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[Intervention Review]

# Sequential versus standard triple first-line therapy for *Helicobacter pylori* eradication

Olga P Nyssen<sup>1</sup>, Adrian G McNicholl<sup>1</sup>, Francis Megraud<sup>2</sup>, Vincenzo Savarino<sup>3</sup>, Giuseppina Oderda<sup>4</sup>, Carlo A Fallone<sup>5</sup>, Lori Fischbach<sup>6</sup>, Franco Bazzoli<sup>7</sup>, Javier P Gisbert<sup>1</sup>

<sup>1</sup>Gastroenterology Unit, Hospital Universitario de la Princesa, Instituto de Investigación Sanitaria Princesa (IIS-IP), and Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBERehd), Madrid, Spain. <sup>2</sup>Bactériologie-Enfants, Hôpital Pellegrin, Bordeaux, France. <sup>3</sup>Dipartimento di Medicina Interna e Specialità Mediche, Università di Genova, Genova, Italy. <sup>4</sup>Paediatric Endoscopy Units, Università del Piemonte Orientale, Novara, Italy. <sup>5</sup>Faculty of Medicine, McGill University Health Centre, Montreal, Canada. <sup>6</sup>Department of Epidemiology, University of Arkansas for Medical Sciences, Little Rock, AR, USA. <sup>7</sup>Dipartimento di Scienze Mediche e Chirurgiche, Università degli Studi di Bologna, Bologna, Italy

**Contact address:** Javier P Gisbert, Gastroenterology Unit, Hospital Universitario de la Princesa, Instituto de Investigación Sanitaria Princesa (IIS-IP), and Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBERehd), Madrid, Madrid, 28006, Spain. [javier.p.gisbert@gmail.com](mailto:javier.p.gisbert@gmail.com).

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## ABSTRACT

### Background

Non-bismuth quadruple sequential therapy (SEQ) comprising a first induction phase with a dual regimen of amoxicillin and a proton pump inhibitor (PPI) for five days followed by a triple regimen phase with a PPI, clarithromycin and metronidazole for another five days, has been suggested as a new first-line treatment option to replace the standard triple therapy (STT) comprising a proton pump inhibitor (PPI), clarithromycin and amoxicillin, in which eradication proportions have declined to disappointing levels.

### Objectives

To conduct a meta-analysis of randomised controlled trials (RCTs) comparing the efficacy of a SEQ regimen with STT for the eradication of *H. pylori* infection, and to compare the incidence of adverse effects associated with both STT and SEQ *H. pylori* eradication therapies.

### Search methods

We conducted bibliographical searches in electronic databases, and handsearched abstracts from Congresses up to April 2015.

### Selection criteria

We sought randomised controlled trials (RCTs) comparing 10-day SEQ and STT (of at least seven days) for the eradication of *H. pylori*. Participants were adults and children diagnosed as positive for *H. pylori* infection and naïve to *H. pylori* treatment.

### Data collection and analysis

We used a pre-piloted, tabular summary to collect demographic and medical information of included study participants as well as therapeutic data and information related to the diagnosis and confirmatory tests.

We evaluated the difference in intention-to-treat eradication between SEQ and STT regimens across studies, and assessed sources of the heterogeneity of this risk difference (RD) using subgroup analyses.

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We evaluated the quality of the evidence following Cochrane standards, and summarised it using GRADE methodology.

### Main results

We included 44 RCTs with a total of 12,284 participants (6042 in SEQ and 6242 in STT). The overall analysis showed that SEQ was significantly more effective than STT (82% vs 75% in the intention-to-treat analysis; RD 0.09, 95% confidence interval (CI) 0.06 to 0.11;  $P < 0.001$ , moderate-quality evidence). Results were highly heterogeneous ( $I^2 = 75\%$ ), and 20 studies did not demonstrate differences between therapies.

Reporting by geographic region (RD 0.09, 95% CI 0.06 to 0.12; studies = 44;  $I^2 = 75\%$ , based on low-quality evidence) showed that differences between SEQ and STT were greater in Europe (RD 0.16, 95% CI 0.14 to 0.19) when compared to Asia, Africa or South America. European studies also showed a tendency towards better efficacy with SEQ; however, this tendency was reversed in 33% of the Asian studies. Africa reported the closest risk difference (RD 0.14, 95% CI 0.07 to 0.22) to Europe among studied regions, but confidence intervals were wider and therefore the quality of the evidence showing SEQ to be superior to STT was reduced for this region.

Based on high-quality evidence, subgroup analyses showed that SEQ and STT therapies were equivalent when STT lasted for 14 days. Although, overall, the mean eradication proportion with SEQ was over 80%, we noted a tendency towards a lower average effect with this regimen in the more recent studies (2008 and after); weighted linear regression showed that the efficacies of both regimens evolved differently over the years, having a higher reduction in the efficacy of SEQ (-1.72% yearly) than in STT (-0.9% yearly). In these more recent studies (2008 and after) we were also unable to detect the superiority of SEQ over STT when STT was given for 10 days.

Based on very low-quality evidence, subgroup analyses on antibiotic resistance showed that the widest difference in efficacy between SEQ and STT was in the subgroup analysis based on clarithromycin-resistant participants, in which SEQ reached a 75% average efficacy versus 43% with STT.

Reporting on adverse events (AEs) (RD 0.00, 95% CI -0.02 to 0.02; participants = 8103; studies = 27;  $I^2 = 26\%$ , based on high-quality evidence) showed no significant differences between SEQ and STT (20.4% vs 19.5%, respectively) and results were homogeneous.

The quality of the studies was limited due to a lack of systematic reporting of the factors affecting risk of bias. Although randomisation was reported, its methodology (e.g. algorithms, number of blocks) was not specified in several studies. Additionally, the other 'Risk of bias' domains (such as allocation concealment of the sequence randomisation, or blinding during either performance or outcome assessment) were also unreported.

However, subgroup analyses as well as sensitivity analyses or funnel plots indicated that treatment outcomes were not influenced by the quality of the included studies. On the other hand, we rated 'length of STT' and AEs for the main outcome as high-quality according to GRADE classification; but we downgraded 'publication date' quality to moderate, and 'geographic region' and 'antibiotic resistance' to low- and very low-quality, respectively.

### Authors' conclusions

Our meta-analysis indicates that prior to 2008 SEQ was more effective than STT, especially when STT was given for only seven days. Nevertheless, the apparent advantage of sequential treatment has decreased over time, and more recent studies do not show SEQ to have a higher efficacy versus STT when STT is given for 10 days.

Based on the results of this meta-analysis, although SEQ offers an advantage when compared with STT, it cannot be presented as a valid alternative, given that neither SEQ nor STT regimens achieved optimal efficacy ( $\geq 90\%$  eradication rate).

## PLAIN LANGUAGE SUMMARY

### First-line sequential versus standard triple therapies for *Helicobacter pylori* eradication

#### Review question

To estimate the difference in cure rates between both treatments, and to identify factors that may improve or reduce the cure rate for both treatments.

#### Background

Gastric ulcer and cancer are mainly caused by infection with the bacteria *Helicobacter pylori*, a harmful micro-organism able to colonise the human stomach. Published data seem to indicate that this bacteria is present in nearly half of the world's population. The bacterial colonisation leads to a chronic infection that, over time, may alter the stomach's function, tissue structure, and even cell cycle, being able to produce a variety of symptoms and diseases.

Although this micro-organism may respond to traditional antibiotics, it has a strong resistance to treatment, and in a high percentage of cases can survive most single and double therapies. Different combinations of antibiotics have therefore been used, and the best treatment is still unclear. The most commonly recommended one is the standard triple therapy (STT), containing two antibiotics (clarithromycin,

and a nitroimidazole or amoxicillin) and a stomach protector (omeprazole). However, several studies have demonstrated that STT fails in more than one in five people, so investigators proposed replacing it with a non-bismuth quadruple sequential sequential (SEQ) treatment, containing a first phase with a dual therapy (amoxicillin and omeprazole), followed by a triple-therapy phase (nitroimidazole, clarithromycin and omeprazole).

### Study characteristics

We searched electronic databases and conference abstracts to identify any relevant studies. We include 44 studies, which tested and compared the cure rates of SEQ therapy against STTs. Our review covers research up to April 2015.

### Key results

The review indicates that before 2008 the cure rate for SEQ was higher than for STT. However, the cure rate of both treatments is lower than we would wish. The review found that effectiveness depended on several factors, including the geographic region of the study, bacterial resistance, and the date of the study. For example, we found a reduction in the cure rate over time in both STT and SEQ therapies, with a stronger reduction for SEQ. This meant that in the studies published after 2008, SEQ was not more effective than triple therapy when they were both given for 10 days.

The evidence collected and combined in this review does not support the use of SEQ therapy, as its effectiveness can be matched and even improved on by better STTs (given for 10 or 14 days, or high acid inhibition). Results for SEQ were only partially successful. We need to find another form of therapy to provide the best treatment for patients.

### Quality of the evidence

The studies included in this review were of mixed quality, but our analyses do not suggest that study quality was influencing cure rates.