Advantages of moxifloxacin and levofloxacin-based triple therapy for second-line treatments of persistent Helicobacter pylori infection: a meta analysis
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CRD summary
The review concluded that second-generation fluoroquinolone-based triple therapy (moxifloxacin and levofloxacin), especially 10-day levofloxacin-based triple therapy, was the regimen of choice for rescue therapy eradication of persistent Helicobacter pylori infection. These conclusions reflect the evidence base, but potential bias in the review process and unknown quality of the included studies mean they should be considered tentative.

Authors' objectives
To compare the efficacy and safety of clarithromycin and second-generation fluoroquinolone-based triple therapy versus bismuth-based quadruple therapy for the treatment of persistent Helicobacter pylori infection.

Searching
PubMed, EMBASE, CNKI and Wangfang databases and Google Scholar were searched from 1981 to March 2009. Recent issues of Digestive Disease Week, United European Gastroenterology Week and European Helicobacter Study Group conferences were searched for relevant studies published in English and Chinese; search terms were included.

Study selection
Eligible studies were randomised controlled trials (RCTs) written in English or Chinese with complete data of patients with a failed course of H. pylori eradication therapy, with confirmation of infection eradication at least four weeks after completion of treatment (urea breath test or gastric mucosal biopsy for histology or culture). Eligible interventions were moxifloxacin and levofloxacin-based triple therapy, clarithromycin-based triple therapy for seven, 10 and 14 days or bismuth-based quadruple therapy for seven and 14 days. Studies were excluded if they contained insufficient details to meet the inclusion criteria.

In the included studies, triple therapy was mostly levofloxacin-based but also included combinations with moxifloxacin and clarithromycin. Therapy was mostly for seven days; a few trials used 10 days. All quadruple therapy was bismuth-based for seven or 14 days. Some participants had clarithromycin and metronidazole-resistant strains of infection.

The authors did not state how many reviewers performed the selection of studies.

Assessment of study quality
Studies were assessed for quality using the Jadad scale (criteria were not reported).

Two reviewers independently undertook the quality assessment. Discrepancies were resolved through consensus.

Data extraction
Data were extracted using the intention-to-treat principle on eradication rates, frequency of side effects and rates of discontinuation due to adverse events. Odds ratios (ORs) and their 95% confidence intervals (CIs) were calculated.

Duration of therapy was extracted.

Two reviewers independently extracted data. Discrepancies were resolved through consensus.

Methods of synthesis
Studies were pooled in meta-analyses and summary effect measures calculated using a fixed-effect model (where there was no heterogeneity) or a random-effects model (where there was heterogeneity). Heterogeneity was assessed using $\chi^2$ and $I^2$. Significant heterogeneity was confirmed by a p value of less than 0.1 or $I^2$ of at least 30%. Separate analyses
were performed according to agent used in triple therapy (clarithromycin, moxifloxacin, levofloxacin), duration of therapy (seven- or 10-day levofloxacin-based triple therapy versus seven-day bismuth-based quadruple therapy or seven-day versus 14-day bismuth-based quadruple therapy) and for participants with clarithromycin and metronidazole-resistant strains of infection.

Results of the review

**Eradication rates:** Clarithromycin-based triple therapy had significantly poorer eradication rates than quadruple therapy (OR 0.53, 95% CI 0.35 to 0.80; three studies with no significant heterogeneity). There was no evidence of a significant difference in eradication between moxifloxacin-based triple and quadruple therapies (OR 1.78, 95% CI 0.98 to 3.22, \(I^2=47\%\); three studies), but there was a strong trend in favour of moxifloxacin-based therapy (p=0.06). There was no evidence of a significant difference in eradication between levofloxacin-based triple therapy and quadruple therapy regardless of duration of therapy (OR 1.43, 95% CI 0.82 to 2.51; 13 studies with heterogeneity not reported). There was no evidence of a difference in eradication between seven-day levofloxacin-based triple therapy and seven-day quadruple therapy (OR 1.04, 95% CI 0.78 to 1.39, \(I^2=55\%\); nine studies). Ten-day levofloxacin-based triple therapy had significantly higher eradication rates than seven-day quadruple therapy (OR 4.79, 95% CI 2.95 to 7.79; four studies with no significant heterogeneity). There was no evidence of a significant difference in eradication between levofloxacin-based therapy and quadruple therapy in three RCTs of patients with clarithromycin and metronidazole-resistant strains of infection (summary effect measures not reported). There was no evidence of a significant difference in eradication between seven- versus 14-day quadruple therapy (OR 0.67, 95% CI 0.39 to 1.14; two studies with heterogeneity not reported).

**Side effects:** Patients who underwent levofloxacin-based triple therapy were less likely to report side effects compared to quadruple therapy (OR 0.41, 95% CI 0.27 to 0.61; 11 studies with significant heterogeneity) and less likely to discontinue their treatment because of adverse events (OR 0.13, 95% CI 0.06 to 0.33; eight studies with no significant heterogeneity).

Authors' conclusions

Second-generation fluoroquinolone-based triple therapy (moxifloxacin and levofloxacin) can be suggested as the regimen of choice for rescue therapy in the eradication of persistent *H. pylori* infection, especially 10-day levofloxacin-based triple therapy.

CRD commentary

The review addressed a clear research question. Inclusion criteria appeared appropriate. Several relevant sources were searched for studies published in English and Chinese; language bias could not be excluded. No explicit attempts were made to find unpublished studies, so publication bias could not be ruled out. Appropriate methods were used to assess studies for quality and extract data, but no methods were reported for selection of studies, so reviewer error and bias could not be excluded. The authors reported that studies were assessed for quality, but the results of this assessment were neither reported nor used to test the robustness of the findings.

Methods used to synthesize studies and assess heterogeneity were appropriate. The authors stated that where significant heterogeneity was demonstrated, analyses would be reported with a random-effects model, but in one case with significant heterogeneity the results were reported with a fixed-effect model (fig 4). No attempts were made to investigate or explain significant heterogeneity.

The authors' conclusions reflect the evidence base, but due to potential bias in the review process and unknown quality of the included studies, the conclusions should be considered tentative.

Implications of the review for practice and research

**Practice:** The authors stated that second-generation fluoroquinolone-based triple therapy, especially for a duration of 10 days, should be the regimen of choice for rescue therapy in the eradication of persistent *H. pylori* infection, but should be confined to rescue therapy in order to avoid rapidly increasing *H. pylori* resistance.

**Research:** The authors stated that further research should be conducted to assess the efficacy of moxifloxacin-based
triple therapy, high dose levofloxacin and duration of bismuth-based quadruple therapy.

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