Sequential therapy or triple therapy for Helicobacter pylori infection: systematic review and meta-analysis of randomized controlled trials in adults and children

Gatta L, Vakil N, Leandro G, Di Mario F, Vaira D

CRD summary
This generally well-conducted review concluded that sequential therapy appeared to be better than triple therapy in the eradication of Helicobacter pylori infection. The authors' conclusions may be reliable, although the variable quality of the included trials should be borne in mind.

Authors' objectives
To compare the efficacy of sequential therapy versus triple therapy in adults and children with Helicobacter pylori infection.

Searching
The following databases were searched, without language restriction, from inception to October 2008: MEDLINE, EMBASE and the Cochrane Library. Search terms were reported. The authors also searched the following conference proceedings: American Gastroenterological Association (1975 to 2008), United European Gastroenterology Federation (1992 to 2008), European Helicobacter pylori Study Group (1988 to 2008), and Asian Pacific Digestive Week (2003 to 2008).

Study selection
Randomised controlled trials (RCTs) or controlled clinical trials that compared sequential therapy with triple therapy (lasting at least seven days), in patients who had not received previous treatment for Helicobacter pylori infection, were eligible for inclusion. The eligible patients had to have a follow-up test to confirm eradication performed no sooner than four weeks after the completion of treatment. The eligible trials had to use intention-to-treat analyses. The review outcomes were rates of successful eradication and side effects.

Most included trials had a control arm of triple therapy lasting seven days, whilst several trials had a control arm of triple therapy lasting ten days. Where reported, included patients had non-ulcer dyspepsia and/or peptic ulcer disease. The majority of included trials used urea breath test to assess the eradication of Helicobacter pylori. Most included trials were conducted in Italy; the others were conducted in Romania, Korea and China.

Two reviewers independently assessed studies for inclusion, with any disagreement resolved by a third reviewer.

Assessment of study quality
The quality of trials was assessed using the Jadad scale, a 5 point scale evaluating randomisation, blinding and withdrawal. Trials that scored at least 4 points were classified as high quality.

The authors did not state how many reviewers performed the validity assessment.

Data extraction
Event rates were extracted to enable the calculation of odds ratios (ORs) with 95% confidence intervals (CIs). Trial authors were contacted to obtain the most recent data.

Two reviewers independently performed the data extraction, with any disagreement resolved by a third reviewer.

Methods of synthesis
The trials were combined in a meta-analysis. A random-effects model was used in the presence of significant heterogeneity; otherwise a fixed-effect model was employed. The pooled odds ratios with 95% confidence intervals
were calculated. The number needed-to-treat (NNT), with 95% confidence intervals, was also calculated. Statistical heterogeneity was assessed using $X^2$ and $I^2$ statistics. Heterogeneity was also visually assessed using the Galbraith plot.

Subgroup analyses were performed on the different age of included patients (adults and children) and the duration of triple therapy (seven days versus ten days). Subgroup analyses were also performed on patients with non-ulcer dyspepsia, patients with peptic ulcer disease, and patients with anti-microbial resistance.

Publication bias was assessed using a funnel plot.

**Results of the review**

Thirteen RCTs were included in meta-analyses (n=3,271 patients). The quality score of RCTs ranged from 1 to 5 points; only one RCT was judged as high quality. The follow-up duration ranged from four weeks to six months.

For adult patients, sequential therapy was associated with a significant increase in eradication of *Helicobacter pylori* infection compared with triple therapy (OR 2.99, 95% CI 2.47 to 3.62; NNT 6, 95% CI 5 to 7; ten RCTs; n=3,011 patients).

For child and adolescent patients, sequential therapy was associated with a non-significant increase in eradication of *Helicobacter pylori* infection compared with triple therapy (OR 1.98, 95% CI 0.96 to 4.07; three RCTs; n=260 patients).

No significant heterogeneity was found for these outcomes. There was no evidence of publication bias.

Results of subgroup analyses were also reported.

There was no significant difference in the rate of side effects between sequential therapy and triple therapy.

**Authors’ conclusions**

Sequential therapy appeared to be better than triple therapy in the eradication of *Helicobacter pylori* infection.

**CRD commentary**

The inclusion criteria of the review were clear. Relevant databases were searched. Efforts were made to find both published and unpublished trials without language restriction, minimising the potential for both language and publication bias. Given that most included trials were conducted in Italy, the generalisability of the findings were limited. Steps were made to minimise errors and biases by having more than one reviewer independently performed the study selection and data extraction, but it was unclear whether validity assessment was also performed in duplicate.

Relevant criteria were used to examine the trial quality. Statistical heterogeneity was assessed and appropriate methods were used to pool the results.

The review was generally well conducted. The authors' conclusions may be reliable, although the variable quality of the included trials should be borne in mind.

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

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

*Research:* The authors stated that further high-quality RCTs from other European countries and North America are required before sequential therapy can be recommended as a first-line treatment for patients with *Helicobacter pylori* infection.

**Funding**

[A: The meta-analysis was not funded by Astra-Zeneca and Axcan (gastrointestinal pharmaceutical manufacturers). The "Financial support” statement (on page 1078) referred to one of the authors, who had been supported by Astra-Zeneca]
and Axcan in the past, but not for the current study.]

**Bibliographic details**

**PubMedID**
19844205

**DOI**
10.1038/ajg.2009.555

**Original Paper URL**
http://www.nature.com/ajg/journal/v104/n12/abs/ajg2009555a.html

**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
Amoxicillin /administration & dosage; Anti-Bacterial Agents /administration & dosage; Anti-Infective Agents /administration & dosage; Anti-Ulcer Agents /administration & dosage; Clarithromycin /administration & dosage; Drug Therapy, Combination; Helicobacter Infections /drug therapy; Helicobacter pylori; Humans; Metronidazole /administration & dosage; Proton Pump Inhibitors /administration & dosage; Randomized Controlled Trials as Topic; Tinidazole /administration & dosage

**AccessionNumber**
12010000702

**Date bibliographic record published**
02/06/2010

**Date abstract record published**
20/10/2010

**Record Status**
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.