced. The use of two reviewers to perform the study selection meant that errors were likely to have been minimised. As it was not stated how many reviewers performed the quality assessment or data extraction, it was not possible to assess the likelihood of errors in the review process at these stages.
Trial quality was assessed using the Jadad scale, which was appropriate for RCTs; the use of intention-to-treat or per-protocol analyses was reported. A subgroup analysis based only on high quality trials confirmed the findings of the review. Heterogeneity was assessed. Appropriate methods of synthesis appear to have been applied. For some comparisons, it was not clear how many trials/participants contributed data to the summary odds ratio.

The authors’ conclusion reflects the evidence presented. Given the potential for bias and error in some parts of the review process, this conclusion should be interpreted cautiously.

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

**Practice:** The routine use of immunonutrition after major gastrointestinal surgery can be recommended.

**Research:** The authors did not state any implications for research.

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