Meta-analysis: the efficacy, adverse events, and adherence related to first-line anti-Helicobacter pylori quadruple therapies

Fischbach L A, Van Zanten S V, Dickason J

CRD summary
This review of the safety and efficacy of first-line anti-Helicobacter pylori quadruple therapies concluded that guidelines should include quadruple therapy with a proton-pump inhibitor, a bismuth compound, metronidazole and tetracycline among recommended first-line therapies. While the authors' conclusion seems reasonable, it is difficult to properly verify it given the lack of information on the individual studies.

Authors' objectives
To summarise the efficacy, safety and adherence of first-line quadruple Helicobacter pylori (H. pylori) therapies in adults.

Searching
MEDLINE was searched from inception to 2004 for articles in English, Spanish, Dutch or French; the search terms were reported. Reference lists from relevant studies and reviews, and abstracts from the journals Gut and Gastroenterology, were also searched.

Study selection
Study designs of evaluations included in the review
The inclusion criteria for study design were not specified.

Specific interventions included in the review
Studies evaluating first-line quadruple H. pylori therapies were eligible for inclusion provided they reported the name, dosage, frequency and duration of the medications used in the quadruple therapy and used a consistent treatment protocol throughout the study. The most commonly used quadruple therapy in the included studies contained metronidazole, tetracycline, a gastric acid inhibitor and a bismuth compound (GBMT). Regimens containing a gastric acid inhibitor, bismuth, metronidazole and amoxicillin (GBNA) and a gastric acid inhibitor, a nitroimidazole, clarithromycin and amoxicillin (GNCA) were also used. The duration of treatment was most commonly 7 days, followed by 14 days and 10 to 12 days for GBMT, less than 4 days followed by 7 days for GBNA, and less than 7 days for GNCA. The comparators used in the included studies were generally unclear, although some of the studies used triple therapy or placebo.

Participants included in the review
Studies of adults who were positive for H. pylori were eligible for inclusion. The participants in the included studies were from 17 different countries.

Outcomes assessed in the review
Studies were eligible for inclusion if they reported sufficient information to enable the calculation of the proportion of patients cured. The primary outcome of interest was the risk difference between first-line quadruple therapy and no anti-H. pylori therapy. Adverse events and treatment adherence were also investigated.

How were decisions on the relevance of primary studies made?
Two authors independently assessed full articles for relevance, with any disagreements resolved by consensus.

Assessment of study quality
The studies were assessed for the following criteria: publication status (whether or not it had been peer reviewed), year
reported, study design, methods used to diagnose H. pylori after treatment, use of intention-to-treat analysis, sample size and funding source. Two authors independently assessed the quality of the studies, with any disagreements resolved by consensus.

**Data extraction**

Two authors independently extracted the data, with any disagreements resolved by consensus. The prevalence of H. pylori in children in the local population was used as a proxy for rate of reinfection and transmission. When this information was not available in a paper, other sources were used (see Other Publications of Related Interest). Where available, this information was used to separate treatment arms according to H. pylori drug resistance status. Intention-to-treat data were used for all outcomes except the primary outcome.

**Methods of synthesis**

How were the studies combined?

The studies were pooled in a multi-level meta-regression (weighted for sample size), for each regimen assessed in more than 4 studies, to estimate the pooled risk difference (RD) and 95% confidence interval (CI). Twenty-seven studies (n=1,654) were excluded from pooling as the particular treatment regimen was used in less than 4 studies. Weighted mean values were used to calculate the RD and 95% CI for homogeneous groups. Where there was residual heterogeneity, the entire range of mean values was calculated. Funnel plots were used to investigate publication bias.

How were differences between studies investigated?

Differences between the studies were assessed graphically, and using the chi-squared and exact tests. A meta-regression (weighted for sample size) was used to assess potential sources of variation in treatment effectiveness. The factors of interest were geographic location, prevalence of drug-resistant strains of H. pylori in the local population, mean age, proportion of males, gastroenterological diagnosis of participants, treatment details, and each of the components of study quality assessed. When sources of variation were identified, statistical heterogeneity was investigated in the subgroups (see Other Publications of Related Interest).

**Results of the review**

Ninety-eight studies (n=7,151) were included: 39 randomised controlled trials and 59 controlled trials.

**GBMT.**

The efficacy of GBMT was heterogeneous across treatment arms. Treatment was 33% less effective when given for 1 to 3 days and 6% less effective when given for 7 days, when compared with 10 to 14 days. Efficacy was similar when treatment was given for 4 days. Treatment was more effective when the study was conducted in the Netherlands, Hong Kong or Australia, but less effective when the study was conducted in Greece. When omeprazole was included in the regimen, 6% more infections were cured. Effectiveness was decreased (by 9%) where the prevalence of metronidazole resistance increased. There was evidence of publication bias.

**GBMT versus triple therapy (14 studies).**

The efficacy of GBMT was 5 to 26% greater than triple therapy containing bismuth, metronidazole and tetracycline in the presence of metronidazole resistance. GBMT was 33 to 75% more effective than proton-pump inhibitor clarithromycin plus amoxicillin (PPI-CA) where there was a high prevalence of clarithromycin resistance. There was no difference in efficacy between the two treatments where clarithromycin resistance was low or where there was metronidazole resistance. The number of adverse events was similar between GBMT and these triple therapies, and were generally mild.

Adherence to GBMT was similar to or greater than other therapies, regardless of the number of drugs in all comparisons but one, and ranged from 85 to 100%.

Similar analyses were reported for GBNA and GNCA, though there were insufficient data to adequately examine efficacy, adherence or adverse events.
Authors' conclusions
Quadruple therapy containing GBMT for 10 to 14 days cures more than 85% of H. pylori infections in populations outside of Greece. It is more efficacious than PPI-CA in the presence of clarithromycin resistance, and as effective in the presence of high prevalence metronidazole.

CRD commentary
The review addressed a clear research question using defined inclusion criteria for the interventions, participants and outcome. The authors searched a relevant electronic database, and also conducted some handsearches, though no specific attempt was made to locate unpublished studies and there was evidence of publication bias. Although papers in any of four languages were eligible for inclusion, language bias may be an issue as the authors were investigating variation between countries. The method for selecting full papers for assessment was not reported, therefore selection bias cannot be ruled out. However, other review processes were conducted in duplicate, thus reducing the risk of error and bias.

The meta-regression investigated a large number of predictor variables, but it was unclear from information reported whether there were sufficient participants in the included studies for some of the analyses conducted. No details of the included studies were reported. While key sources of variation in treatment efficacy seem to have been investigated, the lack of information about the included studies makes it difficult to assess whether there were other important sources of clinical heterogeneity.

Implications of the review for practice and research
Practice: The authors stated that guidelines should include quadruple therapy with proton-pump inhibitor, a bismuth compound, metronidazole and tetracycline among recommended first-line anti-H. pylori therapies.

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

Bibliographic details

PubMedID
15569109

DOI
10.1111/j.1365-2036.2004.02248.x

Other publications of related interest

Indexing Status
Subject indexing assigned by NLM

MeSH
Antacids /therapeutic use; Bismuth /therapeutic use; Drug Resistance, Bacterial; Drug Therapy, Combination /therapeutic use; Guideline Adherence; Helicobacter Infections /drug therapy; Helicobacter pylori; Humans; Metronidazole /therapeutic use; Practice Guidelines as Topic; Tetracycline /therapeutic use; Treatment Outcome

AccessionNumber
12005009086
Date bibliographic record published
31/03/2006

Date abstract record published
31/03/2006

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.