Meta-analysis: Lactobacillus containing quadruple therapy versus standard triple first-line therapy for Helicobacter pylori eradication

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CRD summary
Supplementation with Lactobacilli could be effective in increasing eradication rates of anti-Helicobacter pylori therapy for first treated patients. Lactobacilli may also have reduced Helicobacter pylori therapy-related side effects. The overall conclusions were supported by the results, but subgroup analyses suggested that benefits of Lactobacilli supplementations may have been restricted to specific patient groups.

Authors' objectives
To evaluate the addition of Lactobacilli to Helicobacter pylori (H. pylori) eradication regimens in terms of eradication rates and side effects.

Searching
PubMed, EMBASE, Science Citation Index, Chinese Biomedical Database and Cochrane Central Register of Controlled Trials (CENTRAL) were searched to March 2009. References from selected trials and reviews were scanned. Authors were contacted to enquire about unpublished studies. Records of two relevant conferences from 1995 to 2009 were handsearched. Search terms were reported. Studies in any language were considered for inclusion.

Study selection
Randomised controlled trials (RCTs) that compared triple therapy for H. pylori (proton pump inhibitor plus two antibiotics) plus placebo or on its own versus triple therapy plus Lactobacilli in patients being treated for H. pylori for the first time were eligible for inclusion. Papers were required to report rates of successful eradication and/or side effects.

Most of the included studies came from Italy; single studies were from Czech Republic, Mexico and Poland. Patients included symptomatic and asymptomatic children and adults. Age ranges were not reported. Diagnostic methods included histology, culture, 13C urea breath test and rapid urease test. The antibiotic component of the triple therapy included clarithromycin plus amoxicillin or clarithromycin plus tinidazole. The Lactobacillus component was made up of a variety of strains, strengths and delivery methods. Treatment duration was seven days in all except one of the trials.

Studies were independently selected by two reviewers. Disagreements were resolved by discussion with a third reviewer.

Assessment of study quality
Study quality was assessed using the published Jadad scale of validity based on randomisation, double-blinding and withdrawals/dropouts. Studies were scored from 0 to 5. Less than 3 was considered to be low quality.

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

Data extraction
Standardised data extraction forms were used to record key outcome data in the form of odds ratios (OR) that included eradication rates, occurrence of diarrhoea, nausea, taste disturbance and abdominal pain.

The authors did not report how many reviewers performed data extraction.

Methods of synthesis
Mantel-Haenszel fixed-effect meta-analysis was used where appropriate to calculate pooled odds ratios of eradication...
rates and side effects using intention-to-treat and per protocol data. Heterogeneity was assessed using the $\chi^2$ test. Random-effects models were used where significant heterogeneity was noted.

Subanalyses were planned for type of drugs co-prescribed, duration and subspecies of *Lactobacillus*, age of patients and study quality. Publication bias was assessed with a funnel plot and Egger's regression test.

**Results of the review**

Nine RCTs were identified of which eight (n=766) were included in the meta-analyses. Study quality scores ranged from 2 to 5; one RCT scored 2 and was excluded due to poor quality.

The supplemental *Lactobacillus* regime was associated with more successful eradication (OR 1.78, 95% CI 1.21 to 2.62; eight RCTs) and fewer side effects in terms of diarrhea (OR 0.23, 95% CI 0.11 to 0.48; five RCTs), bloating (OR 0.41, 95% CI 0.23 to 0.75; three RCTs) and taste disturbance (OR 0.23, 95% CI 0.11 to 0.47; four RCTs) compared to standard *Lactobacillus* regime. There was no difference between treatment groups when total side effects were considered (six RCTs) and for the individual symptoms of nausea or abdominal pain.

Subgroup analysis showed that eradication rates differed significantly between treatment arms only for symptomatic patients (two RCTs) and clarithromycin plus amoxicillin plus *Lactobacillus* (five RCTs); differences between treatment groups were not significant for studies conducted in asymptomatic patients (three RCTs), adults (six RCTs) and for clarithromycin plus tinidazole plus *Lactobacillus* (three RCTs).

The funnel plot showed slight asymmetry, but this was not statistically significant. Significant heterogeneity was noted only for the total side effects analysis.

**Authors' conclusions**

Supplementation with *Lactobacilli* could be effective in increasing eradication rates of anti-*H. pylori* therapy for first treated patients. *Lactobacilli* may reduce *H. pylori* therapy-related side effects.

**CRD commentary**

This review addressed a clear clinical question with appropriate inclusion criteria. Searches were comprehensive and likely to have reduced the chances of language and publication biases. The review methodology was only partially described, which made it difficult to rule out reviewer error and bias. Quality assessment was performed and reported, although use of a brief summary scale may have omitted valuable information and exclusion of a study on the basis of quality may have affected the overall results. There was substantial clinical heterogeneity, so the overall pooling of trials may not have been entirely appropriate; however, relatively little statistical heterogeneity was noted. The overall conclusions were supported by the results, but subgroup analyses suggested that the benefits of *Lactobacilli* supplementations may have been restricted to specific patient groups.

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

The authors made no specific recommendations for practice or research.

**Funding**

Not stated.

**Bibliographic details**


**PubMedID**

19751434

**DOI**

10.1111/j.1523-5378.2009.00716.x
Original Paper URL

Indexing Status
Subject indexing assigned by NLM

MeSH
Anti-Bacterial Agents /adverse effects /therapeutic use; Antibiosis; Combined Modality Therapy; Helicobacter Infections /drug therapy /microbiology /therapy; Helicobacter pylori /drug effects /physiology; Humans; Lactobacillus /physiology; Probiotics /adverse effects /therapeutic use; Randomized Controlled Trials as Topic; Treatment Outcome

AccessionNumber
12009109782

Date bibliographic record published
14/04/2010

Date abstract record published
22/09/2010

Record Status
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.