A meta-analysis of the effect of combinations of immune modulating nutrients on outcome in patients undergoing major open gastrointestinal surgery

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CRD summary
This review concluded that immune-modulating nutrition was beneficial for reducing postoperative infectious and noninfectious complications and reducing length of stay in hospital for patients who underwent major open gastrointestinal surgery. This was a fairly well-conducted review with reliable conclusions about postoperative complications. Caution is needed when interpreting the length of stay data due to high heterogeneity.

Authors' objectives
To investigate the effect of immune-modulating nutrition combinations on complications after major open gastrointestinal surgery.

Searching
MEDLINE, EMBASE, Science Citation Index and The Cochrane Library were searched between January 1980 and February 2011 for studies published in any language. Search terms were reported. Bibliographies of trials, systematic reviews and meta-analyses were searched. Pharmaceutical companies were contacted.

Study selection
Randomised controlled trials (RCTs) that compared enteral nutrition containing at least two immune-modulating nutrition components with standard isocaloric and isonitrogenous diets with similar timing of initiation, dose and duration were eligible for inclusion. Interventions had to be given for at least five days pre-, post- or perioperatively to adult patients who underwent major elective open gastrointestinal surgery. Outcomes were postoperative infectious (general, wound-related and organ-specific) and noninfectious complications, length of hospital stay and mortality.

All studies except one included patients with and without weight loss. Immune-modulating nutrition supplements used in the studies were IMPACT, STRESSON, RECONVAN and ALITRA Q. Supplements were given preoperatively or perioperatively for between five and seven days; only a few studies provided interventions postoperatively. Control groups received an isocaloric and isonitrogenous enteral diet; control groups also included some immune-modulating nutrition in four studies. Enteral feeds were administered though nasoenteral, per-oral and jejunostomy routes. Enteral nutrition doses and times taken to reach postoperative nutrition goals varied between studies. Target calorie intakes were 25 to 30kcal/kg, 1.0 to 1.5L/day or 60 to 100mL/hr. Mean patient age was 62 years.

The authors did not report how many reviewers selected studies for the review.

Assessment of study quality
Study quality was assessed using the Jadad scale of randomisation method, allocation concealment, blinding and reporting of protocol violations (maximum possible score of 5).

Assessment was performed by two independent reviewers. Disagreements were resolved by discussion with other members of the review team.

Data extraction
Dichotomous outcomes were extracted and used to calculate risk ratios (RR) and mean differences (MD) were calculated for continuous outcomes, each with 95% confidence intervals (CI).

Data were extracted by two independent reviewers. Disagreements were resolved by discussion with other members of the review team.

Methods of synthesis
Results were combined using either Mantel-Haenszel fixed-effect or inverse-variance random-effects meta-analysis.
Statistical heterogeneity was assessed using the $I^2$ statistic and classed as low ($I^2=25\%$), moderate ($I^2=50\%$) and high ($I^2=75\%$). Subgroup analyses were used to assess the timing of diet initiation.

**Results of the review**

Twenty-six trials (2,496 participants) were included. Fourteen trials had appropriate methods of randomisation, 14 reported allocation concealment, 12 were described as double-blind. Only five trials explained their methods, six had a minimum follow-up of 30 days and 18 reported protocol violations. Eighteen trials scored 3 or more on the Jadad scale and were considered to have a lower risk of bias.

An immune-modulating nutrition diet reduced the risk of infectious complications (RR 0.64, 95% CI 0.55 to 0.74; 26 trials; little heterogeneity $I^2=0\%$) and noninfectious complications (RR 0.82, 95% CI 0.71 to 0.95; 20 trials; little heterogeneity $I^2=0\%$) compared with a standard diet. Mean length of hospital stay was significantly shorter by 1.88 days (95% CI 0.84 to 2.91 days; 20 trials; high heterogeneity $I^2=85\%$) for the immune-modulating nutrition diet group compared to a standard diet. There was no evidence of a difference between diets for mortality.

Results for infectious complications were statistically significant and similar to the main result in all three subgroups based on the timing of the immune-modulating nutrition diet initiation (pre-, peri- or postoperative). Noninfectious complications were only statistically significant in favour of immune-modulating nutrition for diets started in the postoperative period. Length of stay was statistically significant for peri- and postoperative diet initiation.

**Authors’ conclusions**

Immune-modulating nutrition was beneficial for reducing postoperative infectious and noninfectious complications and reducing the length of stay in hospital for patients who underwent major open gastrointestinal surgery.

**CRD commentary**

This review had a clear research question and specified inclusion criteria for study design, interventions, participants and outcomes. Four relevant databases were searched and there were no restrictions by language, which reduced the chance of language bias. Drug companies were contacted in an attempt to locate unpublished research. Quality assessment and data extraction were performed in duplicate to reduce errors and bias; it was unclear whether this also applied to study selection.

Most analyses seemed appropriate. The result for hospital length of stay showed high heterogeneity and may not be reliable. The authors discussed clinical differences between the studies, particularly for timings of the diets and inclusion of patients with various degrees of nourishment.

This was a fairly well-conducted review with reliable conclusions about postoperative complications but caution is needed when interpreting length of stay data.

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

**Practice:** The authors did not make any recommendations for practice.

**Research:** The authors stated that randomised controlled trials with a robust design were needed to evaluate the benefits of preoperative over postoperative supplementation and of well-nourished over malnourished patients. Research was needed into molecular signalling pathways and to identify specific mechanisms by which immune-modulating nutrition improved host defence and at the optimal dose.

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**Bibliographic details**


**PubMedID**
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.