Azithromycin-containing versus standard triple therapy for Helicobacter pylori eradication:
a meta-analysis
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CRD summary
The review concluded that azithromycin-containing triple therapy for first-line Helicobacter pylori eradication was equally effective to standard triple eradication therapy and had a lower occurrence of side effects. In view of some potential limitations arising from the review process, and the overall average quality of included trials, the extent to which the authors’ conclusions are reliable is unclear.

Authors' objectives
To evaluate the safety and effectiveness of the addition of azithromycin to first-line Helicobacter pylori eradication regimes.

Searching
PubMed (from 1966), EMBASE (from 1980), Cochrane Central Register of Controlled Trials (CENTRAL), SciELO Science Citation Index (from 1945), the Chinese Biomedical Database (from 1981), were searched to May 2009 for publications in any language. Search terms were reported. Abstracts of the congresses of the International Workshop of the European Helicobacter Study Group; American Digestive Disease Week; and United European Gastroenterology Week (from 1995 to May 2009), and the bibliographies of each retrieved article and relevant reviews were handsearched. Some authors were contacted for information relating to relevant unpublished studies.

Study selection
Eligible studies were randomised controlled trials (RCTs) of azithromycin-containing triple therapy regimes compared with standard triple-therapy regimes (one proton-pump inhibitor and two antibiotics) for first-line Helicobacter pylori (H. pylori) eradication in patients who had not been treated for H. pylori infection previously. Trials were excluded if azithromycin was used in both comparative regimes or they investigated the relationship between H. pylori and coronary heart disease.

The primary outcomes were H. pylori eradication and/or adverse events. The key adverse events were diarrhoea, nausea, taste disturbance and abdominal pain.

The included trials were distributed globally including Asia and Europe, but there were few in the USA and none in Africa or South America. Included patients, where reported, had duodenal or peptic ulcers, gastritis, non-ulcer dyspepsia, gastro-oesophageal reflux disease, or were reported as symptomatic or asymptomatic. Six trials were of adults. H. pylori infection was diagnosed and checked after treatment most commonly using histology or the rapid urease test, and also using the 13C-urea breath test, serology or H. pylori stool antigen.

The duration of antibiotic treatment was mostly seven days (range seven to 14 days), although the duration of azithromycin treatment ranged from three to seven days. The azithromycin dose was generally 500mg/day (range 250mg to 1g/day). The most commonly used proton-pump inhibitor was omeprazole, then lanzoprazole, esomeprazole and pantorazole. The most commonly used antibiotic was amoxicillin, then metronidazole, clarithromycin, levofloxacin and tinidazole (the doses used were reported).

Two independent reviewers performed the selection, with disagreements resolved by consultation with a third reviewer.

Assessment of study quality
Methodological quality was assessed using the Jadad score based on randomisation, double-blinding and information on withdrawals/ drop-outs, with a score from 1 to 5 points. Trials were considered to be of low quality if they had a Jadad score of less than 3.

The authors did not report how many reviewers performed the validity assessment.
Data extraction
Data were extracted using standardised extraction sheets. The numbers of events for each outcome were extracted in order to calculate odds ratios (OR) and 95% confidence intervals (CI).

The authors did not report how many reviewers performed the extraction.

Methods of synthesis
Odds ratios were pooled using a fixed-effect model (Mantel-Haenszel), with a random-effects model when there was significant heterogeneity, using both an intention-to-treat and per-protocol analysis. Between trial heterogeneity was determined using the $X^2$ test and $I^2$ statistic and significant heterogeneity was present when $p<0.10$.

Publication bias was assessed using Egger's test and visually using funnel plots.

Sub-analyses were planned relating to the type of drugs used in the triple therapy regimes, the duration and dose of azithromycin, the age of the patients, and trial quality.

Results of the review
Fourteen relevant RCTs were identified ($n=1,622$ participants, range 47 to 247); four trials with a Jadad score of 4, eight with a Jadad score of 3, and two trials has a low Jadad score of 2. Follow-up was generally after eight weeks (range four to eight weeks).

There was no significant difference between the pooled *Helicobacter pylori* eradication rates with azithromycin (72.01%, 95% CI 58.09 to 85.93) and without azithromycin (69.78%, 95% CI 66.47 to 73.09), with an odds ratio of 1.17 (95% CI 0.64 to 2.14; 14 RCTs; $I^2=81%$), with significant heterogeneity, using an intention-to-treat analysis.

There were significantly fewer total side effects with azithromycin (15.81%, 95% CI 12.50 to 19.12) than without azithromycin (25.20%, 95% CI 21.44 to 28.96), with an odds ratio of 0.58 (95% CI 0.41 to 0.82; 10 RCTs; $I^2=21%$). There were also significantly lower incidences of diarrhoea (OR 0.33, 95% CI 0.12 to 0.96; four RCTs; $I^2=0%$), nausea (OR 0.37, 95% CI 0.14 to 0.96; three RCTs; $I^2=19%$) and taste disturbance (OR 0.28, 95% CI 0.11 to 0.70; four RCTs; $I^2=0%$) with azithromycin than without azithromycin.

The subgroup analysis for eradication rate for duration of azithromycin showed no significant difference for a long-course (seven RCTs) or short-course of treatment (seven RCTs), with significant heterogeneity for both analyses. Subgroup analyses for eradication rate that compared the antibiotic given with azithromycin (amoxicillin, six RCTs; levofloxacin, three RCTs; metronidazole/tinidazole, five RCTs) also found no significant difference in the pooled eradication rates for each regime, and significant heterogeneity for each sub-analysis.

Egger's test showed that there was no evidence of substantial publication bias.

Authors' conclusions
Azithromycin was a promising compound in first-time treatment regimens for *Helicobacter pylori* eradication. Azithromycin-containing triple therapy has equal efficacy to standard triple eradication therapy and a lower occurrence of side effects. A combination of azithromycin, amoxicillin and a proton pump inhibitor was suggested as a first-line therapy.

CRD commentary
The review addressed a well-defined question in terms of participants, interventions, study design and relevant outcomes. Relevant databases were searched in any language and unpublished studies were considered. Publication bias was assessed. Although study selection was carried out with efforts to reduce error and bias, it was not clear whether this process applied to other aspects of the review process.

Trial quality was assessed using suitable criteria; the overall quality of the included trials was medium. Relevant trial
details were reported. Statistical heterogeneity was assessed and there was evidence for heterogeneity with some outcomes. The statistical method used for the meta-analysis of the RCTs seemed appropriate. Relevant subgroup analyses were reported.

In view of some potential limitations arising from the review process and the overall average quality of included trials, the extent to which the authors’ conclusions are reliable is unclear.

**Implications of the review for practice and research**

**Practice**: The authors stated that the use of azithromycin-containing triple therapy as first-line therapy for *H. pylori* eradication could reduce the physiological burden and cost of a second course of therapy.

**Research**: The authors identified a need for further studies to optimise the dose of azithromycin and to improve *H. pylori* eradication rates which are only up to 80% [at the time of writing].

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