Meta Analysis

Efficacy and safety of high-dose dual therapy for *Helicobacter pylori* rescue therapy: A systematic review and meta-analysis

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OBJECTIVE: Although some studies have reported >90% success with high-dose dual proton pump inhibitor (PPI)–amoxicillin dual therapy for *Helicobacter pylori* (*H. pylori*) eradication, the efficacy of this therapy remains controversial. We aimed to re-evaluate the efficacy and safety of high-dose dual therapy on *H. pylori* eradication.

METHODS: We searched PubMed, the Cochrane Library, and EMBASE for randomized clinical trials (RCTs) evaluating the efficacy of high-dose PPI–amoxicillin dual therapy as the rescue therapy on *H. pylori* eradication. Treatment effect was determined with a fixed-effect model using the inverse variance method and was expressed as risk ratio (RR) with 95% confidence interval (CI).

RESULTS: Because of significant statistical heterogeneity ($\chi^2$ 15.98, $I^2 = 69\%$) among the six studies that qualified, four RCTs that included 473 patients with *H. pylori* infection after eradication failure were assessed. The meta-analysis showed that high-dose dual therapy and guideline-recommended rescue therapies achieved similar efficacy (81.3% vs 81.5%, RR 1.00 [95% CI 0.93–1.08], intention-to-treat analysis), compliance (95.3% vs 95.4%, RR 1.00 [95% CI 0.97–1.03]), and side effects (17.9% vs 19.7%, RR 0.88 [95% CI 0.62–1.25]).

CONCLUSIONS: High-dose PPI–amoxicillin dual therapy is comparable to recommended rescue therapies for *H. pylori* infection. More researches are needed to determine the efficacy of high-dose dual therapy as a first-line therapy.

KEY WORDS: clarithromycin, *Helicobacter pylori*, high-dose dual therapy, meta-analysis, resistance.

INTRODUCTION

Standard triple therapies currently fail to eradicate up to 80% of *Helicobacter pylori* (*H. pylori*) infections in most populations due to increasing antibiotic resistance, especially that to clarithromycin.1–4 To circumvent the limiting effect of clarithromycin-resistant therapeutic regimens such as hybrid, sequential and non-bismuth quadruple (concomitant) therapies have emerged.5,6 Proton pump inhibitor (PPI) plus bismuth,
metronidazole and tetracycline (PBMT), levofloxacin-containing therapies and rifabutin-containing triple therapy have been recommended as rescue therapies after the failure of standard triple therapy.\textsuperscript{2,7}

Unlike that to clarithromycin, \textit{H. pylori} resistance to amoxicillin, either primary or acquired, remains uncommon.\textsuperscript{1,8–11} Amoxicillin–PPI dual therapy has been used in several countries and regions but its actual efficacy remains controversial due in part to the differences in doses and treatment durations of the therapeutic regimens.\textsuperscript{10,12–31} The efficacy of a typical dual therapy consisting of standard-dose amoxicillin (2.0 g/day or less) and PPI has been found to be unacceptable compared with triple therapies.\textsuperscript{10,14–18,25,28,30,32–35} On the other hand, high-dose dual therapy, defined as the administration of both amoxicillin (≥2.0 g/day) and PPI more than twice daily for 14 days, has been reported to have greater efficacy (i.e., over 90%) compared with typical dual therapy.\textsuperscript{29,31,36,37} For example, as early as in 1995, a randomized multicenter clinical study in Germany reported a cure rate of \textit{H. pylori} infection of 91% with 40 mg omeprazole and 750 mg amoxicillin both given thrice a day for 14 days.\textsuperscript{36} In 2007, Shirai \textit{et al.} reported an eradication rate of 90.9% for dual therapy with high doses of rabeprazole (10 mg four times daily) and amoxicillin (500 mg four times daily) after eradication failure using standard triple therapy.\textsuperscript{29} Furuta \textit{et al.} reported an eradication rate of 95.5% for dual therapy with 500 mg amoxicillin four times a day and dosing schedules of PPI capable of providing an intragastric pH ≥5.0 with clarithromycin-resistant \textit{H. pylori} infection.\textsuperscript{37} Moreover, in 2015 a multicenter randomized trial confirmed \textit{H. pylori} eradication rate of 95.3% in patients treated with high-dose dual therapy that was superior to standard regimens as empirical first-line or guideline-recommended rescue therapy, with similar tolerability and safety profiles.\textsuperscript{31}

Amoxicillin is a time-dependent antibiotic that is rapidly absorbed into the plasma but is excreted between 6 h and 8 h after administration.\textsuperscript{38} A dosage of 500–750 mg per 6 h, compared with 1000 mg twice daily, may therefore more likely to maintain higher plasma concentrations of amoxicillin. The bactericidal effect of amoxicillin against \textit{H. pylori} is also pH-dependent because amoxicillin is more stable at a higher intragastric pH.\textsuperscript{37} Moreover, \textit{H. pylori} are replicative when the intragastric pH increases to over 6 and become susceptible to amoxicillin. On the contrary, the bacteria move into a non-replicative but viable state when the pH is less than 6.\textsuperscript{39} Higher PPI doses\textsuperscript{37,40,41} or doses given at shorter intervals\textsuperscript{10} increase their effectiveness in maintaining a high pH level and also improves the stability and bioavailability of amoxicillin in the gastric juice.\textsuperscript{37,42} A regimen of four daily doses of PPI maintained the intragastric pH of higher than 6.5, regardless of the cytochrome P450 2C19 (CYP2C19) genotype.\textsuperscript{43} However, current guidelines for the treatment of \textit{H. pylori} infection do not include high-dose dual therapy as a regimen for \textit{H. pylori} eradication.\textsuperscript{2,7,44,45} Therefore, we aimed to re-evaluate the efficacy and safety of high-dose dual therapy for \textit{H. pylori} eradication as a rescue therapy by performing a systematic review and meta-analysis to provide evidence-based recommendations.

MATERIALS AND METHODS

Search strategy

A literature search was conducted on the PubMed, the Cochrane Library, and EMBASE databases covering all articles published in English up to June 2016. The following terms were used for the search: ‘\textit{Helicobacter pylori}’ OR ‘\textit{H. pylori}’ AND (‘amoxicillin’) AND (‘dual therapy’).

Inclusion and exclusion criteria

The studies included in this systematic review and meta-analysis were randomized controlled trials (RCTs) which evaluated the efficacy and safety of high-dose PPI–amoxicillin dual therapy for rescue eradication therapy of \textit{H. pylori}. Reviews, meta-analyses, comments, letters, case reports or case series, studies on animals, those without controls were excluded. We also excluded studies in which amoxicillin was administrated at <2.0 g/day, and those in which either amoxicillin or PPI was given less than thrice daily in the dual therapy. This study was conducted according to the PRISMA agreement reporting guidelines.\textsuperscript{46}

Data extraction

Data extraction was performed by two authors (Cai Ping GAO and Zhou ZHOU) independently, and any disagreement was resolved by discussion with a third reviewer (Sheng Xi HAN). For each selected publication the following information was extracted: first author, year of publication, country, study design, participants’ characteristics (including previous \textit{H. pylori} eradication), number of patients in each treatment arm, therapeutic regimens, duration of treatment, tests used to confirm \textit{H. pylori} infection prior to study enrollment and eradication of \textit{H. pylori} infection at least 4
weeks after the completion of treatment, number of patients in whom *H. pylori* infection was successfully eradicated (either provided directly or calculated from the intention-to-treat [ITT] and per-protocol [PP] analyses), number of patients who discontinued therapy due to side effects, and number of patients with side effects as defined within each included trial.

**Assessment of the risk of bias**

Two independent reviewers (Cai Ping GAO and Zhou ZHOU) evaluated the risk of bias according to the risk of bias assessment tool (RevMan 5.3; Nordic Cochrane Centre, Cochrane Collaboration, Copenhagen, Denmark) recommended by the Cochrane Collaboration. Any disagreement was resolved by consensus. The risk of bias of the included publications was assessed using domain-based risk of bias tables. Each study was assessed independently across different areas of potential bias, including randomization, allocation, blinded grouping of participants and outcomes, attrition and reporting bias. Each criterion was scored as low or high risk of bias (unlikely or likely to significantly influence the results), or an uncertain risk of bias.

**Statistical analysis**

To evaluate the heterogeneity among the pooled studies the inconsistency index ($I^2$) statistic and $\chi^2$ test were performed. $I^2$ greater than 50% or $P < 0.1$ for the $\chi^2$ test indicated significant statistical heterogeneity. Statistical heterogeneity was evaluated by sensitivity analyses to discern whether any clinical heterogeneity was responsible for such statistical difference. Both ITT and PP analyses were used for clinical outcomes. We summarized dichotomous outcome measures as the risk ratio (RR) along with 95% confidence interval (CI) using RevMan 5.3 (Nordic Cochrane Centre, Cochrane Collaboration). A fixed-effects model was used to pool studies for all analyses.

**RESULTS**

**Characteristics of the published studies**

Altogether 340 studies were identified during the primary literature search; among them 281 were excluded because they were duplicated, irrelevant to the current analysis, not RCTs, or not published in English. Fifty-nine articles were retrieved for further review, and 42 were further excluded because amoxicillin was given at a dose of $<2.0$ g/day, or either amoxicillin or PPI was given less than thrice daily in the dual therapy, nine studies did not use PPI-containing triple or quadruple therapies as controls, one not published in English and one not a RCT.

Finally, six prospective RCTs met the inclusion criteria. However, there was significant statistical heterogeneity ($\chi^2 = 15.98$, $P = 0.007$, $I^2 = 69\%$) among the six studies, which was possibly due to the reason that high-dose PPI-amoxicillin dual therapy could not be distinguished as first-line or rescue therapy in two studies and one study recruited patients infected with high clarithromycin-resistant (15.3–17.3%) strains and used clarithromycin-containing triple therapy as a first-line treatment. Four studies (without publication bias, Fig. S1) using high-dose PPI-amoxicillin dual therapy used as a second-line regimen after the failure of clarithromycin-containing therapy, including 473 participants (235 were treated with high-dose dual therapy and 238 with the control therapy), met the inclusion criteria and were included in the final systematic review and meta-analysis. The flowchart of study selection is shown in Figure 1.

The characteristics of the four included studies are shown in Table 1. All the four studies were prospective RCTs. Shirai et al.’s study29 had a high risk for bias and the rest had an unclear risk for bias (Figs S2, S3). The rescue therapies (controls) differed among the studies, namely levofloxacin-containing triple therapy was recommended by Yang et al., rifabutin-containing triple therapy by Miehlke et al., traditional bismuth-based quadruple therapy (PBMT) by another Miehlke et al.’s study, and metronidazole-containing triple therapy (PPI + amoxicillin + metronidazole) by Shirai et al.’s study29.

**Meta-analysis**

**Overall eradication rate**

The eradication rates of *H. pylori* with high-dose dual therapy as a rescue therapy in all four studies were evaluated. In the ITT analysis, the pooled eradication rate was 81.3% (95% CI 71.3–91.3%) in high-dose dual therapy groups compared to 81.5% (95% CI 71.3–91.4%) in the control groups (RR 1.00, 95% CI 0.93–1.08, $P = 0.97$) without significant statistical heterogeneity ($\chi^2 = 3.21$, $P = 0.36$, $I^2 = 6\%$; Fig. 2). In the PP analysis the pooled eradication rate was 85.3% (95% CI 76.0–94.6%) in high-dose dual therapy groups compared to 85.5% (95% CI 76.3–94.7%) in the control groups (RR 0.99, 95% CI 0.93–1.06, $P = 0.77$) without significant statistical heterogeneity ($\chi^2 = 3.85$, $P = 0.28$, $I^2 = 22\%$; Fig. 3).
Compliance

Both therapies showed a high compliance rate, with 95.3% (95% CI 89.9–100%) for high-dose dual therapy and 95.4% (95% CI 90.1–100%) for the control rescue therapies. No significant difference was observed (RR 1.00, 95% CI 0.97–1.03, \( P = 0.95; \chi^2 = 0.21 \); Fig. 4).

Side-effects

The use of high-dose dual therapy was not associated with an increased risk of side effects (RR 0.88, 95% CI 0.62–1.25, \( P = 0.47 \)). The overall side effect rate was 17.9% (95% CI 8.1–27.7%) for high-dose dual therapy, and 19.7% (95% CI 9.6–29.8%) for recommended rescue therapies. No significant heterogeneity was observed (\( \chi^2 = 1.70, P = 0.64, I^2 = 0\% \); Fig. 5).

Sensitivity analysis

We performed a sensitivity analysis in which we excluded one study at one time. The sensitivity analyses did not change either the direction or the statistical significance of any of the RR or the level of heterogeneity in any of the analyses.

DISCUSSION

Dual therapy of PPI plus amoxicillin has fallen into oblivion because of its poor efficacy with the administration of standard-dose amoxicillin and PPI twice a day. However, when using a higher dosage at shorter intervals for both PPI and amoxicillin dual therapy appears to be effective and is possibly superior to standard first-line or rescue therapy for \( H. pylori \) infection in some populations.

Clarithromycin has been a key antibiotic in the treatment of \( H. pylori \) infection over the past three decades. Secondary resistance to clarithromycin is common following the failure of clarithromycin-containing therapy. This is consistent with the high prevalence of clarithromycin-resistant strains in the four included studies, which recruited patients after eradication failure (Table 1).

This systematic review and meta-analysis included four prospective RCTs and showed that high-dose...
### Table 1. Study characteristics

<table>
<thead>
<tr>
<th>Authors (publication year)</th>
<th>Country or region</th>
<th>H. pylori infection (initial diagnosis/re-diagnosis)</th>
<th>Subgroup</th>
<th>Patients, n (CAM-R% [n/N])</th>
<th>Regimens</th>
<th>Eradication rate, % (ITT/PP)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yang et al. (2015)</td>
<td>Taiwan</td>
<td>Culture or $^{13}$C-UBT plus histology/ $^{13}$C-UBT</td>
<td>HDDT</td>
<td>56 (85.7 [48/56])</td>
<td>RAB 20 mg and AMO 750 mg, both q.i.d. for 14 days</td>
<td>89.3/89.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Control</td>
<td>56 (80.4 [45/56])</td>
<td>RAB 20 mg, AMO 1000 mg and LEV 250 mg, all b.i.d. for 7 days</td>
<td>78.6/78.6</td>
</tr>
<tr>
<td>Shirai et al. (2007)</td>
<td>Japan</td>
<td>Culture, $^{13}$C-UBT or RUT/$^{13}$C-UBT</td>
<td>HDDT</td>
<td>66 (87.0 [40/46])</td>
<td>RAB 10 mg and AMO 500 mg, both q.i.d. for 14 days</td>
<td>90.9/93.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Control</td>
<td>66 (85.0 [34/40])</td>
<td>RAB 10 mg, AMO 750 mg and MTZ 250 mg, all b.i.d. for 7 days</td>
<td>92.4/95.3</td>
</tr>
<tr>
<td>Miehlke et al. (2006)</td>
<td>Germany</td>
<td>Histology and culture/histology, or $^{13}$C-UBT</td>
<td>HDDT</td>
<td>72 (100 [72/72])</td>
<td>OME 40 mg and AMO 1000 mg, both t.i.d. for 14 days</td>
<td>69.5/74.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Control</td>
<td>73 (100 [73/73])</td>
<td>ESO 20 mg b.i.d., RIF 150 mg b.i.d., AMO 1000 mg b.i.d.; for 7 days</td>
<td>74.0/78.3</td>
</tr>
<tr>
<td>Miehlke et al. (2006)</td>
<td>Germany</td>
<td>Culture/histology, culture, RUT and $^{13}$C-UBT (at least two tests)</td>
<td>HDDT</td>
<td>41 (100 [41/41])</td>
<td>OME 40 mg and AMO 750 mg, both q.i.d. for 14 days</td>
<td>75.6/83.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Control</td>
<td>43 (100 [43/43])</td>
<td>OME 20 mg b.i.d., BIS 107 mg q.i.d., MTZ 500 mg q.i.d. and TCY 500 mg q.i.d.</td>
<td>81.4/92.1</td>
</tr>
</tbody>
</table>

AMO, amoxicillin; b.i.d., twice daily; BIS, bismuth citrate; CAM-R, clarithromycin-resistant; ESO, esomeprazole; HDDT, high-dose dual therapy; H. pylori, Helicobacter pylori; LEV, levofloxacin; ITT, intention-to-treat; MTZ, metronidazole; OME, omeprazole; PP, per-protocol; q.i.d., four times daily; RAB, rabeprazole; RIF, rifabutin; RUT, rapid urease test; TCY, tetracycline; t.i.d., thrice daily; UBT, urea breath test.

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**Figure 2.** Forest plot of *Helicobacter pylori* eradication rate (intention-to-treat) with high-dose dual proton pump inhibitor–amoxicillin therapy (high-dose dual therapy [HDDT]) compared to recommended rescue therapies (control). CI, confidence interval. [Color figure can be viewed at wileyonlinelibrary.com]

**Figure 3.** Forest plot of *Helicobacter pylori* eradication rate (per-protocol) with high-dose dual proton pump inhibitor–amoxicillin therapy (high-dose dual therapy [HDDT]) compared to recommended rescue therapies (control). CI, confidence interval. [Color figure can be viewed at wileyonlinelibrary.com]
dual therapy and recommended rescue therapies achieved similar efficacy (ITT analysis: 81.3% vs 81.5%; PP analysis: 85.3% vs 85.5%), compliance and rates of side effects. In contrast to our study, a review by Marin et al. evaluated different second-line regimens, including amoxicillin dual therapies, after a PPI-clarithromycin-amoxicillin failure. Three of these studies on dual therapy, consistent with our definition, reported optimal results (eradication rates of 100%, 90.9% and 95.5%, respectively). However, one study using 20 mg rabeprazole plus 1 g amoxicillin twice a day reached an unacceptably low eradication rate (59%).

The authors did not find any benefit of dual therapy for clarithromycin-resistant strains. We attribute this difference to varied study designs, especially the high-dose dual therapies. That review did not include three studies in our article (studies by Yang et al., and Miehlke et al.).

No meta-analysis was performed on the effect of high-dose dual therapy in comparison to bismuth-containing quadruple and concluded that both therapies were effective in curing H. pylori infection resistant to both clarithromycin and metronidazole in patients who experienced treatment failure. Yang et al. compared high-dose dual therapy to levofloxacin-containing therapy and concluded that the former was superior to the latter as rescue therapy for H. pylori infection, with similar safety profiles and tolerability.

Few studies have reported the comparison between high-dose dual therapy and guideline-recommended therapy as first-line treatment options for H. pylori eradication. Two studies, Schwartz et al. and Kim et al., did not distinguish between first-line and rescue treatments. Only one study (Yang et al.) compared high-dose dual therapy to first-line therapy for H. pylori eradication, but the study recruited patients with high clarithromycin-resistant (15.3–17.3%) strains who were treated with clarithromycin-containing triple therapy.

There were some limitations to our analysis. First, some well designed studies were excluded because they were not published in English. Second, two of...
the four included publications\textsuperscript{23,24} were performed by the same research team. However, the patient population was different with no overlap. Third, most RCTs were not blinded studies. Lack of blinding might have influenced compliance and the reporting of side effects. Additionally, different types of PPIs and controls might have generated some bias.

Does high-dose dual therapy play a role in current \textit{H. pylori} management? The variability of treatment success with current versions makes it hard to recommend it as a routine first-line therapy. However, there may be a role for it as a second-line therapy as bismuth salts are not available worldwide and even where they are available, the efficacy of second-line bismuth-based quadruple therapy for \textit{H. pylori} infection may be compromised by its side effects.\textsuperscript{50} In addition, the efficacy of levofloxacin-containing triple therapy may continue to drop due to the increasing prevalence of levofloxacin-resistant \textit{H. pylori} strains in many countries, with rates as high as 34.5\% in China,\textsuperscript{4} 31.3\% in the USA\textsuperscript{11} and 22.1\% in Italy.\textsuperscript{51} \textit{H. pylori} resistance to amoxicillin, both primary and acquired, remains rare\textsuperscript{1,8–11} and, based on our findings, there may be a role for high-dose dual therapy after the failure of clarithromycin-containing standard triple therapy or in those infected with clarithromycin-resistant \textit{H. pylori} strains.

In conclusion, our findings showed that high-dose PPI–amoxicillin dual therapy was comparable to the recommended rescue therapies, such as bismuth-based quadruple therapy, levofloxacin-containing therapy and rifabutin-containing triple therapy, for clarithromycin-resistant \textit{H. pylori} strains. High-dose dual therapy is effective and safe. Well-powered double-blind RCTs are needed to better determine the true efficacy of high-dose dual therapy. The current theory is that treatment success with high-dose dual therapy requires the gastric pH to be reliably maintained at 6 or more, at least during the time that the minimal inhibitory concentration for amoxicillin is achieved in the mucosa. Future studies with drugs, doses, the frequency of drug administration and the duration of treatment are needed to critically identify the parameters that will achieve reliable results as a first-line \textit{H. pylori} eradication therapy.

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metronidazole in the eradication treatment of
study of amoxycillin and omeprazole with and without
eradication of
alone or with amoxycillin and metronidazole in the
cure of
evaluation of lansoprazole and amoxicillin dual therapy for
randomized trial.
therapy with lansoprazole and amoxicillin.
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infection in Korea.
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blind randomized placebo controlled study.
pylori
as a rescue regimen for
therapy with rabeprazole, amoxicillin, and metronidazole
versus
high doses of rabeprazole and amoxicillin
therapy for treatment of
Helicobacter pylori
Omeprazole-based dual and triple therapy for the treatment
Helicobacter pylori
eradication with 2 week combination
treatment of lansoprazole and amoxicillin: intragastric
SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

**Figure S1** Funnel plot of high-dose dual proton pump inhibitor-amoxicillin therapy (high-dose dual therapy, HDDT) VS recommended rescue therapies (control).

**Figure S2** Risk of bias graph.

**Figure S3** Risk of bias summary.