Use of pre-, pro- and synbiotics in patients with acute pancreatitis: a meta-analysis
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CRD summary
This review assessed clinical outcomes of pre-, pro- and synbiotics therapy in patients with acute pancreatitis, and found no significant effect and a lack of evidence supporting their use in this area. The authors' conclusions reflect the lack of high quality evidence available and their recommendation, that further well-designed RCTs are needed, appears appropriate.

Authors' objectives
To assess the clinical outcomes of pre-, pro- and synbiotics therapy in patients with acute pancreatitis.

Searching
MEDLINE, EMBASE, Cochrane Library, Web of Science, and the Chinese Biomedicine Database were searched for relevant studies up to March 2010. Search terms were reported. No language restrictions were applied. Reference lists of relevant papers and reviews were handsearched for further relevant studies.

Study selection
Eligible studies were randomised controlled trials (RCTs) that evaluated the use of prebiotics, probiotics or synbiotics in patients with acute pancreatitis. Eligible trials had to report at least one of a pre-specified range of mortality and morbidity outcomes including number of infections, number of pancreatic infectious complications, number of multiple organ failures and systemic inflammation response syndromes, surgical interventions, length of hospital stay, and mortality.

In included trials, the duration of treatment ranged from seven days (most trials) to 28 days (one trial). Over half of the included trials used enteral nutrition as a control group. A wide range of pre-, pro-, and synbiotics were used in included trials. Most trials reported mean or range of APACHE II (second acute physiology and chronic health evaluation) patient characteristics, and mean C-Reactive Protein; one trial used the Glasgow score and one trial used the Imrie score. Included trials were published between 2002 and 2009. Trials were conducted in China, the UK, Turkey and the Netherlands. Adverse effects were reported in some trials.

The authors did not state how many reviewers selected studies for inclusion.

Assessment of study quality
Trial risk of bias was assessed using the Jadad scale, awarding a score out of 5 points based on adequacy of randomisation, allocation concealment, blinding and follow-up.

The authors did not state how many reviewers performed quality assessment.

Data extraction
Two authors independently extracted data required to calculate odds ratios (ORs) with 95% confidence intervals (CIs) for dichotomous outcomes, or mean differences with 95% confidence intervals for continuous outcomes. If more than one paper reported data from the same trial, data from the most recent trial was extracted. Disagreements were resolved by consensus.

Methods of synthesis
Odds ratios with 95% confidence intervals (for dichotomous outcomes) and mean differences with 95% confidence intervals (for continuous outcomes) were pooled using fixed-effect models if no statistical heterogeneity was identified; random-effects models were used if statistical heterogeneity was identified. Statistical heterogeneity was assessed using the $\chi^2$ statistic (and considered present if $p<0.05$) and quantified using the $I^2$ index.
Subgroup analyses were performed, stratified by disease severity and for higher-quality trials only.

Publication bias was assessed through visual inspection of funnel plots.

Results of the review
Seven RCTs were included in the review (n= 559 patients, range 25 to 296). The mean Jadad score was 2.9 out of five: three trials had clear descriptions of the randomisation process. Three trials had adequate allocation concealment. Four trials were double-blinded. Two trials had adequate reporting of follow-up. All trials had similar baseline characteristics between treatment and control groups.

For length of hospital stay, the pooled estimate favoured the probiotics/synbiotics group over the control group (mean difference -3.87 days, 95% CI -6.20 to -1.54; $I^2=55\%$; four RCTs; fixed-effect model).

There was a borderline statistically significant pooled estimate favouring the treatment over the control group for infectious morbidity (OR 0.30, 95% CI 0.09 to 1.02; $I^2=84\%$; five RCTs; random-effects model).

Differences were not statistically significant for the outcomes of pancreatic infections (three RCTs), multiple organ failure and systemic inflammatory response syndrome (five RCTs), and mortality (five RCTs), even though the results favoured treatment over control groups in each case.

Adverse effects (three RCTs) included bowel ischaemia, catheter-related sepsis, tube intolerance, and re-intubation.

Subgroup analyses found that outcomes were not affected by pancreatitis severity or by only including trials with clear allocation concealment and blinding.

The funnel plot was slightly asymmetric, so the potential for publication bias could not be ruled out.

Authors' conclusions
Pre-, pro- and synbiotics treatment showed no significant influence on patients with acute pancreatitis. There was a lack of available evidence to support the use of probiotics or synbiotics in this area.

CRD commentary
This review addressed a clear research question. The study selection criteria were clear for outcomes, patient population, and study design. The search appeared to be thorough and well reported, although no measures were reported to identify unpublished studies. The number of reviewers involved at most stages of the review was not clearly reported, reducing review transparency; the risk of reviewer error and bias could not be ruled out.

Primary study details were clear and relatively thorough, increasing review transparency. A standard and appropriate tool was used to assess risk of study bias. Data extraction was clearly reported. The method of synthesis seemed appropriate for most analyses, but the clinical significance of reported heterogeneity in the fixed-effect analysis for length of hospital stay was unclear.

The conclusions reflect the lack of high quality evidence available and the recommendation (that further well designed RCTs are needed) appears appropriate.

Implications of the review for practice and research
Practice: The authors stated that clinicians should be cautious in the use of pre-, pro- and synbiotics in critically-ill patients, especially patients with severe acute pancreatitis, because of concerns raised by this review about their safety and effectiveness.

Research: The authors stated that well-designed RCTs are needed to explore interactions between mechanistic issues and probiotic interactions, and to assess the effectiveness and safety profile of pre-, pro- and synbiotics.
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