Sequential therapy vs standard triple therapies for Helicobacter pylori infection: a meta-analysis
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CRD summary
This review evaluated effectiveness of sequential therapy compared with standard 7-day and 10-day triple therapy in eradicating Helicobacter pylori infection. The authors concluded that sequential therapy was associated with a higher eradication rate than standard triple therapies. The review was largely well-conducted and the conclusion is likely to be reliable.

Authors' objectives
To evaluate the effectiveness of sequential therapy compared with standard triple therapy in eradicating Helicobacter pylori infection.

Searching
MEDLINE, EMBASE, Chinese Biomedical Database, Science Citation Index (search dates ranging from 1966 to February 2008) and Cochrane Central Register of Controlled Trials (CENTRAL) (Cochrane Library, Issue 1, 2008) were searched without language restriction. Search terms were reported. Reference lists of identified articles and reports were scanned. ClinicalTrials.gov and Current Controlled Trials were searched for additional material. Conference abstracts from American Gastroenterological Association and World Congress of Gastroenterology and European Helicobacter Study Groups were reviewed for the preceding five years. Authors and experts were contacted.

Study selection
Randomised controlled trials (RCTs) that compared sequential treatment with 7-day or 10-day standard triple therapies in patients with Helicobacter pylori (H. pylori) infection were eligible for inclusion in the review. Studies had to use intention-to-treat analysis. Infection status had to be determined by at least one of rapid urease test, H. pylori stool antigen test, histology or urea breath test before treatment and at least four weeks after treatment. Sequential therapy had to include a proton pump inhibitor and amoxicillin for the first five days followed by a triple therapy (proton pump inhibitor and clarithromycin and tinidazole) for the remaining five days. Where reported, included patients had a mean age range between 11 and 69 years. One of the included trials considered metronidazole instead of clarithromycin in the triple therapy. Two trials included both 7-day and 10-day standard triple therapy as the comparator.

Patients with previous H. pylori treatment who had used proton pump inhibitors, H2-receptor antagonists, bismuth preparations and antibiotics in the previous four weeks were excluded from the review. The primary outcome of interest was eradication of infection. Secondary outcomes included adverse events and eradication rates in patients with peptic ulcer and non-ulcer dyspepsia, and in those with antibiotics resistance.

Trials were selected independently by two reviewers. Disagreements were resolved by a third reviewer.

Assessment of study quality
Trial quality was assessed using the Jadad scale on aspects of randomisation, double-blinding, and description of withdrawals and dropouts. The maximum achievable score was 5 and scores of less than 3 were considered to represent low quality.

Quality assessment was performed by two independent reviewers. Disagreements were resolved by a third reviewer.

Data extraction
Data were extracted on the primary and secondary outcomes of interest and risk ratios (RR) and 95% confidence intervals (CI) calculated. Eradication rates were considered in intention-to-treat and per-protocol analyses. In trials with three or more arms, number of events and total number of patients was halved to facilitate comparisons of sequential...
therapy and 7-day or 10-day standard therapies in patients with peptic ulcer dyspepsia and non-ulcer dyspepsia.

The authors did not state how many reviewers performed the data extraction.

Methods of synthesis
Where there was no significant heterogeneity ($p<0.1$), risk ratios and 95% CIs were pooled in a fixed-effect meta-analysis (Mantel-Haenszel method). Heterogeneity was assessed using the Breslow-Day test and $I^2$ statistic. Where heterogeneity was found to be significant, a random-effects meta-analysis was conducted (DerSimonian and Laird). Sensitivity analyses were conducted to take account of patient age (children, adults and elders), treatment regimens (different proton pump inhibitors) and study quality. Publication bias was assessed visually using a funnel plot. Formal assessment of this was performed using influence analysis (where each study estimate was omitted from the data set and pooled estimates were recalculated), and in regression and correlation analyses.

Results of the review
Eleven RCTs (eight full-text articles $n=2,288$ and three abstracts $n=595$) were included in the review: 1,338 patients received sequential therapy and 1,545 received standard triple therapy. One trial achieved a Jadad score of 5, six scored 3, three scored 2 and one scored 1.

Eradication rates:
Pooled analyses showed that sequential therapy was significantly more effective than 7-day standard therapy (RR 1.23, 95% CI 1.19 to 1.27; nine trials) and 10-day standard therapy (RR 1.16, 95% CI 1.10 to 1.23; four trials). There was no significant heterogeneity. Influence analysis was reported for comparison with 7-day standard therapy and produced a similar result. Inspection of funnel plot indicated no evidence of publication bias.

For patients with peptic ulcer dyspepsia, pooled analysis showed that sequential therapy was more effective than 7-day and 10-day standard therapy (RR 1.24, 95% CI 1.15 to 1.34; three trials), but there was significant heterogeneity ($I^2=77.1\%, p=0.013$). Heterogeneity was eliminated when the two regimens were analysed separately, but the superiority of sequential therapy remained.

For patients with non-ulcer dyspepsia, sequential therapy was more effective than the standard triple regimens (RR 1.26, 95% CI 1.19 to 1.33). There was no significant heterogeneity. Pooled risk ratios for studies in patients with clarithromycin and metronidazole resistance were 2.01 (95% CI 1.35 to 2.98; four trials) for clarithromycin and 2.07 (95% CI 1.30 to 3.31; three trials) for metronidazole. All results were unaffected in the sensitivity analyses.

Adverse events:
Commonly reported adverse events were diarrhoea, glossitis, abdominal pain, nausea and vomiting. Frequency of these events (six trials) were similar across the study groups (8.4% for sequential therapy and 8.7% for 7-day triple regimens). Pooled analysis showed no significant differences between the groups. There was no significant heterogeneity.

Authors' conclusions
Sequential therapy was associated with a higher $H. pylori$ eradication rate than standard triple therapies.

CRD commentary
This review addressed a clear question. Inclusion criteria were sufficiently explicit to allow potential reproduction. Of note, was the inclusion in the primary outcome analysis of an antibiotic that did not form part of the inclusion criteria and post-hoc analysis (for a secondary outcome) of a trial not included in the review. The search strategy appeared to include many relevant sources, included unpublished material and apparently was not restricted to English-language articles, which meant that attempts were made to maximise retrieval of relevant studies and minimize language and publication biases. An appropriate validity assessment tool was used. Reviewers attempted to minimise errors and bias in most of the review process. Study characteristics were adequately reported. Methods of synthesis and exploration of heterogeneity and publication bias were appropriate and detailed. The authors acknowledged some limitations of small
sample sizes, lack of blinding and failure to evaluate antibiotic resistance. Overall, the review was largely well-conducted and the authors’ conclusion is likely to be reliable.

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

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

**Research**: The authors stated that high-quality trials should be conducted outside Italy. These should include head-to-head comparisons of sequential therapy with 14-day triple therapy, investigations of differential effects of dose and treatment durations and look into the mechanisms and generalisability of observed effects.

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