Evaluation of treatment regimens to cure Helicobacter pylori infection: a meta-analysis
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Authors' objectives
To assess the effectiveness of treatments to cure Helicobacter pylori infection.

Searching
MEDLINE (1983 to 1997) was searched with the following subject heading terms: 'Campylobacter or Helicobacter pylori', eradict, 'Human in TG' or 'Helicobacter-infections-drug-therapy in TI, AB, MeSH'. Volumes of the 'American Journal of Gastroenterology', 'Gastroenterology', 'Gut' and the 'Scandinavian Journal of Gastroenterology' published between 1986 and January 1998 were handsearched for additional studies. Additional publications were retrieved by reviewing references in reviews and meta-analyses. Only studies published in English, German, French and Dutch were included. Studies were excluded if they were not available in any Dutch library or if they were reviews, meta-analyses or commentaries.

Study selection
Study designs of evaluations included in the review
All clinical trials. Studies were excluded if there was insufficient data about the medication used, the number of patients or the cure rate within 4 weeks of treatment. In addition studies were excluded if patients received acid suppressive therapy in the 4 weeks after treatment.

Specific interventions included in the review
No medication was excluded a priori. The following medications were assessed in the review.

Proton-pump inhibitors (omeprazole, lansoprazole, pantoprazole and rabeprazole), H2-receptor antagonists (cimitidine, famotidine, nizatidine, ranitidine and roztadine, ranitidine bismuth citrate), bismuth salts (bismuth subnitrate, bismuth subsalicylate, colloidal bismuth subcitrate and tripotassium dicitrato bismuthate), tetracyclines (doxyxyclin, oxytetracycline and tetracycline), penicillins (amoxycillin, ampicillin, bacampicillin, penicillin, pivampicillin and axacillin), nitromidazoles (furazolidone, odinazole, ornidazole, metronidizale and tinidazole), cephalosporins (cefixin,cefuroximaxetil), fluoroquinolones (ciprofloxacin, norfloxacin and oflocacin), antimycotium (itraconazole and rifampacin), lincomycin (clindamycin).

Dose regimens varied.

Participants included in the review
Patients with H.pylori infection, as determined by biopsy-based methods or breath test.

Outcomes assessed in the review
The proportion of patients cured for each treatment protocol and for the total patient sample, as assessed by a biopsy base or breath test.

How were decisions on the relevance of primary studies made?
All retrieved publications were checked by two independent reviewers to ensure that they met inclusion criteria. Disagreements between the two reviewers were resolved by consensus.

Assessment of study quality
Studies were stratified to a number of methodological aspects including publication year, whether or not the study population was a consecutive patient series, nationality of study population, diagnosis of the patients, reference standard used to monitor treatment, duration of follow-up period, whether or not treatment allocation was random, whether or not antibiotic susceptibility was measured, whether or not a total patient sample (intention-to-treat) cure rate could be
calculated and the therapeutic regimen applied. The authors do not state how the papers were assessed for validity, or how many of the reviewers performed the validity assessment.

**Data extraction**
The authors do not state how many of the reviewers were involved in the process of data extraction. The following data were presented in tables: report type, publication year, whether consecutive patients were enrolled, nationality, disorder, reference standard, check-up time, how treatments were allocated, blinding, antibiotic susceptibility measured, multicentre study, medication combination, loss to follow-up mentioned. For each study the proportion of patients successfully cured using per protocol and intention to treat analyses were calculated.

**Methods of synthesis**
How were the studies combined?
To correct for outlying values and to stabilise the variance in cure rate, arcsin transformation was performed. Cure rates were pooled using a weighted regression analysis, in which all the clinical features and methodological aspects were included simultaneously and this was used to model the heterogeneity in the model. Studies were weighted proportionally to four times the size of the study population. This allowed for the correction of heterogeneity between studies caused by the different study sizes. A random intercept for the study was included to model dependency between outcomes within the same study (it appears that each treatment arm was included separately in the regression analysis and this was included to incorporate the controlled elements for comparison of outcomes that came from the same trial). For each regression model an overall F-test (NDF, DDF) was used to examine whether the hypothesis of no fixed effect should be rejected. NDF is the degree of freedom in the numerator and DDF the degree of freedom n the denominator in the F-test. Each model was corrected for features and methodological aspects that had a substantial bearing on the difference in cure rates between studies. Dose-response and dose-duration relationships were estimated for each drug separately. If the dosage of the drug/treatment was not significant the lowest dose was described.

How were differences between studies investigated?
Heterogeneity was assessed by means of an ordinary least square regression equation in which all the clinical features and methodological aspects were included simultaneously.

**Results of the review**
A total of 666 manuscripts were included. These related to 1295 trials of 132 different medication combinations.

The average number of patients treated per trial was small, median = 30 (inter-quartile range (IQR): 19-50). The overall cure rate was 71% (IQR: 44-85) in the per protocol analysis and 67% (IQR:42-82) in the intention-to-treat analysis. Variation in eradication rates in the per protocol analysis was related to nationality (F(48;513)=2.04, p<0.01), therapeutic regimen (F(171;513)=21.85, p<0.01) and whether the studies mentioned loss to follow-up (F(1;513), p<0.01). The same variables were associated with variation in eradication rates in the intention-to-treat analysis.

Adjusted cure rates showed that no therapeutic regimen was optimal. The most frequently investigated therapeutic regimen that provided sufficient effectiveness were triple therapies (n=296): two anti-microbial drugs supplemented with a proton-pump inhibitor. A combination of the proton-pump inhibitor plus macrolide plus nitroimidazole (n=122 and 80) cured 87.1% and 82.9% of the patients per protocol and intention to treat respectively. No differences between the proton-pump inhibitors (lansoprazole, omeprazole and panteprozole) or the type of nitroimidazole (metronidazole or tinidazole) used was found. Of the 2 macrolides evaluated, clarithromycin was superior to azithromycin. The dose of clarithromycin influenced the cure rate; 1.5 g of clarithromycin cured H.pylori in more patients than 500mg, 600mg, 750mg or 1g. The dosage of the other drugs did not influence the cure rate. The same antibiotics in combination with ranitidine bismuth subcitrate also performed very well (n=26 and 24),90.8% and 78.4% of patients were cured per protocol and on intention-to-treat bases, respectively. Overall cure rates of between 80 and 85% were achieved using combinations of a proton-pump inhibitor or ranitidine bismuth citrate with 2 antibiotics including clarithromycin, amoxycillin and metronidazole or tinidazole. Comparable cure rates were also achieved using a combination of a proton-pump inhibitor of H2-receptor antagonist with bismuth subcitrate or tripotassium dicitrato bismuthate, metronidazole and tetracycline. The duration of any of the treatments did not influence the cure rate of any of the treatment regimens.
Authors' conclusions
Several therapeutic regimens can be used to treat patients with an H.pylori infection. Although most studies report excellent cure rates, the success rate will frequently be below 80% in routine clinical practice. The author found that the success rate of H.pylori eradication was dependent only on the country in which the study was performed and the therapeutic regimen. A seven-day triple therapy using lansoprazole (LAC15) is an efficient and economical regimen for the eradication of H.pylori.

CRD commentary
A reasonable review of the area. A literature search was conducted. Restricting the search to one database (MEDLINE) and only including studies published in 4 languages (English, German, French and Dutch), however, may have led to important studies being missed. The authors do not appear to have attempted to identify and include unpublished studies thus the results may be subject to publication bias. Inclusion criteria were reasonably clearly stated, although more precise details of study designs could have been provided (it appears that only clinical trials were included). Additional individual study details were not provided, although this may not have been practical in view of the large number of studies included in the review. Insufficient details were provided on the methods used to combine studies and investigate heterogeneity. The method used to investigate heterogeneity appears to have been appropriate. It was not clear what dependent variable was used in the regression analyses to investigate the heterogeneity between studies. While this was probably the cure rate this was not explicitly stated. The variables found to contribute to the heterogeneity were controlled for in the regression analysis used to calculate the cure rates which was appropriate. It appears that the analysis separated the different arms of the study and then included the random-effects section of the trial to control for this. This method was appropriate though the authors fail to state explicitly that this was the method used. Although the results presented do appear to support the authors conclusions, they should be interpreted with some degree of caution due to the limitations outlined above.

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

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