Meta-analysis: sequential therapy for *Helicobacter pylori* eradication in children

A. Horvath, P. Dziechciarz & H. Szajewska

Department of Paediatrics, The Medical University of Warsaw, Warsaw, Poland.

Correspondence to:
Dr A. Horvath, Department of Paediatrics, The Medical University of Warsaw, 01-184 Warsaw, Dzialdowska 1, Poland.
E-mail: andrea.hania@gmail.com

Publication data
Submitted 8 June 2012
First decision 21 June 2012
Resubmitted 3 July 2012
Accepted 4 July 2012

As part of AP&T's peer-review process, a technical check of this meta-analysis was performed by Dr Y. Yuan.

SUMMARY

Background
Problems with the standard triple treatment recommended for *Helicobacter pylori* eradication therapy include unsatisfactory (less than 80%) eradication rates among children.

Aim
To assess the evidence for sequential therapy compared with triple therapy on *H. pylori* eradication rates in children.

Methods
The Cochrane Library, MEDLINE and EMBASE databases were searched in May 2012, with no language restrictions, as were abstracts from major gastroenterology conferences, for randomised controlled trials (RCTs) comparing sequential therapy with standard triple therapy for *H. pylori* eradication. Additional references were obtained from reviewed articles. Authors were contacted for extra information. Dichotomous data were pooled to obtain the relative risk (RR) of the eradication rate, with a 95% CI.

Results
Ten RCTs involving a total of 857 children aged 3–18 years met the inclusion criteria. Of the 409 patients in the sequential therapy group, 318 (78%, 95% CI 73–82) experienced eradication compared with 314 of the 444 patients (71%, 95% CI 66–75) in the standard triple therapy group (RR 1.14, 95% CI 1.06–1.23, number needed to treat 15; fixed-effects model). Sequential therapy was superior to 7-day standard triple therapy, but was not significantly better than 10-day or 14-day triple therapy. There were no significant differences between groups in the risk of adverse effects.

Conclusions
The pooled evidence suggests that 10-day sequential therapy compared with standard triple therapy may be considered as an option for increasing the eradication rates in children; however, it is still less than desired.

*Aliment Pharmacol Ther*
INTRODUCTION
Evidence-based guidelines from the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and North American Society of Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) recommend triple therapy using a proton pump inhibitor (PPI) plus amoxicillin plus imidazole, or a PPI plus amoxicillin plus clarithromycin, or bismuth salts plus amoxicillin plus imidazole as the first choice treatment for Helicobacter pylori infection in children. In addition, sequential therapy is recommended. This is a two-step, 10-day therapy typically consisting of a PPI combined with amoxicillin given for the first 5 days, followed by a triple therapy including a PPI, clarithromycin and metronidazole/tinidazole for another 5 days. Although multiple randomised controlled trials (RCTs) evaluating the effectiveness of sequential therapy compared with standard triple therapy have been performed, the results of these studies have been conflicting. Furthermore, although several meta-analyses including the most recent one that identified 13 trials involving more than 3000 patients, concluded that the sequential therapy appears to be superior to either 7-day or 10-day standard triple therapy, none have focused on the paediatric population only. The objective of this systematic review was to update evidence on sequential treatment compared with a standard triple therapy for H. pylori eradication, with a focus on children only.

METHODS
The guidelines from the Cochrane Collaboration for undertaking and reporting the results of a systematic review and meta-analysis and the PRISMA statement were followed for this systematic review and meta-analysis. However, the review protocol was not registered prior to the review.

Criteria for considering studies for this review
Included RCTs had to meet the following criteria: (i) participants: children aged 0–18 years and H. pylori-infected, as assessed using generally accepted methods [e.g. culture, the 13C-urea breath test (13C-UBT), histopathology, or the rapid urease test], (ii) intervention: sequential therapy, (iii) comparison: standard triple H. pylori eradication therapy, (iv) the primary outcome measure: the rate of H. pylori eradication, which had to be confirmed by a negative 13C-UBT or other generally accepted method at least 4 weeks after treatment and (v) the secondary outcome measures: the frequencies of adverse effects (overall and specific, including diarrhoea, taste disturbance, nausea, vomiting, bloating, loss of appetite, abdominal pain and constipation), compliance and the need for discontinuation of the H. pylori therapy.

Search methods for identification of studies
The Cochrane Central Register of Controlled Trials (CENTRAL, the Cochrane Library), MEDLINE and EMBASE databases were searched for relevant studies in May 2012. No language restrictions were imposed. The principal search text word terms and medical subject headings (MESH) used were Helicobacter pylori/ H. pylori, and sequential therapy/treatment (‘Helicobacter pylori’ OR ‘helicobacter’[MeSH Terms] OR ‘helicobacter’[All Fields]) AND (‘treatment’[All fields] OR ‘therapy’[Subheading] OR ‘therapy’[All Fields] OR ‘therapeutics’[MeSH Terms] OR ‘therapeutics’[All Fields]) OR (‘sequential therapy’ [All Fields] OR ‘triple therapy’ [All Fields] OR ‘standard therapy’ [All Fields] OR ‘eradication’ [All Fields] OR ‘eradication therapy’ [All Fields]) AND (‘child’[MeSH Terms] OR ‘child’[All Fields] OR ‘children’[All Fields] OR ‘adolescents’ [All Fields]). The reference lists from identified studies and key review articles were also searched to identify any other relevant studies. The ClinicalTrials.gov website http://clinicaltrials.gov/ and EU Clinical Trials Register website https://www.clinicaltrialsregister.eu were also searched for RCTs that were registered, but not yet published. In addition, the conference abstract books of the following organisations were reviewed to identify potentially eligible studies published only in abstract form: ‘European Paediatric Gastroenterology, Hepatology and Nutrition’, ‘North American Pediatric Gastroenterology, Hepatology and Nutrition’, ‘American Gastroenterological Association’, ‘United European Gastroenterology Federation’, ‘European Helicobacter pylori Study Group’ (all from 2010 to 2012). Attempts were made to obtain a full set of data from the authors of three studies mainly to assess the risk of bias and or for clarification of the results. However, we failed to obtain any additional information.

Data collection and analysis
Two reviewers (AH, PD) independently undertook the literature search, data extraction and quality assessment. The data sought included baseline characteristics of the participants, details of the H. pylori eradication therapy, details related to the use of standard triple therapy and sequential therapy (including dose and duration), type of outcome measure (primary vs. secondary), detection...
methods for H. pylori infection and/or assessment of side effects. A third reviewer (HS) was involved to resolve any disagreements.

In one RCT,11 participants were randomly assigned to three groups: an intervention group that received sequential therapy, a 7-day standard triple therapy group and another 14-day standard triple therapy group. As the objective of our review was to compare sequential therapy with triple therapy, we combined both triple therapy arms into a single standard triple therapy group; we did not split the sequential group into two in the subgroup analysis of duration of treatment.

Risk of bias assessment
The reviewers independently, but without being blinded to the authors or journal, assessed the risk of bias in the studies that met the inclusion criteria. The Cochrane Collaboration’s tool for assessing risk of bias was used, which includes the following criteria: adequacy of sequence generation, allocation concealment and blinding of participants, personnel and outcome assessors; and extent of loss to follow-up, i.e. the proportion of patients in whom the investigators were not able to determine outcomes (incomplete outcome data). In all cases, an answer of ‘yes’ indicates a low risk of bias, and an answer of ‘no’ indicates a high risk of bias.12 In addition, data on sample size calculations were searched. Funnel plots using RevMan software to assess the risk of publication bias for the included RCTs were also created.

Measures of treatment effect
The dichotomous outcomes, the results from individual studies and pooled statistics are reported as the risk ratio (RR) between the experimental and control groups with 95% CI.

Dealing with missing data
We assessed pooled data using intention-to-treat analysis where all drop-out are assumed to be treatment failures.13

Assessment of heterogeneity
Heterogeneity was quantified using the I² statistic, which can be interpreted as the percentage of the observed variation between studies that is attributable to heterogeneity rather than to chance. The values of 25%, 50% and 75% as edge limits for low, moderate and high heterogeneity were used.14 If there was heterogeneity greater than 50%, all analyses were based on the random effects model if it was still considered appropriate to pool the data.

Data synthesis (Statistical methods)
The data were analysed using Review Manager (RevMan) (Computer program Version 5.1.; The Nordic Cochrane Centre, The Cochrane Collaboration, 2011, Copenhagen, Denmark). The number needed to treat (NNT), with a 95% CI, was calculated using StatsDirect statistical software (http://www.statsdirect.com)[version 2.7.8 (2010-03-15)].

Subgroup and sensitivity analyses
For the primary outcome, preplanned subgroup analysis based on the duration of standard therapy was performed. Post-hoc, we also performed a subgroup analysis to compare the results of RCTs available as full-text publications with those reported in abstract form only. In addition, when there was statistically significant heterogeneity in the primary outcome across studies, sensitivity analyses were planned to determine the impacts of allocation concealment (adequate vs. inadequate and/or unclear) and attrition (<20% vs. ≥20%). The latter were not performed, as there was no heterogeneity in the primary outcome.

RESULTS
The literature search yielded 25 records, which were reviewed in full text and/or as abstracts (details of the study flow are documented in Figure S1). A funnel plot did not display overt asymmetry that would suggest publication bias. Of the included studies, 10 RCTs met the inclusion criteria.11, 15–23 However, only five were full-text publications15, 18–20, 23, the remaining five trials were published only in abstract form.11, 16, 17, 21, 22 Except one publication in Chinese23 that was translated, all trials were published in English. Table S1 summarises the characteristics of the included studies. The characteristics of the excluded trials and the reasons for exclusion are available from the authors on request.

The included trials randomised a total of 857 participants aged between 3 and 18 years. The sample size ranged from 30 to 165 participants. The studies were undertaken in European countries, such as Belgium, France, Italy, Poland, Romania and Turkey, or in Asia (China). Except for one multi-centre trial,18 the included studies were single-centre trials.

In almost all the studies, the standard triple therapy consisted of a PPI (omeprazole or lansoprazole) and two15, 17–23 or three11, 16 antibiotics. In almost all the included trials, clarithromycin was one of the antibiotics used. In five out of 10 RCTs, the duration of triple therapy was 7 days.11, 15, 18, 20, 22 In the remaining studies, the duration of triple therapy ranged from 5 days.
through 10 days\textsuperscript{21, 23} to 14 days.\textsuperscript{11, 17, 19} Except for one RCT\textsuperscript{11}, all were two-armed studies. The sequential therapy consisted of a PPI (omeprazole or lansoprazole) and amoxicillin administered for the first 5 days,\textsuperscript{11, 15–18, 20–23} or 7 days,\textsuperscript{19} and then a PPI and two antibiotics administered for the next 5\textsuperscript{11, 15–18, 20–23} or 7 days.\textsuperscript{19} In one RCT, the time of administration of the PPI was extended to 30 days.\textsuperscript{19} Details of the sequential therapy and standard triple therapy are presented in Table S2. The eradication treatment was considered as first-line therapy in four trials,\textsuperscript{15, 19, 20, 23} and as second-line eradication therapy in one trial.\textsuperscript{18} In the remaining trials, it remains unclear.

Risk of bias
Only five RCTs were published as full-text publications with methodological details reported. Only two of these studies were judged to be at low risk of bias.\textsuperscript{15, 20} Blinding was achieved in one study only.\textsuperscript{15} A power calculation for the eradication rate was reported only in three trials.\textsuperscript{15, 19, 20} The trials published only in abstract form had a number of methodological limitations or lacked adequate information to assess the overall risk of bias (Table S3).

No trial was industry sponsored; five trials did not clarify the role of funding,\textsuperscript{11, 19, 20, 22, 23} and five trials clearly stated no conflict of interest.\textsuperscript{15–18, 21} The funnel plot of studies reporting the primary outcome did not suggest publication bias; however, with the small number of trials available, interpretation is difficult (Figure S2).

Effects of interventions
Primary outcome: \textit{H. pylori} eradication rates. Data regarding the efficacy of sequential eradication therapy in increasing \textit{H. pylori} eradication rates were available from all 10 trials, which reported data from 857 participants (411 in the experimental group and 446 in the control group) (Figure 1).\textsuperscript{11, 15–23} In all RCTs, the eradication rate was a primary outcome. We found a significant difference between the sequential therapy group and the standard triple therapy group (regardless of its treatment duration) with respect to \textit{H. pylori} eradication rates (10 RCTs, RR 1.14, 95% CI 1.06–1.23). Of the 411 patients in the sequential therapy group, 318 (78%, 95% CI 73–82) experienced eradication compared with 314 of the 446 patients (71%, 95% CI 66–75) in the standard triple therapy group. The NNT was 15 (95% CI 8–88). The RR (95% CI) results of trials published as full-text papers and abstracts are shown in Figure 1. Only trials published as full-text publications showed a statistically significant advantage of the sequential therapy.

The results of trials based on the duration of standard triple therapy are shown in Figure 2. Only sequential eradication therapy compared with 7-day standard triple therapy resulted in a higher eradication rate (five RCTs, \(n = 487\), RR 1.17, 95% CI 1.07–1.28). No such effect was reported when sequential therapy was compared with 10-day or 14-day triple therapy. There was also no significant effect when sequential therapy was compared with 5-day triple therapy, but the study was underpowered so no firm conclusion can be made.

Secondary end points: adverse effects and compliance. Data regarding therapy-related adverse effects were available from six of the included trials\textsuperscript{15, 17–20, 23} (Figure S3). We found no significant difference between the study groups with respect to the risk of overall adverse effects (six RCTs, \(n = 513\), RR 1.27, 95% CI 0.94–1.70). In addition, we found no significant difference between the study groups with respect to abdominal pain, nausea/vomiting and diarrhoea (Figure S3). The need for discontinuation of the eradication treatment was reported in four trials\textsuperscript{15, 17, 18, 20} with no significant differences between the study groups (altogether in three patients – two in the sequential therapy groups\textsuperscript{17, 18} and one in the triple therapy group).\textsuperscript{17}

Compliance was assessed in six RCTs.\textsuperscript{15–20} In all these studies, compliance was high (>95%) with no significant differences between the study groups.

**DISCUSSION**

Summary of evidence
This meta-analysis of RCTs shows that in children aged 3–18 years with \textit{H. pylori} infection, sequential therapy compared to standard triple therapy only moderately improves eradication rates. The NNT for one additional child to be eradicated is 15.

Currently, it is recommended that the duration of triple therapy be 7–14 days. While evidence is limited, our review showed that sequential therapy was superior compared to 7-day triple therapy, but not compared to 10-day or 14-day triple therapy. These results suggest that the duration of therapy, not the model of drug delivery, is important. The sequential therapy did not reduce overall therapy-related adverse effects, nor any of the individual symptoms, such as diarrhoea, nausea/vomiting, or abdominal pain. The compliance rate between groups was similar.
Strengths and limitations
To our knowledge, this systematic review is the first to assess the effectiveness of sequential therapy for H. pylori eradication in children only. We gathered more data than previous reviews of RCTs conducted in adults and in children. The strength of our conclusions may be reduced by the varied methodological quality of the included trials. Potential limitations included unclear or inadequate allocation concealment and no blinding in almost all the trials. This can overestimate the effect and skew the results in favour of either treatment, depending on the biases of the investigators. Study limitations also included a small sample size in many trials. In only two RCTs, sample size calculations were available. However, to increase power is one of the reasons why a meta-analysis is performed within a systematic review.6

For the sake of completeness, our analysis included data from RCTs published in an abstract form only provided we were able to obtain and extract relevant data from a given study. Interestingly, the pooled data from RCTs available as full-text publications differed from those available as abstracts only.

Comparison with other reviews
Our findings are consistent with and add to a previously published meta-analysis by Gatta et al.5 documenting that compared with standard triple therapy, sequential therapy may be more effective for H. pylori eradication. However, this effect was evident for the adult population only [10 RCTs, odds ratio (OR) 2.99, 95% CI 2.47–3.62]. For the paediatric population, on the basis of pooled data from three RCTs involving 260 participants, sequential therapy was associated with a nonsignificant increase in H. pylori eradication (OR 1.98, 95% CI 0.96–4.07). The size of the effect in the studies conducted in adults was higher compared with the size of the effect in children documented in our review. As in our analysis, Gatta et al.5 did not find a significant difference in the rate of adverse effects between the sequential and standard triple therapy groups.
In adults, the results from the meta-analysis by Gatta et al.\textsuperscript{5} suggest that sequential therapy is effective in adult patients with clarithromycin-resistant strains of \textit{H. pylori}. In our review, this has not been systematically assessed. However, limited data from three trials\textsuperscript{18, 19, 21} suggest a similar effect in paediatric patients with clarithromycin-resistant strains of \textit{H. pylori}. Also, data from a study by Francavilla et al.\textsuperscript{24} indicate that sequential therapy may overcome clarithromycin resistance. Still, more research is needed.

While our review shows that sequential therapy appears to be superior to triple therapy, still it did not achieve the desired level of success. In 2007, Graham et al.\textsuperscript{25} proposed that one judge the effectiveness of \textit{H. pylori} eradication therapy against an established target, such as a ‘report card’ According to the proposed classification system, only therapies that score excellent, i.e. those that achieve $\geq 95\%$ eradication success in the local populations, should be prescribed. In our review, the \textit{H. pylori} eradication rate in the triple therapy group was 71\% and increased to 78\% with the sequential therapy. Nevertheless, despite the lower than desired effect, it seems reasonable to consider the mode of therapy with higher efficacy when making clinical decisions.

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Sequential therapy</th>
<th>Triple therapy</th>
<th>Weight</th>
<th>Risk ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>5 days</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anania 2011</td>
<td>13</td>
<td>15</td>
<td>14.00</td>
<td>0.93 [0.73, 1.18]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>15</td>
<td>15</td>
<td>100.00</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>13</td>
<td>14</td>
<td></td>
<td>0.93 [0.73, 1.18]</td>
</tr>
</tbody>
</table>

Heterogeneity: Not applicable
Test for overall effect: $Z = 0.60 \ (P = 0.55)$

| **7 days**       |                   |               |        |                                 |
| Francavilla 2005 | 36                | 38            | 28.00  | 1.25 [1.03, 1.53] |
| Lerro 2006       | 23                | 25            | 20.00  | 1.15 [0.92, 1.44] |
| Hurduc 2007      | 39                | 45            | 36.00  | 1.08 [0.90, 1.30] |
| Albrecht 2011    | 45                | 54            | 35.00  | 1.26 [1.01, 1.58] |
| Bontems 2011     | 68                | 83            | 59.00  | 1.14 [0.96, 1.35] |
| Subtotal (95\% CI)| 245               | 242           | 100.00 |                          |
| Total events     | 211               | 178           |        |                          |

Heterogeneity: Tau² = 0.00; Chi² = 1.66, df = 4 (P = 0.80); $I^2 = 0\%$
Test for overall effect: $Z = 3.43 \ (P = 0.0006)$

| **10 days**      |                   |               |        |                                 |
| Lu 2010          | 36                | 40            | 26.00  | 1.25 [0.99, 1.56] |
| Kutluk 2012      | 29                | 53            | 33.00  | 0.99 [0.71, 1.39] |
| Subtotal (95\% CI)| 93                | 96            | 100.00 |                          |
| Total events     | 65                | 59            |        | 1.15 [0.91, 1.44] |

Heterogeneity: Tau² = 0.01; Chi² = 1.38, df = 1 (P = 0.24); $I^2 = 28\%$
Test for overall effect: $Z = 1.18 \ (P = 0.24)$

| **14 days**      |                   |               |        |                                 |
| Hurduc 2007      | 39                | 45            | 42.00  | 0.93 [0.81, 1.07] |
| Baysoy 2010      | 14                | 42            | 8.00   | 0.83 [0.42, 1.66] |
| Erdur 2012       | 15                | 16            | 13.00  | 2.02 [1.33, 3.07] |
| Subtotal (95\% CI)| 103               | 93            | 100.00 |                          |
| Total events     | 68                | 63            |        | 1.17 [0.66, 2.10] |

Heterogeneity: Tau² = 0.22; Chi² = 13.65, df = 2 (P = 0.001); $I^2 = 85\%$
Test for overall effect: $Z = 0.54 \ (P = 0.59)$
Our review indicates that more studies are still required before sequential therapy may replace standard triple therapy for treating *H. pylori* infection in children. An open question remains regarding how to design such trials and what should constitute the ideal control group/s in future trials. The use of standard triple therapy control groups has raised some ethical concerns, such as the use of inferior treatments.26–28 One position is that comparison trials should be restricted to comparisons between therapies that achieve at least 90%, and preferably 95% or greater, success.29

**CONCLUSIONS**

There is evidence to recommend the use of 10-day sequential therapy as an option for increasing *H. pylori* eradication rates, although only moderately, in the paediatric population. However, the beneficial effect might depend on the duration of triple therapy. Caution is advised in following this recommendation in view of the methodological concerns regarding some of the included studies.

**ACKNOWLEDGEMENT**

Declaration of personal and funding interests: None.

**REFERENCES**

15. Albrecht P, Kotowska M, Szajewska H. Sequential therapy compared with standard triple therapy for *Helicobacter pylori* eradication in children: a double-

**SUPPORTING INFORMATION**

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

- **Figure S1.** Identification process for eligible trials.
- **Figure S2.** Funnel plot comparing sequential therapy with standard triple therapy on *Helicobacter pylori* eradication rates.
- **Figure S3.** Secondary outcomes. Efficacy of sequential therapy compared with standard triple therapy on *Helicobacter pylori* eradication therapy-related adverse effects.

- **Table S1.** Characteristics of included studies.
- **Table S2.** Details of sequential therapy and standard triple therapy.
- **Table S3.** A summary table of review authors’ judgements for each risk of bias item for each study.

Please note: Wiley-Blackwell are not responsible for the content or functionality of any supporting materials supplied by the authors. Any queries (other than missing material) should be directed to the corresponding author for the article.
A. Horvath et al.
