Meta-analysis: duration of first-line proton-pump inhibitor-based triple therapy for Helicobacter pylori eradication

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CRD summary
This well-conducted review concluded that extending proton-pump inhibitor-based triple therapy beyond 7 days for the eradication of Helicobacter pylori is unlikely to be clinically useful. This conclusion is supported by the data presented, but it may not be reliable given the poor methodological quality of the included studies.

Authors' objectives
To evaluate the efficacy of different durations of proton-pump inhibitor (PPI)-based triple therapy for the eradication of Helicobacter pylori (H. pylori).

Searching
PubMed, EMBASE and the Cochrane Library were searched up to 31 May 2007; the search terms were reported. The reference lists of included studies were screened for relevant articles. Abstracts from the United European Gastroenterology Week meeting and the International Workshop of the European Helicobacter Study Group (both 1995 to 2006) and the Digestive Disease Week (through to 2007) were searched for relevant articles. Only articles published in English were eligible.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for inclusion.

Specific interventions included in the review
Studies comparing different durations (7, 10 or 14 days) of PPI-based triple therapy, as a first-line eradication therapy for H. pylori, were eligible for inclusion. Eligible therapies included a PPI with clarithromycin and amoxicillin or a PPI with clarithromycin and metronidazole, administered twice daily at recommended doses. The included studies used various regimens (details provided). The PPIs in the included studies were omeprazole, lansoprazole, pantoprazole, rabeprazole and esomeprazole. In the majority of studies, PPIs were combined with amoxicillin (1 g) and clarithromycin (500 mg).

Participants included in the review
Studies of patients being treated for H. pylori infection were eligible for inclusion, including patients with a diagnosis of peptic ulcer disease or nonulcer dyspepsia at enrolment. The presence of H. pylori infection needed to be demonstrated by at least one high-accuracy diagnostic test (urea breath test, stool antigen test, gastric mucosal biopsy for histology, rapid urease test, or culture). The majority of included studies were of patients with peptic ulcer.

Outcomes assessed in the review
Studies assessing the eradication of H. pylori infection were eligible for inclusion. Eradication of the infection needed to be confirmed at least 4 weeks after completion of treatment, based on an appropriate diagnostic test. The included studies had to report intention-to-treat data. The majority of studies assessed eradication using the urea breath test alone or in combination with another test. The frequency and type of adverse events were also evaluated.

How were decisions on the relevance of primary studies made?
Two reviewers independently selected studies for inclusion.

Assessment of study quality
Two reviewers independently assessed methodological quality using the Jadad scale; any discrepancies were resolved by consensus. The criteria included randomisation, double-blinding and loss to follow-up; the maximum possible score was 5.
Data extraction
Two reviewers independently extracted the data and authors were contacted for additional information. Relative risks (RRs) with 95% confidence intervals (CIs) were calculated for the incidence of eradication.

Methods of synthesis
How were the studies combined?
The studies were grouped and 7-day therapies compared with 10- and 14-day therapies. Pooled RRs with 95% CIs were calculated using both fixed-effect and random-effects models, although only the fixed-effect data were reported. Funnel plots and Begg and Egger tests were used to assess publication bias.

How were differences between studies investigated?
Heterogeneity was assessed using Galbraith plots, the Cochran Q test and the Higgins test. Potential sources of heterogeneity were investigated using subgroup analyses (type of triple therapy, disease indication and study quality) and meta-regression.

Results of the review
Twenty-one RCTs were included. Thirteen studies compared 7- and 14-day treatments (n=2,849) and 11 studies compared 7- and 10-day treatments (n=1,982).

Only 2 studies achieved the maximum score of 5 points; one scored 4 points, five scored 3 points, ten scored 2 points and two scored only 1 point. Only 8 studies reported methods for the generation of allocation sequence, of which one used inadequate methods. Four studies were designed as double-blind and double dummy; the remaining studies were open label.

There was no evidence of publication bias (data not presented).

The RR for H. pylori eradication after 7-day amoxicillin-based therapy was 1.05 (95% CI: 1.01, 1.10) in comparison with 10-day amoxicillin-based therapy (11 studies), and 1.07 (95% CI: 1.03, 1.12) in comparison with 14-day amoxicillin-based therapy (11 studies). These RRs suggested a slight, but statistically significant difference in favour of longer duration therapy. No statistically significant differences were shown between 7- and 14-day metronidazole-containing therapy (3 studies). There was no evidence of statistical heterogeneity and the analysis-of-influence plots showed that no single study appeared to be excessively influential on the results. Subgroup analysis showed a slight but significant increase in eradication rates after 10-day therapy, compared with 7-day therapy, in patients with nonulcer dyspepsia (RR 1.10, 95% CI: 1.02, 1.20; 6 studies), but not in those with peptic ulcer. All other analyses according to study quality and the indication for eradication therapy failed to show any statistically significant differences in effect size.

No statistically significant differences in the incidence of adverse events were reported (15 studies). The most frequently reported adverse events were diarrhoea and taste disturbance (5%).

Authors’ conclusions
Evidence suggests that the extension of PPI-based triple therapy beyond 7 days is unlikely to be clinically useful.

CRD commentary
The review addressed a clear question that was defined in terms of the participants, intervention, outcomes and study design. Several relevant sources were searched and attempts were made to locate unpublished studies, thus limiting the possibility of publication bias. However, by including only English language studies, relevant data might have been excluded, especially given that most of the studies appear to have been conducted in non-English speaking countries. Methods were used to minimise reviewer error and bias in the study selection, validity assessment and data extraction processes. Adequate details of each included study were given. No evidence of statistical heterogeneity was found and possible sources of clinical heterogeneity were investigated. Overall, this was a generally well-conducted review, but the poor quality of the included studies makes the reliability of the conclusions uncertain.
Implications of the review for practice and research
Practice: The authors stated that PPI-based triple therapy beyond 7 days is unlikely to be clinically useful, but clinicians in developing countries should also consider the lack of well-conducted RCTs in these countries when recommending treatment for eradication strategies.

Research: The authors stated that further research is needed to assess therapy using metronidazole and whether the induction of secondary antibiotic resistance is related to the duration of treatment. Future studies should be well-designed and reported, stratifying outcomes according to the presence of peptic ulcer disease or nonulcer dyspepsia. The frequency, severity and type of adverse events should be reported in full. A cost-analysis is required before extending treatment beyond 7 days.

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