Do patients with non-ulcer dyspepsia respond differently to Helicobacter pylori eradication treatments from those with peptic ulcer disease: a systematic review

CRD summary
This review assessed whether patients with non-ulcer dyspepsia respond differently to Helicobacter pylori eradication treatment than those with peptic ulcer disease. No convincing evidence for a difference in eradication rate was identified. Despite uncertainty about the quality of the included studies, this was generally a good-quality systematic review and the authors' conclusions are likely to be reliable.

Authors' objectives
To assess whether patients with non-ulcer dyspepsia (NUD) respond differently to Helicobacter pylori (H. pylori) eradication treatment than those with peptic ulcer disease (PUD).

Searching
The Cochrane Controlled Trials Register, MEDLINE and EMBASE were searched to June 2004 without any language restrictions; the search terms were reported. The authors also searched several online trials registers including the United Kingdom National Research Register, Current Science register of controlled trials and ClinicalTrials.gov. Reference lists, review articles, editorials and abstracts from major relevant international meetings were handsearched.

Study selection
Study designs of evaluations included in the review
Clinical trials were eligible for inclusion. The authors did not state the design of the included studies.

Specific interventions included in the review
Studies that used one of the following H. pylori eradication combination regimens, given in the recommended doses, were eligible for inclusion: a proton-pump inhibitor (PPI) or ranitidine bismuth citrate plus two antibiotics (clarithromycin, amoxicillin, metronidazole or tinidazole); or PPI-based quadruple therapies.

The PPIs used in the included studies were omeprazole, lansoprazole, pantoprazole and rabeprazole, given for 7 to 14 days in doses from 20 to 40 mg once or twice daily. Ranitidine bismuth citrate was given for 5 or 7 days in doses of 350 or 400 mg twice daily. The antibiotics used were clarithromycin, tinidazole, furazolidone, tetracycline, amoxicillin and metronidazole. Full details of the regimens used were given.

Participants included in the review
Studies of adults with H. pylori infection, diagnosed by rapid urease test, histology, culture or urea breath test, were eligible for inclusion in the review. Studies of patients with chronic gastritis alone were excluded. No details of the actual patients included in the studies were provided.

Outcomes assessed in the review
Studies that provided comparative data on H. pylori eradication rates (confirmed at least 4 weeks after stopping all medications) between patients with NUD and patients with PUD were eligible for inclusion. The studies had to provide raw data for intention-to-treat (ITT) analysis, or ITT data, to be eligible for inclusion.

How were decisions on the relevance of primary studies made?
Two reviewers independently assessed the identified articles. Any disagreements were resolved by discussion to reach consensus between the reviewers.

Assessment of study quality
The authors stated that the quality assessment focused primarily on the quality of presentation of study results, such as whether ITT results were clearly presented. Two reviewers independently assessed the quality of the included studies.

**Data extraction**

Two reviewers independently extracted the data from the included studies. Any disagreements were resolved by discussion to reach consensus between the reviewers. Details of the publication, study design, participants, diagnosis methods, treatment and H. pylori eradication were extracted. The H. pylori eradication rates were extracted by ITT analysis and by disease category (PUD, including duodenal and gastric ulcer, or NUD).

**Methods of synthesis**

How were the studies combined?

Pooling was undertaken if 3 or more studies were available for each analysis. Summary relative risks (RRs), risk differences and 95% confidence intervals (CIs) were calculated using a random-effects model. The number-needed-to-treat (NNT) was also calculated. In cases when less than 3 studies were available, the results of the individual studies were described.

Publication bias was assessed using Egger's regression method.

How were differences between studies investigated?

The Cochran Q method was used to assess statistical heterogeneity. Where heterogeneity was statistically significant (P<0.1), sources of methodological heterogeneity were sought.

Subgroup analyses were performed according to the treatment regimen (including dose and treatment duration) and by type of publication (meeting abstract or full article).

**Results of the review**

Twenty-one studies (n=3,655) were included in the review.

Ranitidine bismuth citrate-containing regimens (6 trials).

Seven different combination regimens and ten treatment arms were reported. The only combination with sufficient studies to combine using a meta-analysis was a triple therapy consisting of ranitidine bismuth citrate 400 mg, clarithromycin 500 mg and amoxicillin 1 g, all given twice daily for 7 days. There was no statistically significant difference in eradication rate between patients with PUD and those with NUD (summary RR 0.96, 95% CI: 0.84, 1.11). Heterogeneity was not statistically significant (P=0.56).

One study reported a statistically significant difference in H. pylori eradication between patients with PUD and those with NUD. The combination regimen consisted of ranitidine bismuth citrate 400 mg, clarithromycin 400 mg, amoxicillin 1 g and metronidazole 500 mg, all given twice daily for 5 days. The eradication rate was 100% in 174 patients with PUD and 87.3% in 71 patients with NUD (P<0.05).

PPI-based quadruple therapies (5 trials).

Four different combination regimens and six treatment arms were reported. A meta-analysis was not possible because of variability in the drug combinations. None of the studies reported a statistically significant difference in H. pylori eradication between patients with PUD and those with NUD.

Triple therapies comprising PPI, clarithromycin and amoxicillin (9 trials).

Nine different combination regimens and twelve treatment arms were reported. Six studies using a triple therapy consisting of a standard dose of a PPI, clarithromycin 500 mg and amoxicillin 1 g, all given twice daily for 7 days, were combined. The eradication rate in patients with PUD was statistically significantly higher than for patients with NUD (summary RR 1.15, 95% CI: 1.01, 1.29). However, there was statistically significant heterogeneity between studies.
(P=0.037). The summary risk difference was estimated at 0.11 (95% CI: -0.01, 0.22), giving an estimated NNT of 9. There was no evidence of statistically significant publication bias when using Egger's regression test (P=0.08).

A subgroup analysis was performed according to the type of publication. When the 4 studies that were published in abstract form were pooled, the difference in eradication rate was of borderline statistical significance in favour of PUD (summary RR 1.23, 95% CI: 1.00, 1.52). However, there was still statistically significant heterogeneity between studies (P=0.037).

Three studies using a triple therapy consisting of a standard dose of a PPI, clarithromycin 500 mg and amoxicillin 1 g, all given twice daily for 10 days, were combined. There was no statistically significant difference in eradication rate between patients with PUD and those with NUD (summary RR 1.03, 95% CI: 0.95, 1.12). Heterogeneity was not statistically significant (P=0.42).

Triple therapies comprising PPI, metronidazole and clarithromycin or amoxicillin (4 trials).

Five different combination regimens and five treatment arms were reported. A meta-analysis was not possible because of the variability in the drug combinations. None of the studies reported a statistically significant difference in H. pylori eradication between patients with PUD and those with NUD.

Authors' conclusions
There was no convincing evidence to suggest that patients with NUD respond differently to H. pylori eradication treatments than those with PUD, although a trend exists with the 7-day triple therapy comprising a standard dose of PPI, clarithromycin and amoxicillin.

CRD commentary
The review question was clear in terms of the study design, participants, interventions and outcomes of interest. A number of relevant electronic databases and trials registers were searched for relevant studies and the search terms were reported. Unpublished data were sought and language restrictions were not applied, thus reducing the potential for publication or language bias. Publication bias was assessed. The study selection, data extraction and quality assessment processes were carried out in duplicate, thereby reducing the potential for reviewer bias or error.

Details of the included studies were restricted to treatment regimens and results; no details of the participants were presented. The results of the quality assessment exercise were not reported. Nine of the included studies were only reported in abstract format, therefore study details are likely to have been limited. Appropriate measures of effect were calculated and statistical heterogeneity was assessed and investigated when found. Overall, this was a good-quality systematic review and the authors' conclusions follow from the evidence presented. However, the small number of studies available for analysis and the lack of study quality assessment results are limitations of the review.

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

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