Meta-analysis: the relationship between Helicobacter pylori infection and gastro-oesophageal reflux disease

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CRD summary
This review assessed the relationship between treatment for Helicobacter pylori (H. pylori) infection and gastro-oesophageal reflux disease (GERD). The authors concluded that there is a significant positive relationship between anti-H. pylori treatment and de novo GERD and recurrent or exacerbated GERD. The results of the studies differed, suggesting that the relationship may not be constant.

Authors' objectives
To examine the relationship between treatment for Helicobacter pylori (H. pylori) infection and de novo and rebound or exacerbation of pre-existing gastro-oesophageal reflux disease (GERD). The review also investigated the relationship between H. pylori and GERD, but this abstract only refers to the relationship between H. pylori infection treatment and GERD.

Searching
MEDLINE (from 1966 to September 2002) and EMBASE (from 1988 to September 2002) were searched for studies published in English; the keywords were given. In addition, the reference lists of identified papers were handsearched. Abstracts, review articles, commentaries and book chapters were excluded.

Study selection
Study designs of evaluations included in the review
Controlled clinical trials (including non-randomised controlled trials) with at least one month of follow-up were eligible for inclusion. The duration of follow-up in the included studies ranged from 6 to 104 weeks.

Specific interventions included in the review
Clinical trials of eradication treatment for H. pylori were eligible for inclusion if the treatment groups were given the same acid-suppression treatment after eradication treatment.

Participants included in the review
The inclusion criteria were not specified in terms of the participants. The included studies were conducted in patients with duodenal ulcers, oesophagitis, or active or previous peptic ulcer, and in H. pylori positive patients with heartburn.

Outcomes assessed in the review
The review assessed the presence of de novo and rebound or exacerbated GERD symptoms or oesophagitis after at least one month.

How were decisions on the relevance of primary studies made?
Two reviewers independently selected the studies and resolved any disagreements on inclusion through recourse to a third author.

Assessment of study quality
The authors did not state that they assessed validity.

Data extraction
Two reviewers independently extracted the data and resolved any disagreements through recourse to a third author.
Data on the whole population were not extracted from 4 studies. The odds ratios (ORs) and the number-needed-to-harm were calculated for each study, together with their respective 95% confidence intervals (CIs).

**Methods of synthesis**

How were the studies combined?
The RCTs were combined using a meta-analysis. Pooled ORs and 95% CIs were calculated using the Mantel-Haenszel fixed-effect model. A funnel plot was used to assess publication bias.

How were differences between studies investigated?
Studies accounting for statistical heterogeneity were identified.

Logistic regression was used to explore the following potential sources of heterogeneity: blinding; clinical outcome used to assess GERD (symptoms and/or oesophagitis); outcome patterns (de novo or recurrent GERD); the duration of follow-up; type of patients (all patients treated versus only patients with successful eradication of H. pylori); type of analysis (per protocol versus intention-to-treat); and study location (Europe, Asia or North America). A sensitivity analysis was conducted by reanalysing the data after excluding studies responsible for heterogeneity.

The meta-analysis was repeated as follows: after excluding non-randomised trials; for studies with H. pylori negative patients in the control arms; only including studies that assessed endoscopically or histologically confirmed oesophagitis; including only studies of patients with peptic ulcer disease; after excluding studies in which data were not extracted for the whole sample; and after excluding studies that were conducted in Asia. The influence of baseline risk of GERD on the effect of anti H. pylori treatment was explored by plotting the OR of GERD against the average rate of GERD (both de novo and rebound or exacerbated) in the active treatment and control groups.

**Results of the review**

Ten randomised controlled trials (RCTs) were included in the meta-analysis (2,150 patients).

The funnel plot showed no evidence of publication bias or outliers.

Anti-H. pylori treatment was associated with an increased risk of developing de novo GERD (OR 3.25, 95% CI: 2.09, 5.33). The overall pooled OR for de novo or recurrent GERD was 2.54 (95% CI: 1.92, 3.37). Significant heterogeneity was detected for both meta-analyses (P<0.001). The pooled OR for rebound or exacerbated GERD was 1.65 (95% CI: 1.14, 2.40).

After excluding 3 RCTs that contributed significantly to the heterogeneity, the OR remained significant (OR 3.03, 95% CI: 2.09, 4.47; chi-squared 32.71).

The pooled OR for any GERD outcome remained significant in the following sensitivity analyses: after excluding trials with H. pylori negative patients in the control arms; only including studies that assessed endoscopically or histologically confirmed oesophagitis; including only studies of patients with peptic ulcer disease; including only studies of patients without peptic ulcer disease; after excluding studies in which data were not extracted for the whole sample; and after excluding studies performed in Asia (the results were reported).

The baseline risk of GERD did not appear to influence the risk of developing GERD after H. pylori eradication (the data were not reported).

The pooled OR for GERD after adjusting for factors that were potential sources of heterogeneity was 2.13 (95% CI: 1.54, 2.94; chi-squared 21.27).

**Authors’ conclusions**

There is a significant positive relationship between anti-H. pylori treatment and de novo and recurrent or exacerbated GERD. The strength of the relationship varied according to geographical location and between different studies.
The review question was clear in terms of the study design, intervention and outcomes; the inclusion criteria relating to the participants were not specified. By limiting the included studies to those in English language publications listed in two databases and bibliographies of identified studies, the authors might have missed some relevant studies. No attempt to locate unpublished studies was made, but the authors did assess the possibility of publication bias. Two reviewers independently selected the studies and extracted the data, which reduces the potential for bias and errors. A formal assessment of validity was not reported, but sensitivity analyses examined the effect of study characteristics on the pooled outcome.

The data were combined using a meta-analysis and statistical heterogeneity was assessed. The review found an association between anti-H. pylori treatment and the occurrence of GERD. The authors found considerable variation between the studies, and their advice that the individual risk or benefit should be determined appears appropriate.

Implications of the review for practice and research
Practice: The authors stated that clinical practice must balance the risk and benefits of anti-H. pylori treatment in individual patients.

Research: The authors did not state any implications for further research.

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