Meta-analysis: four-drug, three-antibiotic, non-bismuth-containing "concomitant therapy" versus triple therapy for Helicobacter pylori eradication
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CRD summary
This review compared concomitant quadruple therapy with standard triple therapy for Helicobacter pylori infection. Based on the available data, the conclusion that concomitant therapy appeared to be an effective, safe and well-tolerated treatment option for H. pylori infections appears reliable.

Authors' objectives
To compare concomitant quadruple therapy with standard triple therapy for Helicobacter pylori infection.

Searching
PubMed, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL) were searched from January 1998 to December 2007. Abstracts of three major gastrointestinal meetings were searched. Reference lists of identified articles were checked for additional references. Search terms were reported.

Study selection
Randomised controlled trials (RCTs) that compared concomitant quadruple to standard triple therapies in the treatment of adults with Helicobacter pylori or any study that reported H. pylori eradication rates for concomitant quadruple therapy were eligible for inclusion. Concomitant quadruple therapy was defined as a proton pump inhibitor plus amoxicillin, clarithromycin and metronidazole or tinidazole and traditional triple therapy as a proton pump inhibitor plus two of the three antibiotics amoxicillin, clarithromycin or metronidazole. Eligible studies had to demonstrate H. pylori infection by at least one high-accuracy diagnostic test. Eradication of infection had to be confirmed by appropriate diagnostic tests at least four weeks after treatment completion. Studies needed to report intention-to-treat and per-protocol results or sufficient data to enable them to be calculated. The primary outcome was H. pylori eradication rates.

Studies were conducted between 1997 and 2000. Four were conducted in Japan and the remaining five in western European countries. Mean age of patients was 41 to 57 years. H. pylori infection included peptic ulcer disease and non-ulcer dyspepsia. Treatment duration was three to seven days with concomitant therapy and five to 10 days with triple therapy. Concomitant therapy included amoxicillin, clarithromycin or roxithromycin, metronidazole or tinidazole, lansoprazole, omeprazole or rabeprazole; triple therapy included amoxicillin, clarithromycin or metronidazole, lansoprazole, omeprazole or rabeprazole.

Two reviewers independently identified studies for inclusion.

Assessment of study quality
No formal validity assessment was reported, but the effects of study quality indicators (including randomisation and study size) on outcome estimates were examined by univariate meta-regression.

Data were extracted independently by two of the reviewers. Disagreements were resolved by consensus.

Data extraction
Data extracted from each study were: drug regimens; doses; treatment duration; number of patients enrolled and in each group; enrolment period; test used to assess diagnosis and eradication; rates of adverse effects; and eradication rates. When necessary, authors were contacted for additional information. Outcome data were used to calculate odds ratios (ORs) and corresponding 95% confidence intervals (CI).

Two reviewers independently extracted data. Disagreements were resolved by consensus.
Methods of synthesis

The pooled odds ratios of *H. pylori* eradication rates and 95% CI were calculated from RCTs that compared concomitant quadruple therapy to triple therapy for per-protocol and intention-to-treat results. The weighted pooled log odds of the eradication rates were calculated for all intention-to-treat and per-protocol data from randomised and non-randomised studies. These were converted back to eradication rates for reporting of results.

Cochran’s Q and I² tests were used to assess the heterogeneity of the results. If the p-value was less than 0.10 for the Q-test or the I² score was 50% or more, a random-effects model was used for the analysis. Univariate metaregression analysis was conducted to explore possible reasons for heterogeneity, which included: study year; study size; whether it was a randomised trial; mean age and gender of participants; method used to assess diagnosis and eradication; drug regimen; duration of treatment; and country of origin. A p-value of less than 0.05 was used to determine significance.

A funnel plot was used to investigate the possibility of publication bias for all outcomes. Egger’s regression intercept and Begg’s rank correlation tests were used to formally test asymmetry. Influence analysis was used to check the robustness of the pooled estimate. A p-value of less than 0.05 was considered as significant.

Results of the review

Nine studies with 1,054 patients in 10 treatment arms were included. Five of these were RCTs (n=576) that compared concomitant (n=293) and triple therapy (n=283). The four other non-randomized studies evaluated concomitant therapy in 478 patients. Two trials were single-blinded; all others were unblinded and open-label.

Pooled estimates of the five RCTs showed superiority of concomitant therapy over triple therapy for *Helicobacter pylori* infection, with an intention-to-treat pooled odds ratio of 2.86 (95% CI 1.73 to 4.73). There was no significant heterogeneity between trials. The pooled eradication rate with concomitant therapy based on the intention-to-treat analysis in 695 of 771 patients over all 10 treatment arms was 89.7% (95% CI 86.8 to 92.1%).

Anaphylaxis to medication was reported in three patients in three studies. No other severe side-effects were reported. Mild to moderate side-effects were reported in 27% to 51% of patients treated with the concomitant quadruple therapy versus 21% to 48% of patients treated with triple therapy.

Univariate meta-regression analysis of the five RCTs did not identify any variables that could explain outcome variation. However, analyses of the 10 treatment arms showed that age and treatment duration were significant variables that might explain variation of eradication rates.

There was evidence of possible publication bias for the per protocol analysis of eradication rates, but not for other analyses in this review.

Authors’ conclusions

Concomitant therapy appeared to be an effective, safe and well-tolerated treatment option for *H. pylori* infections.

CRD commentary

The review question and inclusion criteria were clear. The search strategy was good, with several databases and other sources searched. Efforts to limit publication and language biases were taken; there was some evidence of possible publication bias for eradication rates. The reviewers reported methods designed to reduce bias in the selection of studies, assessment of validity and extraction of data. Multiple methods were used to assess statistical heterogeneity and publication bias. The conclusions of this generally well-conducted review reflected the overall conclusion that concomitant therapy appears to be an effective, safe and well-tolerated treatment option for *H. pylori* infections.

Implications of the review for practice and research

Practice: The authors did not state any implications for practice.

Research: The authors stated that further research that compared concomitant and sequential therapy was required to determine whether concomitant therapy provided equivalent or superior results. Future studies should compare dose, duration, concomitant versus sequential therapy and evaluate pre-treatment susceptibility.
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