Meta-analysis: the effect of supplementation with probiotics on eradication rates and adverse events during Helicobacter pylori eradication therapy

Tong J L, Ran Z H, Shen J, Zhang C X, Xiao S D

CRD summary
The authors concluded that the addition of probiotics to Helicobacter pylori (H. pylori) eradication regimens may increase H. pylori eradication rates and reduce side-effects. This was generally a well-conducted review and the authors' conclusions are likely to be reliable.

Authors' objectives
To evaluate the effects of adding probiotics to anti-Helicobacter pylori (H. pylori) regimens on H. pylori eradication rates and adverse effects.

Searching
PubMed, EMBASE, the Cochrane CENTRAL Register, the Science Citation Index and the Chinese Biomedical Database were searched from inception to October 2006; the search terms were reported. In addition, reference lists of reviews and original studies and abstracts of major gastroenterological meetings were screened, and authors of some identified studies were contacted for details of unpublished RCTs. Studies reported in English or Chinese were included; studies reported in other languages were only included if a translation was available.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for inclusion in the review.

Specific interventions included in the review
Studies in which the control intervention consisted of a proton-pump inhibitor (PPI) plus two antibiotics with placebo or no additional treatment, and the intervention treatment consisted of the same eradication regimen plus probiotics, were eligible for inclusion. The included studies evaluated a variety of probiotic regimens including subspecies of the following, either alone or in combination: Bacillus, Lactobacillus, Propionibacterium, Saccharomyces, Bifidobacterium, faecal streptococci and Clostridium. One study evaluated AB-Yoghurt. Some studies used viable preparations while others used inactive preparations. Treatment duration ranged from 7 days to 3 months. The studies used various triple and quadruple therapy H. pylori eradication regimens (details were reported), and were conducted in Europe, Turkey, Taiwan, China and Argentina.

Participants included in the review
Studies of patients who had not previously been treated for H. pylori infection and studies of patients who had previously failed H. pylori eradication treatments were eligible for inclusion, regardless of age or symptoms at study entry. The included studies were of symptomatic and asymptomatic adults and symptomatic children.

Outcomes assessed in the review
Studies that assessed successful H. pylori eradication and/or side-effects were eligible for inclusion. The studies had to confirm H. pylori eradication by histology or the carbon-13-urea breath test at least 4 weeks post-treatment. The review assessed total side-effects and specific individual side-effects (diarrhoea, nausea, taste disturbance and epigastric pain). In the included studies, the outcomes were assessed from 2 weeks to 4 months post-treatment.

How were decisions on the relevance of primary studies made?
Two reviewers independently selected the studies; any disagreements on inclusion were resolved through recourse to a third author.
Assessment of study quality
Validity was assessed and scored using the Jadad scale, which considers randomisation, blinding and the reporting of withdrawals. The maximum possible score was 5 points. Studies scoring less than 3 points were considered to be of a low quality. Two reviewers independently assessed validity; any disagreements were resolved through recourse to a third author.

Data extraction
Data were extracted onto a standardised form, but the authors did not state how many reviewers performed the data extraction. For each study, eradication and side-effects data were extracted and used to calculate odds ratios (ORs).

Methods of synthesis
How were the studies combined?
Pooled ORs and 95% confidence intervals (CIs) were calculated using fixed-effect methods in the absence of significant heterogeneity (p>0.10) and random-effects models when significant heterogeneity was found. Analyses of eradication rates were performed on an intention-to-treat (ITT) basis and a per-protocol basis. Publication bias was assessed using a funnel plot and tested using the regression asymmetry test of Egger.

How were differences between studies investigated?
Statistical heterogeneity was assessed using the chi-squared statistic. Subgroup analysis was used to examine the influence on eradication rate of age (adult or child), presence of symptoms at baseline, type of probiotic and study quality.

Results of the review
Fourteen RCTs (n=1,671) were included.

The Jadad scores ranged from 2 to 5 out of a possible 5. Six trials scored 2 points and were considered to be of a low quality.

Eradication rates. For patients who had not been previously treated for H. pylori infection, probiotics were associated with significantly increased eradication rates compared with no probiotics: 83.6% versus 74.8% (OR 1.84, 95% CI: 1.34, 2.54), based on ITT analysis of 11 studies (n=1,074). No evidence of statistical heterogeneity was detected (p=0.65; I-squared 0). The results were similar for the per-protocol analysis and after the exclusion of low-quality studies. For patients who had previously failed treatment for H. pylori infection, probiotics were associated with significantly increased eradication rates compared with no probiotics: 88.5% versus 76.0% (OR 2.47, 95% CI: 1.16, 5.29), based on 2 studies (n=208). Probiotics were associated with a significant increase in eradication rates among patients who were symptomatic at baseline, but not in patients who were symptom-free at baseline. Probiotics were associated with a significant increase in eradication rates among adults and children. Probiotics containing Lactobacillus were also associated with a significant increase in eradication rates (based on 4 studies), but there was no significant difference in eradication rates for combinations of probiotics (5 studies), Bacillus clausii (1 study) or Clostridium butyrium (1 study) compared with no probiotics.

Side-effects.
Probiotics were associated with significantly decreased total side-effects compared with no probiotics: 24.7% versus 38.5% (OR 0.44, 95% CI: 0.30, 0.66). Probiotics were associated with significantly decreased diarrhoea (OR 0.34, 95% CI: 0.22, 0.52), epigastric pain (OR 0.62, 95% CI: 0.39, 0.97), nausea (OR 0.58, 95% CI: 0.38, 0.88) and taste disturbance (OR 0.38, 95% CI: 0.17, 0.85).

The funnel plot was slightly asymmetrical but Egger's test was not statistically significant, suggesting the absence of substantial publication bias.
Authors' conclusions
The addition of probiotics to H. pylori eradication regimens may increase H. pylori eradication rates and reduce side-effects.

CRD commentary
The review addressed a clear question that was defined in terms of the participants, intervention, outcomes and study design. Several relevant sources were searched and some attempts were made to minimise publication bias; the authors found no evidence of substantial publication bias. The inclusion of only studies reported in two specific languages might have resulted in the omission of other relevant studies. Validity was assessed, although only the composite score was presented; this makes it difficult to independently comment upon the reliability of the evidence presented. Methods were used to minimise reviewer errors and bias in the study selection and validity assessment processes, but it was unclear whether similar steps were taken for the extraction of data. The studies were appropriately pooled using meta-analysis, statistical heterogeneity was assessed, and the influence of various factors on the results was examined. This was generally a well-conducted review and the authors' conclusions are likely to be reliable.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors stated that further research is required to confirm positive review findings in patients who have failed previous H. pylori eradication treatment, and that larger studies are required to confirm review findings that probiotics may reduce side-effects. Studies are also needed to evaluate effects in asymptomatic volunteers and symptomatic patients, and to determine the optimal strain(s) of probiotics.

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Other publications of related interest
These additional published commentaries may also be of interest. Moayyedi P. Review: eradication therapy supplemented by probiotics increased eradication rates and reduced side effects in H. pylori infection. ACP J Club 2007;145:63. Moayyedi P. Review: eradication therapy supplemented by probiotics increased eradication rates and reduced side effects in H. pylori infection. Evid Based Med 2007;12:84.

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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.