A systematic comparison of triple therapies for treatment of Helicobacter pylori infection with proton pump inhibitor/ranitidine bismuth citrate plus clarithromycin and either amoxicillin or a nitroimidazole


Authors’ objectives
To evaluate whether there is a difference in the efficacy between triple therapies with proton-pump inhibitor (PPI) or ranitidine bismuth citrate (RBC) plus clarithromycin and either amoxicillin or a nitroimidazole, for the treatment of Helicobacter pylori (H. pylori) infection.

Searching
MEDLINE was searched to August 2000 for reports of clinical studies. A manual review of all abstracts from the following major international meetings was also performed: the Digestive Disease Week of the American Gastroenterological Association (from 1996 to 2000), the European Helicobacter pylori Study Group meeting (from 1995 to 1999), and the United European Gastroenterology Week (from 1994 to 1999). In addition, all the papers and reviews were examined to identify citations to any other relevant studies.

Study selection
Study designs of evaluations included in the review
Randomised trials. All the included studies used a randomised comparative design. The types of blinding methods used in the studies, where reported, were double-blind, single-blind and open-label. H. pylori eradication had to be confirmed at least 4 weeks after treatment by at least one reliable method (culture, histology, or urea breath test). Studies had to have at least an abstract in English, Dutch, German or French. Duplicate reports or studies obviously reporting results from the same population were eliminated, and only the most recent abstract or full paper was used.

Specific interventions included in the review
Triple regimens containing a PPI or RBC, plus clarithromycin and either amoxicillin or a nitroimidazole (metronidazole, tinidazole or ornidazole). Extended use of a PPI or H2-receptor antagonist was allowed.

In studies examining RBC, the length of therapy ranged from 5 to 10 days. The RBC and amoxicillin dosages were 400 mg twice daily (b.d.) and 1,000 mg b.d., respectively, in all such studies. The clarithromycin dosage ranged from 250 mg three times a day (t.d.s.) to 500 mg b.d. The nitroimidazole dosage ranged from 250 to 500 mg b.d.

In studies examining a PPI, the length of therapy ranged from 5 to 15 days. The PPIs included omeprazole (20 mg b.d. or once daily, o.d.), lansoprazole (30 mg b.d. or o.d.), pantoprazole (40 mg b.d. or o.d.) and rabeprazole (20 mg b.d.). The dosage of clarithromycin ranged from 250 mg b.d. or t.d.s. to 500 mg b.d. and t.d.s. The amoxicillin dosage ranged from 500 mg b.d. or four times daily (q.d.s.) to 1,000 mg b.d. The nitroimidazole dosage ranged from 250 mg b.d. or q.d.s. to 500 mg b.d. or t.d.s.

Participants included in the review
The authors do not state any specific inclusion or exclusion criteria relating to the participants. The participants included were insulin-dependant diabetic patients or healthy individuals with Helicobacter infection who had either peptic ulcers or non-ulcer dyspepsia.

Outcomes assessed in the review
H. pylori eradication. The main outcome of interest was the cure rates.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the reviewers performed the selection.
Assessment of study quality
The authors do not state that they assessed validity.

Data extraction
The authors do not state how the data were extracted for the review, or how many of the reviewers performed the data extraction. Data were extracted on the study design, participants studied and intervention details.

Methods of synthesis
How were the studies combined?
The cure rates from intention-to-treat (ITT) and per protocol analyses for the different treatment modalities were combined. Studies were grouped according to the type of acid inhibitor used, i.e. a PPI or RBC. Funnel plots were constructed as a crude measure to detect bias in the selection of studies (see Other Publications of Related Interest no.1). The weighted differences were plotted against study sample size. Differences in the pooled cure rates and the drop-out rates between the different treatment modalities were calculated, along with 95% confidence intervals (CIs). The methods used to calculate the pooled differences weighted for effect size were based on the chi-squared function for the comparative analysis of two rates (see Other Publications of Related Interest no.2).

How were differences between studies investigated?
There was no formal assessment of heterogeneity.

Results of the review
Forty-seven randomised comparative studies: 8 used a double-blind design, 9 a single-blind, 9 were open-label, and 21 did not report whether or not a blinding method was used. The data required to calculate the overall sample size were not provided.

RBC-clarithromycin-amoxicillin versus RBC-clarithromycin-nitroimidazole (8 studies).

The pooled ITT cure rates for the amoxicillin and nitroimidazole arms were 81% (range: 71 to 96) and 88% (range: 78 to 94), respectively. One study reached significantly better results for the nitroimidazole-containing regimen. The weighted difference between the pooled cure rates for the two treatment arms was statistically significant in favour of RBC-clarithromycin-nitroimidazole, with a weighted difference of 6% (95% CI: 2.10). The pooled per protocol cure rates for the amoxicillin and nitroimidazole arms were 88% (range: 82 to 100%) and 91% (range: 84 to 96), respectively. The weighted difference between the pooled cure rates, in favour of RBC-clarithromycin-nitroimidazole, was not statistically significant.

There was no significant difference in the cure rates for nitroimidazole-susceptible and -resistant strains in the only study that measured antibiotic susceptibility.

No serious side-effects were reported, and the pooled drop-out rates were equal. The number and size of the studies were too small to draw any conclusions regarding publication bias.

PPI-clarithromycin-amoxicillin versus PPI-clarithromycin-nitroimidazole (40 studies). The pooled ITT cure rates for the amoxicillin and nitroimidazole arms were 79% (range: 24 to 95) and 79% (range: 42 to 100), respectively. In 5 studies, the difference was statistically significant in favour of the nitroimidazole-containing regimen, and in one study it was in favour of the amoxicillin-containing regimen. The weighted difference between the pooled cure rates, in favour of PPI-clarithromycin-nitroimidazole, was not statistically significant.

The pooled per protocol cure rates for the amoxicillin and nitroimidazole arms were 83% (range: 33 to 100) and 84% (range: 52 to 100), respectively. In 6 studies, the difference was statistically significant in favour of the nitroimidazole-containing regimen. The weighted difference between the pooled cure rates, in favour of PPI-clarithromycin-nitroimidazole, was not statistically significant.

In nitroimidazole-susceptible strains, PPI-clarithromycin-nitroimidazole performed better, and in nitroimidazole-
resistant strains, PPI-clarithromycin-amoxicillin performed better.

No serious side-effects were reported, and the pooled drop-out rates were equal. The funnel plot was symmetrical, indicating that the amount of selection bias was limited.

**Authors’ conclusions**
In general, the PPI-clarithromycin-nitroimidazole and PPI-clarithromycin-amoxicillin regimens were equally effective. Therefore, other factors such as local prevalence of restraint strains, cost of therapy and options for second-line treatment, should determine which regimen should be preferred. When using RBC, the nitroimidazole-containing combination was somewhat superior to the amoxicillin-containing combination.

**CRD commentary**
The review question was clearly stated and was supported by the inclusion and exclusion criteria. Only one database was searched and there were no details of the search terms used. Papers other than those in English were considered for inclusion. The authors did not specify whether the search was restricted to published papers only; however, publication bias was assessed.

The validity of the included studies was not assessed. Some study details were provided in the text of the review, and it was stated that tables summarising all the data are available from the authors. The data were synthesised by combining cure rates for different treatment modalities; however, heterogeneity was not formally assessed. The authors did not provide any details of the review process with regard to how decisions were made on the relevance of the primary studies and how the data were extracted.

The authors’ conclusion appears to follow from the results of the review, but should be viewed with caution in light of the caveats highlighted.

**Implications of the review for practice and research**
Practice: The authors 'recommend that when using clarithromycin and a nitroimidazole, these antibiotics should be combined with RBC instead of a proton-pump inhibitor'.

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

**Bibliographic details**

**PubMedID**
11328254

**Other publications of related interest**

**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
Amoxicillin /administration & dosage /therapeutic use; Anti-Bacterial Agents /administration & dosage /therapeutic
use; Anti-Ulcer Agents /administration & dosage /therapeutic use; Bismuth /administration & dosage /therapeutic use; Clarithromycin /administration & dosage /therapeutic use; Drug Costs; Drug Resistance; Drug Therapy, Combination; Helicobacter Infections /drug therapy /pathology; Helicobacter pylori /drug effects /pathogenicity; Humans; Nitroimidazoles /administration & dosage /therapeutic use; Patient Care Planning; Penicillins /administration & dosage /therapeutic use; Proton Pump Inhibitors; Randomized Controlled Trials as Topic; Ranitidine /administration & dosage /analog & deriv/therapeutic use; Treatment Outcome

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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.