Global eradication rates for Helicobacter pylori infection: systematic review and meta-analysis of sequential therapy
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CRD summary
The review concluded that sequential therapy was superior to seven day triple therapy and similar to regimens of longer duration or those that included more than two antimicrobial agents for Helicobacter pylori eradication. Eradication rates with pre-existing and new therapies for H. pylori were suboptimal. Despite limitations in the available evidence, the authors’ conclusions appear appropriate.

Authors’ objectives
To assess the efficacy of sequential therapy compared with other eradication regimens for eradication of Helicobacter pylori.

Searching
MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trials (CENTRAL) were searched up to May 2013; search terms were reported. Conference abstracts from the major European, American, and Asian gastroenterological meetings were also searched. Bibliographies of all relevant studies were examined. No language restrictions applied.

Study selection
Randomised controlled trials (RCTs) that examined the eradication rate of H. pylori sequential therapy compared with other treatments were eligible for inclusion. To be eligible, patients must not be treated for H. pylori prior to therapy and must be aged 18 years or older. Also, eradication rate had to be assessed for at least four weeks after the end of treatment.

The primary outcome was H. pylori eradication. The secondary outcomes were safety and efficacy according to the antimicrobial resistance pattern. Sequential treatment was defined as proton pump inhibitors twice daily plus amoxicillin 1g twice daily for five days, followed by proton pump inhibitors twice daily plus clarithromycin 500mg twice daily plus nitroimidazole derivatives twice daily for next five days. Various types of proton pump inhibitors were used.

Two reviewers independently evaluated the abstracts from the initial search but it was unclear how many reviewers selected studies for eligibility.

Assessment of study quality
Trial quality was assessed based on the Cochrane risk of bias tool which included sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and any other source of bias. RCTs were considered low risk of bias if they satisfied all domains except blinding of participants.

[A: The authors confirmed that two reviewers were involved with quality assessment.]

Data extraction
Data were extracted to calculate relative risks and their 95% confidence intervals. Eradication data were extracted based on intention to treat analysis. Trial authors were contacted for additional information if necessary.

Two reviewers independently extracted data; any disagreements were resolved by discussion with the involvement of other two reviewers.

Methods of synthesis
A random-effects model was used to calculate pooled eradication rates and relative risks of efficacy and safety between treatments, with related 95% confidence intervals. Heterogeneity was assessed using X² and I² (I²>25% was considered
evidence of heterogeneity). These data were also presented as numbers needed to treat.

If heterogeneity was identified, subgroup analyses were performed based on intervention and trial characteristics. Publication bias was assessed using Egger’s test and funnel plots.

Results of the review
Forty-six RCTs were included in the review. Follow-up period ranged from four to 12 weeks.

The overall *H. pylori* eradication rate of sequential therapy was 84.3% (95% CI 82.1% to 86.4%).

**Sequential therapy versus triple therapy lasting seven days (22 RCTs):** None of the trials were at low risk of bias. Two trials did not report full data on the proton pump inhibitor used. The pooled analysis favoured sequential treatment (RR 1.21, 95% CI 1.17 to 1.25; I²=29.3%); the number needed to treat was six (95% CI 5 to 7). Publication bias was not observed.

**Sequential therapy versus triple therapy lasting 10 days (14 RCTs):** Only two trials were at low risk of bias. Three trials did not report full data on the proton pump inhibitor used. The pooled analysis slightly favoured sequential treatment (RR 1.11, 95% CI 1.04 to 1.19; I²=67.2%); the number needed to treat was 10 (95% CI 7 to 15). Publication bias was not observed.

**Sequential treatment versus triple therapy lasting 14 days (seven RCTs):** None of the trials were at low risk of bias. One trial did not report full data on the proton pump inhibitor used. The pooled analysis showed no significant difference between the two regimens. Publication bias was not observed.

**Sequential therapy versus bismuth containing therapy (three RCTs):** None of the trials were at low risk of bias. There was no significant difference between the two regimens. There was no evidence of publication bias.

**Sequential therapies versus non-bismuth quadruple therapy (six studies):** One trial was at low risk of bias. One trial did not report full data on the proton pump inhibitor used. There was no significant difference between the two regimens. There was no evidence of publication bias.

Prediction intervals (the results for regimes not included in meta-analysis), subgroup analyses and adverse events were also reported in the paper.

**Authors’ conclusions**
Sequential therapy was superior to seven day triple therapy and similar to regimens of longer duration or those that included more than two antimicrobial agents for *Helicobacter pylori* eradication. Eradication rates with pre-existing and new therapies for *H. pylori* were suboptimal. Regional monitoring of resistance rates should help to guide treatment and new agents for treatment need to be developed; until such an agent has been discovered, any single therapy would be unlikely to be effective all over the world.

**CRD commentary**
The review addressed a clear question and was supported by appropriate inclusion criteria. The search covered a range of relevant sources including searching of conference abstracts and no language restrictions applied, which minimised the risk of language and publication bias. Appropriate methods were used to reduce the risk of reviewer error and bias in data extraction and quality assessment, although it was unclear whether similar methods were used for study selection.

An appropriate quality assessment tool was applied; the results showed that most of the trials had problems with concealment of allocation and blinding. Appropriate methods were used to pool data, assess heterogeneity, and perform subgroup analyses.

Although included trials had methodological limitations and variable results, the authors’ conclusion (that sequential therapy was superior to seven day triple therapy but similar to regimens of longer duration or including more than two antimicrobial agents) appears appropriate.
Implications of the review for practice and research

**Practice:** The authors stated that the choice of treatment regimen should be based on a knowledge of the underlying prevalence of resistant *H. pylori* strains in the community and the patient's history.

**Research:** The authors stated that the search for a new agent to treat *H. pylori* was important and should continue.

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