Effect of fermented milk-based probiotic preparations on Helicobacter pylori eradication: a systematic review and meta-analysis of randomized-controlled trials

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CRD summary
The authors concluded that fermented milk-based probiotic products potentially improved Helicobacter pylori eradication by approximately 10%, but the findings were limited by the small number and marginal quality of some trials. Further research is needed. The authors’ conclusions follow from the data presented, but given the moderate quality of the included trials, their caution is justified.

Authors’ objectives
To investigate the effectiveness of fermented milk-based probiotic preparations on Helicobacter pylori eradication.

Searching
AMED, CIAP (Clinical Access Information Program), Cochrane Central Register of Controlled Trials, EMBASE, KoreaMed, medIND, MEDLINE and SCOPUS were searched from inception up to December 2007 for articles in any language. Search terms were reported. Reference lists of identified articles, relevant reviews, books and articles were handsearched. Abstracts of major gastroenterological were scanned. Authors of some identified trials were contacted to identify further unpublished studies.

Study selection
Randomised controlled trials (RCT) or quasi-randomised controlled trials evaluating the impact of fermented milk-based probiotic preparations containing Lactobacillus, Bifidobacterium or other bacteria, on Helicobacter pylori improvement or eradication in symptomatic or asymptomatic Helicobacter-infected patients, were eligible for inclusion. Helicobacter infection had to be measured using urea breath test, histology or stool antigen test. Studies where other drugs were administered were eligible for inclusion only if the difference between the intervention and control group was the administration of a fermented milk-based product.

Included studies were of milk or yogurt fermented with Bifidobacterium animalis, Bifidobacterium lactis, Lactobacillus bulgaris, Lactobacillus casei, Lactobacillus johnsonii or Streptococcus thermophilus alone or in combination in varying doses, administered between one and three times over a period ranging from two to 12 weeks. The majority of studies co-administered single, triple or quadruple drug therapy regimes. The majority of patients in the included studies were symptomatic or asymptomatic Helicobacter-infected adults. Studies of children and of adults with duodenal ulcers were also included. The definition of Helicobacter eradication varied between studies. Adverse events were also included for review. The majority of studies were conducted in high income countries.

Two reviewers independently selected the studies for inclusion.

Assessment of study quality
The methodological quality of the included studies was evaluated according to randomisation, allocation concealment, loss to follow-up and blinding. The authors did not state how many reviewers performed the validity assessment.

Data extraction
The number of events for eradication rates and adverse events was extracted and used to calculate odds ratios with 95% confidence intervals. Eradication rates were extracted as reported in the studies or calculated using the mean pre-C urea breath test. The mean pre-C urea breath test and post-C urea breath test values with corresponding standard deviations and the correlation between pre-test and post-test values were extracted for each study. Authors were contacted for clarification where necessary. For one study where follow-up data were unavailable for the C urea breath test, they were assumed to be equal to values at baseline. Data were extracted onto standardised data abstraction sheets.

The authors did not state how many reviewers performed the data abstraction.
Methods of synthesis
Pooled odds ratios with corresponding 95% confidence intervals were calculated using the Mantel-Haenszel fixed-effect model or by the DerSimonian and Laird random-effects model according to whether there was statistically significant heterogeneity. Both intention-to-treat and per protocol analyses were carried out. The risk difference for *Helicobacter* eradication was also calculated. The pooled difference in mean C-urea breath test values was calculated using a fixed-effect model. Heterogeneity was assessed using the Cochran Q test and visual inspection of forest plots. Sensitivity analyses were performed excluding each trial in turn. Univariate meta-regression analysis was performed investigating age of patients, quality of trial, bacterial preparation and co-intervention. Publication bias was investigated using funnel plots and Egger's test.

Results of the review
Ten trials were included (n=963 participants); two double-blind randomised controlled trials (RCTs), two single-blind RCTs, one double-blind quasi-RCT, two unblinded quasi RCTs and three quasi RCTs with unclear blinding (n not available for individual studies). Six of the trials were placebo-controlled. Allocation concealment was deemed adequate in only one trial, unclear in six trials and inadequate in three trials. Loss to follow-up was less than 5% in six trials, between 5% to 9% in three trials, and 10% or more in one trial.

Eradication rates: Significantly more patients treated with fermented milk-based probiotic preparations achieved *Helicobacter* eradication compared to controls (odds ratio 1.91, 95% CI: 1.38 to 2.65; nine trials, n=943 participants) and eradication rates improved by approximately 10% with the use of fermented milk-based probiotics (risk difference 0.10, 95% CI: 0.05, 0.15; ten trials, n=963 participants).

Change in C-urea breath test values: Fermented milk probiotic supplements were associated with a greater reduction in C-urea breath test values compared to controls (standardised mean difference -0.46, 95% CI: -0.73, -0.20; three trials, n=227 participants). There was no significant difference between groups in the incidence of adverse events (six trials, n=719 participants).

There was no evidence of statistically significant heterogeneity or publication bias for any of the findings. Sensitivity analyses and per-protocol analyses did not alter the findings significantly. Univariate meta-regression analyses did not reveal any significant effect of trial quality, bacterial preparation, duration of supplement, co-intervention or age group on outcomes.

Authors' conclusions
Fermented milk-based probiotic products potentially improved *Helicobacter pylori* eradication by approximately 10%. The findings were limited by the small number and marginal quality of some trials. Further research is needed.

CRD commentary
The review addressed a clear question with well-defined inclusion criteria. Several relevant databases were searched and appropriate steps were taken to minimise the risk of language and publication bias. Publication bias was assessed and no evidence was found, though for some outcomes; there were insufficient studies to definitively rule it out. Suitable steps were taken in the study selection process to minimise reviewer error and bias. It was unclear whether similar steps were taken in the validity assessment and data extraction processes. Overall, suitable methods of synthesis were used, statistical heterogeneity was assessed, sensitivity analyses were conducted and potential sources of variance were explored. The authors' conclusions follow from the data presented. Given the moderate quality of the included trials, their caution is justified.

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 needed comparing fermented milk-based probiotic products with capsule/sachet based preparations. Strain and preparation-specific effects should be documented in patients receiving first-line or eradication-failure regimes. Further research is also needed into long-term treatment with fermented milk-based probiotic products and their use in developing countries.
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