Cochrane
Library

Cochrane Database of Systematic Reviews

Proton pump inhibitor- and clarithromycin-based triple therapies for *Helicobacter pylori* eradication (Protocol)

Vieira RR, Fontes LES, Pacheco RL, Fernandes MAP, Malta PP, Riera R

Vieira RR, Fontes LES, Pacheco RL, Fernandes MAP, Malta PP, Riera R.
Proton pump inhibitor- and clarithromycin-based triple therapies for *Helicobacter pylori* eradication (Protocol).
Cochrane Database of Systematic Reviews 2020, Issue 9. Art. No.: CD013734.
DOI: [10.1002/14651858.CD013734](https://doi.org/10.1002/14651858.CD013734).

www.cochranelibrary.com

TABLE OF CONTENTS

HEADER	1
ABSTRACT	1
BACKGROUND	2
OBJECTIVES	2
METHODS	2
ACKNOWLEDGEMENTS	6
REFERENCES	7
APPENDICES	8
WHAT'S NEW	11
HISTORY	11
CONTRIBUTIONS OF AUTHORS	11
DECLARATIONS OF INTEREST	12
SOURCES OF SUPPORT	12

[Intervention Protocol]

Proton pump inhibitor- and clarithromycin-based triple therapies for *Helicobacter pylori* eradication

Regis R Vieira¹, Luís Eduardo S Fontes², Rafael L Pacheco³, Marcos AP Fernandes⁴, Paloma P Malta⁵, Rachel Riera⁶

¹Department of Family Medicine, Hospital Israelita Albert Einstein, São Paulo, Brazil. ²Department of Evidence-Based Medicine, Intensive Care, Gastroenterology, Petrópolis Medical School, Petrópolis, Brazil. ³Cochrane Brazil, Centro de Estudos de Saúde Baseada em Evidências e Avaliação Tecnológica em Saúde, São Paulo, Brazil. ⁴General & Bariatric Surgery, Vivere Clinic, Petrópolis, Brazil. ⁵Department of Medical Education, Icahn School of Medicine at Mount Sinai, New York City, New York, USA. ⁶Cochrane Brazil Rio de Janeiro, Cochrane, Petrópolis, Brazil

Contact address: Regis R Vieira, regisaiu@gmail.com.

Editorial group: Cochrane Gut Group.

Publication status and date: Edited (no change to conclusions), published in Issue 8, 2021.

Citation: Vieira RR, Fontes LES, Pacheco RL, Fernandes MAP, Malta PP, Riera R. Proton pump inhibitor- and clarithromycin-based triple therapies for *Helicobacter pylori* eradication (Protocol). *Cochrane Database of Systematic Reviews* 2020, Issue 9. Art. No.: CD013734. DOI: [10.1002/14651858.CD013734](https://doi.org/10.1002/14651858.CD013734).

Copyright © 2020 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

ABSTRACT

Objectives

This is a protocol for a Cochrane Review (intervention). The objectives are as follows:

To assess the effectiveness and safety of proton pump inhibitor- and clarithromycin-based triple therapies for *Helicobacter pylori* (*H. pylori*) eradication.

BACKGROUND

Description of the condition

Helicobacter pylori (*H. pylori*) is one of the most widespread infectious pathogens in the world, affecting approximately 4.4 billion individuals (Hooi 2017). Overall, *H. pylori*'s prevalence is lowest in developed countries; however, some still have considerable infection rates, such as Sweden's 18.9%, which corresponds to approximately 1.6 million people (Hooi 2017). On the other hand, *H. pylori*'s prevalence is highest in underdeveloped countries in Latin America, Asia, the Caribbean, and Africa where the rate has reached 79% (Zamani 2018).

H. pylori is a gram-negative, microaerophilic and flagellated bacterium, which normally would not survive acidic conditions. A widely accepted explanation for the bacterium's survival in acidic environments, such as the stomach, is that it can produce large quantities of urease (Gu 2017). Urease hydrolyzes urea into ammonia and carbon dioxide, the former interacts with the gastric epithelium creating a more basic environment, which protects the microbe against acidity. In a favourable environment, *H. pylori*'s adhesion to gastric epithelium stimulates the release of inflammatory cytokines, particularly the CagA (cytotoxin-associated gene A) and the VacA (vacuolating cytotoxin A) toxins. If left untreated, the infection can result in chronic inflammation and metaplasia (Vaziri 2018).

Although most *H. pylori* carriers are asymptomatic, the infection is linked to several comorbidities: gastric ulcers, duodenal ulcers, gastric adenocarcinoma, and gastric MALT lymphoma. Gastric cancer is the third leading cause of death by cancer in the world, resulting in more than 700,000 deaths annually (Mahachai 2018). Regardless of phase, an infection by *H. pylori* is listed as an infectious disease; therefore, it is recommended that eradication be an outcome of therapy (Sugano 2015). However, eradication has proved challenging, evidenced by the decreased effectiveness of first-line treatment, which consists of a proton pump inhibitor (PPI), clarithromycin, and amoxicillin or metronidazole (Savoldi 2018).

Description of the intervention

First-line treatment for *H. pylori* eradication consists of a 14-day regimen of a PPI (twice daily), clarithromycin (500 mg twice daily), and amoxicillin (1 g twice daily) or metronidazole (500 mg twice daily) as a substitute for penicillin-allergic individuals (Malfertheiner 2017).

The PPI reduces gastric acidity, thereby improving antibiotic bioavailability in the gastric mucosa. Clarithromycin is a semi-synthetic macrolide with bacteriostatic action that inhibits protein synthesis of gram-positive, gram-negative, aerobic, and anaerobic organisms. Amoxicillin is a semi-synthetic penicillin that inhibits cell wall synthesis of gram-positive and gram-negative bacteria. Metronidazole, from the 5-nitroimidazole class, almost exclusively covers anaerobic organisms (Stollman 2016).

Clarithromycin-based triple therapy has been the treatment of choice since the 1990s. In recent decades, however, eradication has declined mainly due to clarithromycin resistance (Mahachai 2018). In 2012, The European Helicobacter Pylori Study Group (EHPG) published the Maastricht IV/Florence Consensus Report, pioneering the concept of resistance rate assessment in order to

guide treatment. Resistance values between 15% and 20% have been proposed as cut-off points (Malfertheiner 2017).

In 2017, the EHPG published the Maastricht V/Florence Consensus Report, reinforcing the group's previous recommendation that clarithromycin should not be used in regions where the resistance rate is above 15% (Malfertheiner 2017). In regions where resistance rates are below 15%, the 14-day clarithromycin-based triple therapy remains as the recommended treatment option (Malfertheiner 2017).

How the intervention might work

In regions where the clarithromycin resistance rate is below 15%, the standard of *H. pylori* eradication consists of a 14-day triple regimen: a PPI, clarithromycin, and amoxicillin or metronidazole (Malfertheiner 2017). On the other hand, areas with higher resistance rates should test for clarithromycin sensitivity prior to determining the course of treatment (Liu 2013; Malfertheiner 2017; Wenzhen 2010; Zagari 2018a). However, despite all of these recommendations, it is still unclear whether maintaining the clarithromycin-based triple therapy as the first choice is truly effective and safe, especially considering the decreased eradication rates and increased prevalence of severe complications associated with treatment failure (Crowe, 2019; Hooi 2017).

Why it is important to do this review

Many sources, including the EHPG, agree that when clarithromycin resistance rates are lower than 15%, medical professionals should maintain first-line empiric treatment (Savoldi 2018; Malfertheiner 2017). Furthermore, the same sources advise that in countries with high clarithromycin resistance, quadruple therapy with bismuth is the main alternative option (Malfertheiner 2017). Although most of these treatment recommendations suggest the addition of bismuth, one clinical trial demonstrated that there was no difference between triple and quadruple therapy treatment outcomes. Conversely, other trials suggest the addition of bismuth in order to combat high clarithromycin resistance rates (Crowe, 2019). Therefore, considering that resistance rates for first-line treatment are increasing steadily, it is important to evaluate the effectiveness and safety of clarithromycin-based triple therapy as our first option – which no systematic review has done before (Fallone 2016; Zagari 2018a).

OBJECTIVES

To assess the effectiveness and safety of proton pump inhibitor- and clarithromycin-based triple therapies for *Helicobacter pylori* (*H. pylori*) eradication.

METHODS

Criteria for considering studies for this review

Types of studies

We will consider randomised controlled trials (RCTs), as they are considered the gold standard for clinical questions of interventions. We will include RCTs reported as full text, as abstract only and as unpublished data.

We will not include cluster-randomised, cross-over design, and quasi-randomised controlled trials since these study designs could

either lead to an undesirable risk of bias or be unjustifiable given the nature of the intervention.

Types of participants

We will consider RCTs involving adults (16 years and older) with a diagnosis of *Helicobacter pylori* (*H. pylori*) infection, and confirmed by urea breath test, stool antigen test, endoscopic biopsies with rapid urease reaction, histology, or culture.

Types of interventions

We will include RCTs that compared triple clarithromycin-based therapy, composed of (i) PPI standard* or double standard dose twice daily plus (ii) clarithromycin 500 mg twice daily plus (iii) amoxicillin 1 g twice daily or metronidazole 500 mg twice daily for 14 days versus any of the following regimens:

- Bismuth quadruple therapy composed of (i) PPI standard dose twice daily plus (ii) bismuth subcitrate 120 mg to 300 mg or 420 mg or bismuth subsalicylate 300 mg or 524 mg four times daily plus (iii) tetracycline 500 mg four times daily.
- Clarithromycin-based concomitant therapy composed of (i) PPI standard dose twice daily plus (ii) clarithromycin 500 mg twice daily plus (iii) amoxicillin 1 g twice daily plus (iv)
- Clarithromycin-based sequential therapy, in which the first sequence is composed of (i) PPI standard dose plus (ii) amoxicillin 1 g twice daily for 5 days followed by a second sequence composed of (i) PPI standard dose plus (ii) clarithromycin 500 mg twice daily plus (iii) either metronidazole 500mg twice daily or tinidazole 500 mg twice daily for additional 5 days - completing a total of 10 days.
- Clarithromycin-based hybrid therapy, in which the first sequence is composed of (i) PPI standard dose plus (ii) amoxicillin 1 g twice daily for 7 days followed by a second phase composed of (i) PPI standard dose plus (ii) amoxicillin 1 g twice daily plus (iii) clarithromycin 500 mg twice daily plus (iv) either metronidazole 500 mg twice daily or tinidazole 500 mg twice daily for additional 7 days - completing a total of 14 days.

*Standard dose of PPI includes one of the oral daily options: lansoprazole 30 mg, omeprazole 20 mg, pantoprazole 40 mg, rabeprazole 20 mg or esomeprazole 20 mg.

Types of outcome measures

We will consider the outcomes detailed below. Reporting of the primary and/or secondary outcomes listed here will not be an inclusion criterion for the review. We will contact trial authors if a trial has not reported their eradication rates.

Primary outcomes

1. Successful *H. pylori* eradication rate

Measured as the frequency of participants who experienced *H. pylori* eradication.

H. pylori eradication is defined as a negative test at least four weeks after the end of the treatment course, and confirmed by one of the following: urea breath test, stool antigen test, endoscopic biopsies with rapid urease reaction, histology, or culture. We will exclude studies that used serology to confirm eradication and/or studies where eradication was confirmed by a test performed within four

weeks of treatment conclusion, as this could lead to misleading test results (false-negatives) (Malfertheiner 2017).

2. Serious adverse events

Measured as the frequency of participants who experienced at least one serious adverse event. We will consider serious adverse events according to the World Health Organization criteria (i.e. results in death, is life-threatening, requires inpatient hospitalisation or causes prolongation of existing hospitalisation, results in persistent or significant disability/incapacity, may have caused a congenital anomaly/birth defect, or requires intervention to prevent permanent impairment or damage) (WHO 2005). In case any trial reports adverse events at more than one time point, we will consider all events occurring from the beginning to the end of treatment, regardless of the time points.

Secondary outcomes

3. Any adverse event (allergy, toxicity, etc.)

Measured as the frequency of participants who experienced at least one adverse event.

Search methods for identification of studies

Electronic searches

We will conduct a literature search to identify all published or unpublished RCTs that fulfil our eligibility criteria. The literature search will identify potential studies in all languages, with no limits as to the year of publication. We will translate the non-English language papers and fully assess them for potential inclusion in the review as necessary.

We will search the following electronic databases for identifying potential studies.

- Cochrane Central Register of Controlled Trials (CENTRAL) (via Ovid) (Appendix 1)
- MEDLINE (1946 to present) (via Ovid) (Appendix 2)
- Embase (1974 to present) (via Ovid) (Appendix 3)
- CINAHL (1982 to present)
- LILACS (1982 to present)

Searching other resources

We will check reference lists of all primary studies and review articles for additional references. We will contact authors of identified trials and ask them to identify other published and unpublished studies. We will also contact manufacturers and experts in the field, asking them for additional published or unpublished trials. We will check the articles citing the identified studies in order to find additional references.

We will search for errata or retractions from eligible trials on PubMed and report the date this was done within the review. We will search the grey literature databases and clinical trials registers below.

Grey literature databases

- Health Management Information Consortium (HMIC) database www.ovid.com/site/catalog/DataBase/99.jsp
- National Technical Information Service (NTIS) database www.ntis.gov/products/ntisdb.aspx

- OpenGrey www.opengrey.eu

Clinical trials registers/trial result registers

We will also conduct a search of clinical trial registers/trial result registers.

- [Clinical Trials.gov](https://clinicaltrials.gov/) (<https://clinicaltrials.gov/>)

Data collection and analysis

Selection of studies

Two review authors (RRV, LESF) will independently screen titles and abstracts on Covidence in order to identify and include all potential studies, which will be labelled as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve'. We will retrieve the full-text study reports/publications, and two review authors (RRV, LESF) will independently screen the full text and identify studies for inclusion and identify and record reasons for exclusion of the ineligible studies. We will resolve any disagreement by consulting a third review author (RR or RLP). We will identify and exclude duplicates and collate multiple reports of the same study so that each study, rather than each report, is the unit of interest in the review. We will record the selection process in sufficient detail to complete a PRISMA flow diagram and a 'Characteristics of excluded studies' table.

Data extraction and management

Two review authors (RRV, PM) will extract study characteristics from the included studies. We will use the Covidence electronic form, based on the Cochrane standard data collection form, which will be tested a priori on at least one study in the review. We will extract the following study characteristics.

1. Miscellaneous details of the study: report title, year of publication, author contacts, and publication type (abstract or full report).
2. Methods: aim of study, study design, unit of allocation, start and end dates, duration of participation, and ethical approval.
3. Participants: population description, setting, inclusion criteria, exclusion criteria, age, method of recruitment, informed consent obtained, total number randomised, baseline imbalances, withdrawals and exclusions, gender, race/ethnicity, underlying indication for treatment, diagnostic criteria, subgroups measured and reported, and other relevant sociodemographics.
4. Interventions: number randomised in each group, dose, duration of treatment period, timing, delivery, co-interventions, and compliance.
5. Outcomes: primary and secondary outcomes specified and collected, time points measured, outcome definition, person measuring/reporting, unit of measurement, scales, imputation of missing data.
6. Notes: funding for trial, and notable conflicts of interest of trial authors.

Two review authors (RRV, LESF) will independently extract outcome data from included studies. We will note in the 'Characteristics of included studies' table if outcome data are reported in an unusable way. We will resolve disagreements by consensus, or by involving a third person (RR or RLP). One review author (RRV) will cross-copy the data from the data collection form into the Review Manager

file. We will double-check that the data is entered correctly by comparing the study reports with how the data are presented in the systematic review. A second review author (LESF) will spot-check study characteristics for accuracy against the trial report.

Assessment of risk of bias in included studies

Two review authors (RRV, RLP) will independently assess risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2019). Any disagreement will be resolved by discussion or by involving a third person (RR OR LESF). We will assess the risk of bias according to the following domains (sources of bias).

1. Random sequence generation.
2. Allocation concealment.
3. Blinding of participants and personnel.
4. Blinding of outcome assessment.
5. Incomplete outcome data.
6. Selective outcome reporting.
7. Other sources of bias.

We will judge each potential source of bias as high, low or unclear and provide a quote from the study report together with a justification for our judgment from the 'Risk of bias' table. We will judge the following domains separately for different outcomes: blinding of participants and personnel, blinding of outcome assessment, and Incomplete outcome data.

Assessment of bias in conducting the systematic review

We will conduct the review according to this published protocol and report any deviations from it in the 'Differences between protocol and review' section of the systematic review.

Measures of treatment effect

We will analyse dichotomous data (eradication rates, occurrence of adverse events) as risk ratios (RRs) providing 95% confidence intervals (CIs) for the results. We will ensure that higher scores for continuous outcomes have the same meaning for the particular outcome, explain the direction to the reader, and report where the directions were reversed if this is necessary.

We will undertake meta-analyses only where this is meaningful, i.e. if the treatments, participants, and the underlying clinical question are similar enough for pooling to make sense.

A common way that trialists indicate when they have skewed data is by reporting medians and interquartile ranges. When we encounter this, we will note that the data are skewed and consider the implications.

Where multiple trial arms are reported in a single trial, we will include only the relevant arms. If two comparisons are present (e.g. drug A versus placebo and drug B versus placebo), then they must be entered into the same meta-analysis, we will halve the control group to avoid double-counting.

Unit of analysis issues

The unit of analysis will be the individual, with a single measurement of each outcome for each participant being collected and analysed.

Dealing with missing data

We will contact investigators or study sponsors in order to verify key study characteristics and obtain missing outcome data whenever it is possible (e.g. when a study is identified as abstract only). If we cannot obtain the outcome data, we plan to analyse whether the missing data is "not missing at random" or "missing at random". If the data is judged to be "not missing at random", we will input the missing data with replacement values, treating these as if they were observed (e.g. imputing an assumed outcome such as assuming all were poor outcomes). If the data is judged to be "missing at random" we will analyse only the available data, i.e. ignoring the missing data (Higgins 2019).

We intend to perform sensitivity analyses to assess how sensitive results are to reasonable changes in the assumptions that are made. Furthermore, we will address the potential impact of missing data on the findings of the review in the Discussion section (Higgins 2019).

Assessment of heterogeneity

We will assess clinical, methodological and statistical heterogeneity among the included trials. We will use the χ^2 test ($P < 0.10$ indicates significant heterogeneity) and the I^2 statistic to measure statistical heterogeneity among the trials in each meta-analysis (Higgins 2003). If we identify substantial heterogeneity, we will explore it by prespecified subgroup analysis. We will consider an I^2 value greater than 50% as substantial heterogeneity (Higgins 2011). We will use the random-effects model for meta-analyses, provided we expect clinical and methodological heterogeneity between studies, using Review Manager software version 5.3 (Review Manager 2014).

We will use the Inverse Variance for Heterogeneity (IVHET) model proposed by Doi 2015 and colleagues in a sensitivity analysis. This method is a variation of random-effects and fixed-effects models. Inverse Variance for Heterogeneity keeps the weight of the studies as a fixed-effects model does, allowing a wider confidence interval as a random-effects model does. In practice, we have the same point estimate as a fixed-effects model, but wider confidence intervals than fixed-effects, except when heterogeneity is zero. We will use the STATA package software version 15.1 (StataCorp 2017) for this purpose.

Assessment of reporting biases

We will attempt to contact study authors, asking them to provide missing outcome data. When this is not possible, and the missing data are thought to introduce serious bias, the impact of including such studies in the overall assessment of results will be explored by excluding the study in a sensitivity analysis.

If we are able to pool 10 or more trials, we will create and examine funnel plots to explore possible publication biases.

Data synthesis

We will combine the results across studies, undertaking a random-effect model meta-analysis for dichotomous and continuous outcomes by default, as we expect some clinical heterogeneity among them.

Subgroup analysis and investigation of heterogeneity

We plan to carry out the following subgroup analyses for the primary outcomes.

1. **Level of clarithromycin resistance:** Regions with high clarithromycin resistance ($>15\%$), versus regions of high ($>15\%$) dual clarithromycin and metronidazole resistance, versus regions with low clarithromycin resistance ($<15\%$) (Malfertheiner 2017).
2. **Type of PPI used, considering the pharmacokinetic differences:** Pantoprazole has faster action and maintains higher concentration levels over a longer period of time than omeprazole and lansoprazole (Shin 2013). Rabeprazole has proven superior to omeprazole and lansoprazole in urease inhibition (Barth 2002). There is also an omeprazole isomer that shows better stability and greater potential than omeprazole (Hu 2017). The main enzyme in the metabolism of PPIs is CYP2C19, and the effects of PPIs depend on cytochrome P450 and CYP2C19. CYP2C19 polymorphism is highly varied among different ethnic populations and its genotype is a key factor for *H. pylori* eradication in patients using triple therapy with omeprazole or lansoprazole, and has no significant effect on triple therapy with rabeprazole or esomeprazole (Kuo 2014).
3. **Type of test used to assess eradication:** urea breath test, versus stool antigen test, versus endoscopic methods. In terms of analysing the diagnostic tests, the urease breath test is the most recommended for its high sensitivity and specificity because it is expected to have the best results. The stool antigen test also has high sensitivity and specificity, as long as the monoclonal antibody-based ELISA method is used. The endoscopic urease test method has a higher chance of false-negatives, especially in patients with gastrointestinal bleeding, or in those that have been using bismuth and/or an antibiotic for less than four weeks, as well as those that have been using a PPI for less than two weeks (Malfertheiner 2017). We will use the outcome of successful eradication rate in subgroup analysis.

Sensitivity analysis

We will perform sensitivity analysis, defined a priori, to assess the robustness of our conclusions for the primary outcomes, excluding:

- trials with a high or unclear risk of bias for at least one RoB domain.
- trials with missing data judged as "not missing at random", in which we inputted the missing data with replacement values (computing as poor outcomes).

We will perform an additional sensitivity analysis using the Inverse Variance for Heterogeneity (IVHET) model proposed by Doi 2015 and colleagues. This method keeps the weight of the studies as a fixed-effect model does, allowing a wider confidence interval as a random-effects model does. In practice, we have the same point estimate than FE model, but wider confidence intervals than FE, except when heterogeneity is zero. We will use the STATA package software version 15.1 (StataCorp 2017) for this purpose.

Reaching conclusions

We will base our conclusions only on findings from the quantitative or narrative synthesis of included studies for this review. We will avoid making recommendations for practice and our implications for research will give the reader a clear sense of where the focus of

any future research in the area should be, and what the remaining uncertainties are.

Summary of findings and assessment of the certainty of the evidence

We will create a 'Summary of findings' table adding all the outcomes stated under 'Types of outcome measures' for each comparison of clinical interest.

Two review authors (LESF, RRV) will independently assess the certainty of the evidence. We will use the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness, and publication bias) to evaluate the certainty of a body of evidence as it relates to the studies, which contributes data to the synthesis of each outcome. We will report the certainty of evidence as either high, moderate, low, or very low as described in Section 8.5 and 8.7, and Chapters 11 and 12, of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2019). We will use GRADEpro

software to create 'Summary of findings' tables (GRADEpro profiler). We will justify all decisions to downgrade the certainty of the evidence by the use of footnotes and present useful comments for readers when necessary.

ACKNOWLEDGEMENTS

We acknowledge the help and support of the Cochrane Gut Group. The review authors are keen to acknowledge Dr. Rocco Maurizio Zagari (peer reviewer), Ms. Marilyn Walsh (consumer reviewers), editors and other peer referees who provide comments to improve the protocol. We thank copy editor Heather Maxwell for copy editing the protocol.

The methods section of this protocol is based on a standard template used by the Cochrane Gut Group.

The search strategies were designed by Yuhong Yuan (Information Specialist at the Cochrane Gut Group).

REFERENCES

Additional references

Barth 2002

Barth J, Hahne W. Review article: rabeprazole-based therapy in *Helicobacter pylori* eradication. *Alimentary Pharmacology & Therapeutics* 2002;**16 Suppl 1**:31-3. [PMID: 11849125]

Crowe, 2019

Crowe SE. *Helicobacter pylori* Infection. *New England Journal of Medicine* 2019;**380**(12):1158-65. [PMID: 30893536]

Doi 2015

Doi SA, Barendregt JJ, Khan S, Thalib L, Williams GM. Simulation comparison of the quality effects and random effects methods of meta-analysis. *Epidemiology (Cambridge, Mass.)* 2015;**26**(4):e42-4. [PMID: 25872162]

Fallone 2016

Fallone CA, Chiba N, van Zanten SV, Fischbach L, Gisbert JP, Hunt RH, et al. The Toronto Consensus for the treatment of *Helicobacter pylori* infection in adults. *Gastroenterology* 2016;**151**(1):51-69.e14. [PMID: 27102658]

GRADEprofiler [Computer program]

GRADEprofiler (GRADEpro). Brozek J, Oxman A, Schunemann H. Evidence Prime, 2015. Available online: www.gradepr.org.

Gu 2017

Gu H. Role of flagella in the pathogenesis of *Helicobacter pylori*. *Current Microbiology* 2017;**74**(7):863-9. [PMID: 28444418]

Higgins 2003

Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;**327**(7414):557-60.

Higgins 2019

Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al (editors). *Cochrane Handbook for Systematic Reviews of Interventions* version 6.0 (updated July 2019). Cochrane, 2019.. Available from www.training.cochrane.org/handbook..

Hooi 2017

Hooi JKY, Lai WY, Ng WK, Suen MM, Underwood FE, Tanyingoh D, et al. Global prevalence of *Helicobacter pylori* Infection: systematic review and meta-analysis. *Gastroenterology* 2017;**153**(2):420-9. [PMID: 28456631]

Hu 2017

Hu Y, Zhu Y, Lu NH. Novel and effective therapeutic regimens for *Helicobacter pylori* in an era of increasing antibioticResistance. *Frontiers in Cellular and Infection Microbiology* 2017;**7**:168. [PMID: 28529929]

Kuo 2014

Kuo CH, Lu CY, Shih HY, Liu CJ, Wu MC, Hu HM, et al. CYP2C19 polymorphism influences *Helicobacter pylori* eradication. *World Journal of Gastroenterology* 2014;**20**(43):16029-36. [PMID: 25473155]

Liu 2013

Liu WZ, Xie Y, Cheng H, Lu NH, Hu FL, Zhang WD, et al. Fourth Chinese National Consensus Report on the management of *Helicobacter pylori* infection. *Journal of Digestive Diseases* 2013;**14**(5):211-21. [PMID: 23302262]

Mahachai 2018

Mahachai V, Vilaichone RK, Pittayanon R, Rojborwonwitaya J, Leelakusolvong S, Maneerattanaporn M, et al. *Helicobacter pylori* management in ASEAN: the Bangkok consensus report. *Journal of Gastroenterology and Hepatology* 2018;**33**(1):37-56. [PMID: 28762251]

Malfertheiner 2017

Malfertheiner P, Megraud F, O'Morain CA, Gisbert JP, Kuipers EJ, Axon AT, et al. Management of *Helicobacter pylori* infection-the Maastricht V/Florence Consensus Report. *Gut* 2017;**66**(1):6-30. [PMID: 27707777]

Review Manager 2014 [Computer program]

Copenhagen, The Nordic Cochrane Centre: The Cochrane Collaboration Review Manager (RevMan). Version 5.3. Copenhagen, The Nordic Cochrane Centre: The Cochrane Collaboration, 2014.

Savoldi 2018

Savoldi A, Carrara E, Graham DY, Conti M, Tacconelli E. Prevalence of antibiotic resistance in *Helicobacter pylori*: a systematic review and meta-analysis in World Health Organization regions. *Gastroenterology* 2018;**155**(5):1372-1382.e17. [PMID: 29990487]

Shin 2013

Shin JM, Kim N. Pharmacokinetics and pharmacodynamics of the proton pump inhibitors. *Journal of Neurogastroenterology and Motility* 2013;**19**(1):25-35. [PMID: 23350044]

StataCorp 2017 [Computer program]

College Station, TX. StataCorp LLC. *Stata Statistical Software: Release 15*. College Station, TX. StataCorp LLC., 2017.

Stollman 2016

Stollman N. *Helicobacter pylori* Infection in the era of antibiotic resistance. *Gastroenterology & Hepatology* 2016;**12**(2):122-5. [PMID: 27182214]

Sugano 2015

Sugano K, Tack J, Kuipers EJ, Graham DY, El-Omar EM, Miura S, et al. Kyoto global consensus report on *Helicobacter pylori* gastritis. *Gut* 2015;**64**(9):1353-67. [PMID: 26187502]

Vaziri 2018

Vaziri F, Tarashi S, Fateh A, Siadat SD. New insights of *Helicobacter pylori* host-pathogen interactions: the triangle of virulence factors, epigenetic modifications and non-coding RNAs. *World Journal of Clinical Cases* 2018;**6**(5):64-73. [PMID: 29774218]

Wenzhen 2010

Wenzhen Y, Yumin L, Quanlin G, Kehu Y, Lei J, Donghai W, et al. Is antimicrobial susceptibility testing necessary before first-line treatment for *Helicobacter pylori* infection? Meta-analysis of randomized controlled trials. *Internal Medicine (Tokyo, Japan)* 2010;**49**(12):1103-9. [PMID: 20558925]

WHO 2005

World Health Organization. World alliance for patient safety : WHO draft guidelines for adverse event reporting and learning systems: from information to action. World Health Organization. <https://apps.who.int/iris/handle/10665/69797> 2005;**16**:80. [<https://apps.who.int/iris/handle/10665/69797>]

Zagari 2018a

Zagari RM, Rabitti S, Eusebi LH, Bazzoli F. Treatment of *Helicobacter pylori* infection: a clinical practice update. *European Journal of Clinical Investigation* 2018;**48**(1):2-7. [DOI: [10.1111/eci.12857](https://doi.org/10.1111/eci.12857)] [PMID: 29144559]

Zamani 2018

Zamani M, Ebrahimtabar F, Zamani V, Miller WH, Alizadeh-Navaei R, Shokri-Shirvani J, et al. Systematic review with meta-analysis: the worldwide prevalence of *Helicobacter pylori* infection. *Alimentary Pharmacology & Therapeutics* 2018;**47**(7):868-76. [PMID: 29430669]

APPENDICES

Appendix 1. CENTRAL search strategy

1. exp *Helicobacter*/ or exp *Helicobacter* Infections/
2. (*helicobacter* or *campylobacter*).tw,kw.
3. (*pylori* or *pyloridis* or HP).tw,kw.
4. or/1-3
5. exp Proton Pump Inhibitors/
6. proton pump inhibitor*.mp.
7. (PPI or PPIs).tw,kw.
8. (omeprazole or h 16868 or losec or prilosec or rapinex or zegerid).mp.
9. (lansoprazole or lanzoprazole or ag 1749 or agopton or bamalite or lanzor or monolitus or ogast or ogastro or opiren or prevacid or prezal or pro ulco or promeco or takepron or ulpax or zoton).mp.
- 10.(pantoprazole or by 1023 or protium or protonix or skf-96022).mp.
- 11.(esomeprazole or nexium).mp.
- 12.(rabeprazole or aciphex or dexrabeprazole or e 3810 or ly-307640 or pariet).mp.
- 13.(dexlansoprazole or Kapidex or Dexilant or AGN 20194* or AGN20194* or dexrabeprazole).mp.
- 14.(tenatoprazole or CAS 113712-98-4 or STU-Na or TAK-390* or TAK390* or TAK-438 or TAK438 or AZD0865 or "AZD 0865").mp.
- 15.or/5-14
- 16.4 and 15
- 17.exp Clarithromycin/
- 18.clarithromycin.tw,kw.
- 19.(Biaxin or Crixan or Claritron or Clarihexal or Clacid or Claritt or Clacee or Clarac or Clariwin or Claripen or Clarem or Claridar or Cloff or Fromilid or Infex or Kalixocin or Karicin or Klaricid or Klaridex or Klacid or Klaram or Klabax or MegaKlar or Monoclar or Resclar or Rithmo or Truclar or Vikrol or Zeclar).tw,kw.
- 20.(6-o-methylerythromycin or 81103-11-9 or a 56268 or a56268 or h1250jik0a or "te 031" or te031).tw,kw.
- 21.or/17-20
- 22.16 and 21
- 23.exp Amoxicillin/
- 24.exp Metronidazole/
- 25.(amoxicillin* or amoxycillin*).tw,kw.
- 26.(actimoxi or amoxil or clamoxyl or hydroxyampicillin or penamox or polymox or trimox or wymox).tw,kw.
- 27.metronidazole.tw,kw.
- 28.(bayer 5360 or clont or danizol or flagyl or gineflavir or metric or metrogel or metrodzhil or metrogyl or satric or trichazol or trichopol or trivazol or vagilen).tw,kw.
- 29.or/23-28
- 30.22 and 29

Appendix 2. MEDLINE search strategy

1. exp *Helicobacter*/ or exp *Helicobacter* Infections/
2. (*helicobacter* or *campylobacter*).tw,kw.

3. (pylori or pyloridis or HP).tw,kw.
4. or/1-3
5. exp Proton Pump Inhibitors/
6. proton pump inhibitor*.mp.
7. (PPI or PPIs).tw,kw.
8. (omeprazole or h 16868 or losec or prilosec or rapinex or zegerid).mp.
9. (lansoprazole or lanzoprazole or ag 1749 or agopton or bamalite or lanzor or monolium or ogast or ogastro or opiren or prevacid or prezal or pro ulco or promeco or takepron or ulpax or zoton).mp.
- 10.(pantoprazole or by 1023 or protium or protonix or skf-96022).mp.
- 11.(esomeprazole or nexium).mp.
- 12.(rabeprazole or aciphex or dexrabeprazole or e 3810 or ly-307640 or pariet).mp.
- 13.(dexlansoprazole or Kapidex or Dexilant or AGN 20194* or AGN20194* or dexrabeprazole).mp.
- 14.(tenatoprazole or CAS 113712-98-4 or STU-Na or TAK-390* or TAK390* or TAK-438 or TAK438 or AZD0865 or "AZD 0865").mp.
- 15.or/5-14
- 16.4 and 15
- 17.exp Clarithromycin/
- 18.clarithromycin.tw,kw.
- 19.(Biaxin or Crixan or Claritron or Clarihexal or Clacid or Claritt or Clacee or Clarac or Clariwin or Claripen or Clarem or Claridar or Cloff or Fromilid or Infex or Kalixocin or Karicin or Klaricid or Klaridex or Klacid or Klaram or Klabax or MegaKlar or Monoclar or Resclar or Rithmo or Truclar or Vikrol or Zeclar).tw,kw.
- 20.(6-o-methylerythromycin or 81103-11-9 or a 56268 or a56268 or h1250jik0a or "te 031" or te031).tw,kw.
- 21.or/17-20
- 22.16 and 21
- 23.exp Amoxicillin/
- 24.exp Metronidazole/
- 25.(amoxicillin* or amoxycillin*).tw,kw.
- 26.(actimoxi or amoxil or clamoxyl or hydroxyampicillin or penamox or polymox or trimox or wymox).tw,kw.
- 27.metronidazole.tw,kw.
- 28.(bayer 5360 or clont or danizol or flagyl or gineflavir or metric or metrogel or metrodzhil or metroglol or satric or trichazol or trichopol or trivazol or vagilen).tw,kw.
- 29.or/23-28
- 30.22 and 29
- 31.randomized controlled trial.pt.
- 32.controlled clinical trial.pt.
- 33.random*.mp.
- 34.placebo.ab.
- 35.trial.ab.
- 36.groups.ab.
- 37.drug threapy.fs.
- 38.or/31-37
- 39.exp animals/ not humans.sh.
- 40.38 not 39
- 41.30 and 40

Note: lines 31-40, RCT filter: we used the "Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity-maximizing version (2008 revision); Ovid format". We made the following minor revisions: we used "random*" instead of "randomized.ab" or "randomly.ab." to capture word variations such as "randomised, randomization, random".

Appendix 3. EMBASE search strategy

1. exp Helicobacter/ or exp Helicobacter infection/
2. (helicobacter or campylobacter).tw,kw.
3. (pylori or pyloridis or HP).tw,kw.
4. or/1-3
5. exp proton pump inhibitor/

6. proton pump inhibitor*.mp.
7. (PPI or PPIs).tw,kw.
8. (omeprazole or h 16868 or losec or prilosec or rapinex or zegerid).mp.
9. (lansoprazole or lanzoprazole or ag 1749 or agopton or bamalite or lanzor or monolitum or ogast or ogastro or opiren or prevacid or prezal or pro ulco or promeco or takepron or ulpax or zoton).mp.
- 10.(pantoprazole or by 1023 or protium or protonix or skf-96022).mp.
- 11.(esomeprazole or nexium).mp.
- 12.(rabeprazole or aciphex or dexrabeprazole or e 3810 or ly-307640 or pariet).mp.
- 13.(dexlansoprazole or Kapidex or Dexilant or AGN 20194* or AGN20194* or dexrabeprazole).mp.
- 14.(tenatoprazole or CAS 113712-98-4 or STU-Na or TAK-390* or TAK390* or TAK-438 or TAK438 or AZD0865 or "AZD 0865").mp.
- 15.or/5-14
- 16.4 and 15
- 17.exp amoxicillin plus clarithromycin plus lansoprazole/ or exp clarithromycin/ or exp amoxicillin plus clarithromycin plus omeprazole/
- 18.clarithromycin.tw,kw.
- 19.(Biaxin or Crixan or Claritron or Clarihexas or Clacid or Claritt or Clacee or Clarac or Clariwin or Claripen or Clarem or Claridar or Cloff or Fromilid or Infex or Kalixocin or Karicin or Klaricid or Klaridex or Klacid or Klaram or Klabax or MegaKlar or Monoclar or Resclar or Rithmo or Truclar or Vikrol or Zeclar).tw,kw.
- 20.(6-o-methylerythromycin or 81103-11-9 or a 56268 or a56268 or h1250jik0a or "te 031" or te031).tw,kw.
- 21.or/17-20
- 22.16 and 21
- 23.exp amoxicillin/
- 24.exp metronidazole/
- 25.(amoxicillin* or amoxycillin*).tw,kw.
- 26.(actimoxi or amoxil or clamoxyl or hydroxyampicillin or penamox or polymox or trimox or wymox).tw,kw.
- 27.metronidazole.tw,kw.
- 28.(bayer 5360 or clont or danizol or flagyl or gineflavir or metric or metrogel or metrodzhil or metrogyl or satric or trichazol or trichopol or trivazol or vagilen).tw,kw.
- 29.or/23-28
- 30.22 and 29
- 31.random:.tw.
- 32.placebo:.mp.
- 33.double-blind:.mp.
- 34.clinical trial:.mp.
- 35.or/31-34
- 36.exp animal/ not human.sh.
- 37.35 not 36
- 38.30 and 37

Note: Lines 31-35 RCT filter: We used the HIRU filter, combined one term min difference and two terms min difference of high sensitivity and high specificity therapy filter: <https://hiru.mcmaster.ca/hiru/hedges/All-EMBASE.htm>

Appendix 4. Glossary of terms

Adenocarcinoma- a cancerous tumour that starts in mucus-producing glands in the body

Aerobic- requiring oxygen in order to grow and survive

Anaerobic- able to grow and live without oxygen

Asymptomatic- lacking the expected characteristics associated with a disease or condition

Bacteriostatic-capable of stopping the growth or reproduction of bacteria

Bioavailability- the proportion of a substance absorbed and used by the body

Comorbidities- co-existing conditions

Culture-the growth of microorganisms, viruses or tissue cells in a specially prepared nutrient medium under supervised conditions

Proton pump inhibitor- and clarithromycin-based triple therapies for *Helicobacter pylori* eradication (Protocol)

Copyright © 2020 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Duodenal-relating to the first part of the small intestine

Empiric-capable of being proved or disproved by observation or experiments

Epithelium-the thin outside layer of cells that cover all the exposed surfaces of the body

Eradication-complete destruction

Flagellated-referring to small organisms that move by whipping thin tail-like structures

Gastric-relating to the stomach

Gram-negative-bacteria that have a cell wall made up of a thin layer of a particular substance confirmed by a test called a Gram stain

Gram-positive-bacteria that have a cell wall made up of a thick layer of a particular substance confirmed by a test called a Gram stain

Histology-the study of the structure of tissues under a microscope

Hydrolyze- to break down a substance by a chemical reaction with water

Macrolide- one in a class of antibiotics such as clarithromycin

MALT lymphoma- a type of cancer affecting mucosa-associated tissue of the lymphatic system (a system of tissues and organs that rid the body of waste and other unwanted materials)

Metaplasia- the abnormal change of one kind of tissue within the body into another

Microaerophilic- regarding bacteria requiring very little oxygen to survive

Mucosa-the moist inner lining of some organs and cavities of the body, such as the mouth and stomach

Pathogens-organisms that cause disease

Placebo- sham treatment

Prevalence-the number of cases of a disease present in a particular population at a given time

Serology- blood tests that look for antibodies against specific harmful or foreign substances

Stool antigen test- a test which assesses the presence of *H. pylori* bacteria in feces

Toxins- poisonous substances

Urea breath test- a test used to detect the presence of *H. pylori* bacteria

WHAT'S NEW

Date	Event	Description
4 August 2021	Amended	This amendment includes updates to the Methods section of the protocol, including the sub-sections 'Type of interventions' and 'Subgroup analysis and investigation of heterogeneity'.

HISTORY

Protocol first published: Issue 9, 2020

CONTRIBUTIONS OF AUTHORS

Conceiving the protocol: RRV, LESF

Designing the protocol: RRV, LESF, RR, RLP

Co-ordinating the protocol: RRV

Proton pump inhibitor- and clarithromycin-based triple therapies for *Helicobacter pylori* eradication (Protocol)

Copyright © 2020 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Writing the protocol: RRV, LESF

Providing general advice on the protocol: LESF, PM, RR

Performing previous work that was the foundation of the current study: RRV

DECLARATIONS OF INTEREST

None of the review authors are sponsored, employed or involved in clinical trials of antimicrobial therapy with *Helicobacter pylori* (*H. pylori*).

- RRV: none known
- LESF: none known
- PM: none known
- RLP: none known
- MAPF: none known
- RR: none known

SOURCES OF SUPPORT

Internal sources

- Hospital Israelita Albert Einstein, Brazil

Regis Rodrigues Vieira is a physician at Hospital Israelita Albert Einstein and receives a salary

External sources

- No sources of support provided