**Name of Journal:** *World Journal of Gastroenterology*

**Manuscript NO:** 88707

**Manuscript Type:** ORIGINAL ARTICLE

***Clinical Trials Study***

**Optimized sequential therapy *vs* 10- and 14-d concomitant therapy for eradicating *Helicobacter pylori*: A randomized clinical trial**

Seddik H *et al*. *H. pylori* randomized clinical trial

Hassan Seddik, Jihane Benass, Sanaa Berrag, Asmae Sair, Reda Berraida, Hanae Boutallaka

**Hassan Seddik, Jihane Benass, Asmae Sair, Reda Berraida, Hanae Boutallaka,** Department of Gastroenterology II, Mohammed V Military Teaching Hospital of Rabat, Rabat 10100, Morocco

**Hassan Seddik, Jihane Benass, Sanaa Berrag, Asmae Sair, Reda Berraida, Hanae Boutallaka,** Department of Gastroenterology, Mohammed V University in Rabat, Rabat 10100, Morocco

**Sanaa Berrag,** Department of Gastroenterology I, Mohammed V Military Teaching Hospital of Rabat, Rabat 10100, Morocco

**Author contributions:** Seddik H was responsible for study concept and planning and supervised the statistical analysis and manuscript revision; Benass J and Boutallaka H were involved in performing the statistical analysis and writing the manuscript, with input from all authors; Berrag S, Sair A, and Berraida R were involved in patient enrollment and data collection and were involved in manuscript preparation; All authors reviewed the manuscript.

**Corresponding author: Jihane Benass, MD,** **Senior Resident,** Department of Gastroenterology II, Mohammed V Military Teaching Hospital of Rabat, Avenue des Forces Armées Royales, Rabat 10100, Morocco.jihane.benass@gmail.com

**Received:** October 6, 2023

**Revised:** November 26, 2023

**Accepted:** December 29, 2023

**Published online:** February 14, 2024

**Abstract**

BACKGROUND

A cure for *Helicobacter pylori* (*H. pylori*) remains a problem of global concern. The prevalence of antimicrobial resistance is widely rising and becoming a challenging issue worldwide. Optimizing sequential therapy seems to be one of the most attractive strategies in terms of efficacy, tolerability and cost. The most common sequential therapy consists of a dual therapy [proton-pump inhibitors (PPIs) and amoxicillin] for the first period (5 to 7 d), followed by a triple therapy for the second period (PPI, clarithromycin and metronidazole). PPIs play a key role in maintaining a gastric pH at a level that allows an optimal efficacy of antibiotics, hence the idea of using new generation molecules.

AIM

To compare an optimized sequential therapy with the standard non-bismuth quadruple therapies of 10 and 14 d, in terms of efficacy, incidence of adverse effects (AEs) and cost.

METHODS

This open-label prospective study randomized 328 patients with confirmed *H. pylori* infection into three groups (1:1:1): The first group received quadruple therapy consisting of twice-daily (bid) omeprazole 20 mg, amoxicillin 1 g, clarithromycin 500 mg and metronidazole 500 mg for 10 d (QT-10), the second group received a 14 d quadruple therapy following the same regimen (QT-14), and the third group received an optimized sequential therapy consisting of bid rabeprazole 20 mg plus amoxicillin 1 g for 7 d, followed by bid rabeprazole 20 mg, clarithromycin 500 mg and metronidazole 500 mg for the next 7 d (OST-14). AEs were recorded throughout the study, and the *H. pylori* eradication rate was determined 4 to 6 wk after the end of treatment, using the 13C urea breath test.

RESULTS

In the intention-to-treat and per-protocol analysis, the eradication rate was higher in the OST-14 group compared to the QT-10 group: (93.5%, 85.5% *P* = 0.04) and (96.2%, 89.5% *P* = 0.03) respectively. However, there was no statistically significant difference in eradication rates between the OST-14 and QT-14 groups: (93.5%, 91.8% *P* = 0.34) and (96.2%, 94.4% *P* = 0.35), respectively. The overall incidence of AEs was significantly lower in the OST-14 group (*P* = 0.01). Furthermore, OST-14 was the most cost-effective among the three groups.

CONCLUSION

The optimized 14-d sequential therapy is a safe and effective alternative. Its eradication rate is comparable to that of the 14-d concomitant therapy while causing fewer AEs and allowing a gain in terms of cost.

**Key Words:** *Helicobacter pylori*; Quadruple therapy; Sequential; Proton-pump inhibitor; Optimization

**©The** **Author(s) 2024.** Published by Baishideng Publishing Group Inc. All rights reserved.

**Citation:** Seddik H, Benass J, Berrag S, Sair A, Berraida R, Boutallaka H. Optimized sequential therapy *vs* 10 and 14-d concomitant therapy for eradicating *Helicobacter pylori*: A randomized clinical trial. *World J Gastroenterol* 2024; 30(6): 556-564

**URL:** https://www.wjgnet.com/1007-9327/full/v30/i6/556.htm

**DOI:** https://dx.doi.org/10.3748/wjg.v30.i6.556

**Core Tip:** *Helicobacter pylori* infection remains a common infection worldwide. The decline in the efficacy of traditional triple therapies since 2010 has required new combinations of antibiotics. The last guidelines of Maastricht VI recommend bismuth quadruple therapies or concomitant quadruple therapies to reach an eradication rate of at least 90%. These values remain higher than those obtained with standard sequential therapy but are associated with a higher cost and more adverse effects (AEs). The results of the present study demonstrate that optimizing sequential therapy by using second-generation proton-pump inhibitors improved eradication rates and reduced AE incidence. This combination can thus be suggested for use in clinical practice.

**INTRODUCTION**

A cure for *Helicobacter pylori* (*H. pylori*) remains a problem of global concern[1]. This bacterium is a well-known cause of peptic ulcer, gastritis, gastric mucosa-associated lymphoid tissue lymphoma and gastric malignancies[2-4]. *H. pylori* eradication is thus an effective strategy in preventing gastric malignancies[5,6].

Even though *H. pylori* infection management is evolving, no regimen can currently achieve a cure rate of 100%. The most recent Maastricht VI consensus recommends (in the absence of antibiotic susceptibility testing) quadruple Bismuth therapy or non-Bismuth quadruple concomitant therapy to achieve a cure rate of at least 90% despite the association of both regimens with a significant rate of adverse effects (AEs)[7]. Furthermore, the prevalence of antimicrobial resistance is widely rising and becoming a problem of great interest worldwide[8]; in Morocco, a previous study showed clarithromycin resistance of more than 15%[9]. Therefore, the best strategy to increase *H. pylori* eradication rate would be a personalized treatment based on antibiotic susceptibility[10].

However, this strategy is not possible in many developing countries, which is why many studies have instead focused on optimizing the recommended regimens[11]. It can either be an optimization by extending the length of the protocol[12], using a higher dose and/or second-generation proton-pump inhibitors (PPIs) or switching to vonoprazan[13,14], changing the antibiotics used and their posology, or associating other molecules to the eradication protocol, such as probiotics[15].

Optimizing the sequential therapy seems to be one of the most attractive strategies in terms of efficacy, tolerability and cost. The most common sequential therapy consists of a dual therapy (PPI and amoxicillin) for the first period (5 to 7 d), followed by a triple therapy for the second period (PPI, clarithromycin and metronidazole). PPIs play a key role in maintaining a gastric pH at a level that allows optimal antibiotic efficacy[16], hence the idea of using new generation molecules.

The primary aim of this study was to compare the efficacy of the 14-d sequential therapy (optimized by using a second-generation PPI) and standard non-bismuth quadruple therapies of 10 and 14 d. The secondary aims were to compare the tolerability and AEs among the groups, as well as their cost-effectiveness.

**MATERIALS AND METHODS**

***Study design and patient selection***

This was a single center, prospective, open-label, randomized study, conducted between January 2018 and March 2020, at the Mohammed V Military Teaching Hospital of Rabat. We included adult patients with *H. pylori* infection confirmed by histological analysis of gastric biopsies performed during upper endoscopy. Five gastric biopsy samples were taken systematically according to the recommended Sydney system (antrum, incisura, greater and lesser curvature)[17], and then studied for the presence of *H. pylori* using Hematoxylin and eosin staining at the pathology laboratory of our hospital. Patients who previously received an eradication therapy, PPI, H2-blockers, non-steroidal anti-inflammatory drugs or Bismuth containing compounds 4 wk prior to the study, and/or patients who were allergic to the prescribed antibiotics were excluded from the study. Pregnant and breastfeeding females, patients with history of gastric surgery, kidney or liver failure, or severe psychiatric conditions were also excluded. All patients provided written informed consent to be included in the study. The protocol followed Helsinki Declaration guidelines and was approved by our local scientific committee at Mohammed V Military Teaching Hospital of Rabat. Our clinical trial was registered in the Pan African Clinical Trial Registry ([www.pactr.org](http://www.pactr.org)) on December 7, 2021, registration number: PACTR202112632957229.

***Randomization and treatment***

Patients were randomly assigned into three groups in a 1:1:1 ratio, using a computer-generated table: QT-14, QT-10 and OST-14. Allocations were concealed in a sealed opaque envelope which was to be opened during the consultation day. The QT-14 and QT-10 groups received omeprazole 20 mg, amoxicillin 1 g, clarithromycin 500 mg and metronidazole 500 mg, all twice daily for 14 and 10 d, respectively. The OST-14 group received an optimized sequential therapy consisting of twice daily rabeprazole 20 mg and amoxicillin 1 g during 7 d, followed by rabeprazole 20 mg, clarithromycin 500 mg and metronidazole 500 mg, all twice daily for the remaining 7 d. PPI was administered 30 min before breakfast and supper, whereas antibiotics were administered every 12 h after meals.

***Follow-up and outcomes***

The *H.* *pylori* eradication was assessed at least 4 wk after the last day of the treatment using the 13C-urea breath test (UBT), which was performed blindly at the same laboratory for all patients. The cut-off value for the UBT was 2.5 per thousand. The patients did not undergo additional therapy with PPI after completion of eradication therapy.

All patients were evaluated 2 wk after the start of the treatment and at its end to assess AEs and compliance. Drug compliance was defined by taking at least 90% of the prescribed protocol drugs and was assessed at the end of the protocol. AEs were assessed using a pre-established structured questionnaire consisting of dichotomous questions about the occurrence and intensity of AEs including diarrhea, nausea and/or vomiting, gastralgia, metallic taste, dysgeusia, symptoms related to an allergic reaction, headache, dizziness, asthenia, or any other AE.

Cost-effectiveness analysis was assessed by comparing the overall cost of each protocol. The cost of every drug was calculated using a national website: [www.medicament.ma.](http://www.medicament.ma/) The cost-effectiveness ratio for each regimen was calculated by dividing the total cost for 100 patients treated by the percent of patients treated.

***Statistical analysis***

This study sample size was determined as follows. We presumed the eradication rate of OST-14 to be 95% and the eradication rate of QT-10 to be 83% (lowest eradication rate of the three treatment regimens). By setting the bilateral significance level to 0.05, the power to 80% and the drop-out rate to 5%, at least 104 patients were required in each group.
Our hypothesis on the QT-10 eradication rate was based on a previous meta-analysis[18].

The primary endpoint of the study was the eradication rate of *H. pylori*, which was assessed by intention to treat (ITT) and per-protocol (PP) analyses. The safety population included all randomized patients who received at least one treatment dose during the study, ITT population included all patients who received at least one treatment dose during the study and who were examined during the first visit, while the PP population included only patients who completed the study. Therapeutic failure was recorded as outcome for patients with missing data due to incomplete treatment. The secondary outcomes were the incidence of AEs, the therapeutic compliance and the cost-effectiveness of the protocols.

Descriptive and inferential statistical analyses were performed using Software Package Social Science SPSS® for mac OS version 22.0 (IBM Corp, Armonk, NY, United States). For all statistical analyses, *P* valueless than 0.05 was considered statistically significant. Qualitative variables (eradication rates of the three groups) were compared using *χ*2 test and Fisher’s exact test. Continuous variables were compared between the three groups using a one-way ANOVA test.

**RESULTS**

***Population characteristics***

A total of 328 patients were enrolled in the study. They were included in the ITT analysis and randomized into the three groups. After eliminating the dropped-out patients from the study, the PP analysis included 317 patients. The study flow chart is shown in Figure 1. Demographic and clinical characteristics of the three groups are shown in Table 1 and were not significantly different between the groups.

***Eradication rates***

In the ITT analysis, *H. pylori* eradication was achieved in 85.5% of patients in the QT-10 group, 91.8% of patients in the QT-14 group, and 93.5% of patients in the OST-14 group. In the PP analysis, the results were as follows: 89.5%, 94.4%, and 96.2% in the QT-10, QT-14, and OST-14 groups, respectively.

***Comparison of eradication rates***

The eradication rate in the OST-14 group was higher compared to the QT-10 group in the ITT analysis (*P* = 0.04) and in the PP analysis (0.03). However, there was no statistically significant difference between the eradication rate of OST-14 and QT-14 groups (in ITT analysis: *P* = 0.34, in PP analysis *P* = 0.35).

***Safety***

The treatment tolerance was better in the OST-14 group, with an incidence of AEs of 24.7% compared to 42.7% and 39% in the QT-14 and QT-10, respectively (*P* = 0.03) (Table 2). However, the treatment was globally well tolerated among the three groups, and AEs were mild to moderate in all patients. The drug compliance was excellent among the three groups: 97%, 95% and 98.9% in the QT-10, QT-14 and OST-14, respectively (*P* = 0.48).

***Cost-effectiveness***

The overall cost was lower in the OST-14 group [427.10 Moroccan dirhams (MAD)], compared to QT-14 and QT-10 groups (691.90 MAD and 587.10 MAD, respectively). The cost-effectiveness ratio was lower in the OST-14 group, as shown in Table 3.

**DISCUSSION**

According to the Maastricht VI consensus, the most recommended empirical regimens for *H. pylori* infection are Bismuth quadruple therapy and non-Bismuth quadruple concomitant therapy[7]. However, eradication rates widely vary geographically due to varying antimicrobial resistance, especially to clarithromycin and metronidazole[19].

It is important to note that the *H. pylori* eradication rate is significantly influenced by antibiotic resistance. Furthermore, the bismuth agent is not available in all areas. Therefore, in areas where *H. pylori* is highly resistant to clarithromycin, non-bismuth quadruple therapies are still recommended when the bismuth agent is not available.

Several non-bismuth regimens have been tested to improve the management of *H. pylori* infection[20,21]. One of them is modified sequential therapy[12,22]. In the present study, we aimed to compare the results of the standard 10- and 14-d non-bismuth quadruple therapies to an optimized sequential therapy by using a second-generation PPI.

Overall, we found that the optimized 14-d sequential regimen using rabeprazole (OST-14) achieves a higher cure rate than the standard quadruple therapy without bismuth for 10 d (85.5% and 93.5%, respectively, *P* = 0.04), while there was no statistically significant difference between OST-14 and the 14-d quadruple therapy (93.2% and 91.8%, respectively, *P* = 0.34). OST-14 allowed a greater tolerance with fewer AEs compared to quadruple therapies (*P* = 0.01),and there was no difference in term of drugs compliance between the three groups. Furthermore, the cost-effectiveness ratio was lower in the OST-14 group.

The sequential therapy was introduced for the first time in 2000 in Italy by Zullo *et al*[23]. We personally demonstrated its superiority compared to the standard triple therapy in a previous study[24]. A recent metanalysis by Wang *et al*[18] showed that there is no difference in terms of eradication rate between a 14-d sequential and a 14-d concomitant therapy. Another study showed that a 14-d sequential therapy is equivalent to 10 d bismuth quadruple therapy in terms of eradication rate (91.3% and 91.6%, respectively), but bismuth therapy led to more AEs[25]. In a metanalysis, the same team demonstrated that a 14-d sequential therapy is more effective than a 14-d triple therapy[26].

In the present study, the gain in terms of eradication rate can be explained by the use of a second generation PPI (rabeprazole 20 mg bid) in the OST-14 group. In fact, the last Maastricht consensus states that switching omeprazole 20 mg twice daily to rabeprazole 20 mg bid or esomeprazole 40 mg bid may increase eradication rate by 8%-12%[7]. The advantage of PPIs lies in the fact that the majority of proposed regimens are pH-dependent and become less effective when the intragastric pH is low[27], hence the use of higher dose PPIs and second-generation substances. A possible explanation for the superiority of second-generation PPIs (rabeprazole and esomeprazole) may be their metabolism, which is less dependent on CYP2C19 genetic variables and their higher acid inhibition power[28]. A further metanalysis by McNichol *et al*[29] confirmed that both esomeprazole and rabeprazole led to higher eradication rates compared to first generation PPIs (omeprazole, lansoprazole and pantoprazole). High doses of PPIs also improved the efficacy of eradication therapy. In strains resistant to clarithromycin, the eradication rate can be increased using PPI-amoxicillin dual therapy[30].

All therapeutic regimens currently recommended are associated with gastrointestinal AEs[31]. Herein, OST-14 allowed a gain in terms of AE incidence compared to quadruple concomitant therapies. These findings confirm those of previous studies[32-34]. The 14-d sequential therapy consists of the same antibiotics as the 14-d concomitant regimen but for a shorter duration. It should therefore lead to fewer AEs. This was the case in our study with a benefit of 18% in terms of AE occurrence (31.3% *vs* 49.5%; *P* = 0.03).Because treatment cost is a determining factor, especially in developing countries, we carried-out cost- effectiveness analysis and showed that OST-14 is the most cost-effective among our study’s groups. The same result was previously reported by Farhoud *et al*[33], who found that 14-d sequential therapy is cheaper than 14-d triple therapy. Further, Kate *et al*[35] confirmed in a metanalysis that sequential therapies are cheaper than standard therapies. Other cost-analysis studies have shown the same results and found that sequential therapy is the most economically attractive option[36,37]. This benefit can be explained by the fact that clarithromycin is the most expensive drug used in different protocols, and it is used for a shorter duration in sequential therapy.

One of the limitations of this study is that we did not perform *H. pylori* cultures and did not have any data about antibiotic susceptibility. However, a recent study showed that in Morocco, the local primary resistance to clarithromycin was 29%, 40% to metronidazole and 0% to amoxicillin[9]. Another potential limitation is that second line treatments were not included, which makes it difficult to interpret the cost effectiveness analysis. Additionally, it is difficult to generalize our results to other areas, as the study was conducted in a single center. Nonetheless, the sample size was reasonable to allow for correct statistical analysis. However, our results should be validated by further studies in different geographic areas. Other studies could further compare these eradication regimens to others containing vonoprazan. For the moment, this molecule is still not available in Morocco.

**CONCLUSION**

In conclusion, the results of the present study showed that the 14-d sequential therapy using rabeprazole appears to be an optimal therapy that is comparable to 14-d concomitant therapy while causing fewer AEs and allowing a gain in terms of cost.

**ARTICLE HIGHLIGHTS**

***Research background***

A cure for *Helicobacter pylori* (*H. pylori*) remains a problem of global concern and none of the currently available treatments can achieve a cure rate of 100%. With the global rising issue of antibiotic resistance and the difficulty to establish personalized treatments according to antibiotic susceptibility in developing countries, optimizing sequential therapy seems to be one of the most attractive strategies in terms of efficacy, tolerability and cost.

***Research motivation***

*H. pylori* eradication rate is significantly influenced by antibiotic resistance. According to the Maastricht VI consensus, the most recommended empirical regimens for *H. pylori* infection are Bismuth quadruple therapy and non-Bismuth quadruple concomitant therapy when the Bismuth agent is not available. Many studies showed that switching to high doses of second-generation proton-pump inhibitors (PPIs) and using a PPI-amoxicillin dual therapy can improve the eradication rate and could lead to fewer adverse effects (AEs). The cost of treatment is also a determining factor, especially in developing countries.

***Research objectives***

In the present study, we aimed to compare the results of the standard 10- and 14-d non-bismuth quadruple therapies to an optimized sequential therapy by using a second-generation PPI, in terms of efficacy, tolerability and cost-effectiveness. The 14-d sequential therapy using rabeprazole appears to be an optimal therapy that is comparable to 14-d concomitant therapy while causing fewer AEs and allowing a gain in terms of cost. Other studies could further validate the standard eradication regimens *vs* the 14-d sequential therapy using rabeprazole *vs* other regimens containing vonoprazan. For the moment, this molecule is still not available in Morocco.

***Research methods***

We conducted a single center, prospective, open-label, randomized study with patients randomly assigned into three groups in a 1:1:1 ratio using a computer-generated table: QT-14, QT-10 and OST-14. Allocations were concealed in a sealed opaque envelope to be opened during the consultation day.

***Research results***

This study showed that the 14-d sequential therapy using rabeprazole appears to be an optimal therapy that is comparable to 14-d concomitant therapy while causing fewer AEs and allowing a gain in terms of cost.

***Research conclusions***

According to the Maastricht VI consensus, the most recommended empirical regimens for *H. pylori* infection are Bismuth quadruple therapy and non-Bismuth quadruple concomitant therapy. This study suggests the use of an optimized 14-d sequential regimen using rabeprazole to achieve the same eradication rate as the non-bismuth quadruple concomitant therapy while leading to fewer AEs and being more economically attractive.

***Research perspectives***

Given our study’s limitations, these are several future research perspectives: (1) Conduct a multicenter trial (in different geographical areas) to validate our results; (2) Compare the sequential therapy to other therapies containing vonoprazan; and (3) Compare the use of esomeprazole and rabeprazole in a sequential therapy in terms of efficacy, tolerability and cost-effectiveness.

**REFERENCES**

1 **Gatta L**, Vakil N, Vaira D, Scarpignato C. Global eradication rates for Helicobacter pylori infection: systematic review and meta-analysis of sequential therapy. *BMJ* 2013; **347**: f4587 [PMID: 23926315 DOI: 10.1136/bmj.f4587]

2 **Malfertheiner P**, Megraud F, O'Morain CA, Atherton J, Axon AT, Bazzoli F, Gensini GF, Gisbert JP, Graham DY, Rokkas T, El-Omar EM, Kuipers EJ; European Helicobacter Study Group. Management of Helicobacter pylori infection--the Maastricht IV/ Florence Consensus Report. *Gut* 2012; **61**: 646-664 [PMID: 22491499 DOI: 10.1136/gutjnl-2012-302084]

3 **Uemura N**, Okamoto S, Yamamoto S, Matsumura N, Yamaguchi S, Yamakido M, Taniyama K, Sasaki N, Schlemper RJ. Helicobacter pylori infection and the development of gastric cancer. *N Engl J Med* 2001; **345**: 784-789 [PMID: 11556297 DOI: 10.1056/NEJMoa001999]

4 **Alakkari A**, Zullo A, O'Connor HJ. Helicobacter pylori and nonmalignant diseases. *Helicobacter* 2011; **16** Suppl 1: 33-37 [PMID: 21896083 DOI: 10.1111/j.1523-5378.2011.00878.x]

5 **Herrero R**, Park JY, Forman D. The fight against gastric cancer - the IARC Working Group report. *Best Pract Res Clin Gastroenterol* 2014; **28**: 1107-1114 [PMID: 25439075 DOI: 10.1016/j.bpg.2014.10.003]

6 **Tsukamoto T**, Nakagawa M, Kiriyama Y, Toyoda T, Cao X. Prevention of Gastric Cancer: Eradication of Helicobacter Pylori and Beyond. *Int J Mol Sci* 2017; **18** [PMID: 28771198 DOI: 10.3390/ijms18081699]

7 **Malfertheiner P**, Megraud F, Rokkas T, Gisbert JP, Liou JM, Schulz C, Gasbarrini A, Hunt RH, Leja M, O'Morain C, Rugge M, Suerbaum S, Tilg H, Sugano K, El-Omar EM; European Helicobacter and Microbiota Study group. Management of Helicobacter pylori infection: the Maastricht VI/Florence consensus report. *Gut* 2022 [PMID: 35944925 DOI: 10.1136/gutjnl-2022-327745]

8 **Meyer JM**, Silliman NP, Wang W, Siepman NY, Sugg JE, Morris D, Zhang J, Bhattacharyya H, King EC, Hopkins RJ. Risk factors for Helicobacter pylori resistance in the United States: the surveillance of H. pylori antimicrobial resistance partnership (SHARP) study, 1993-1999. *Ann Intern Med* 2002; **136**: 13-24 [PMID: 11777360 DOI: 10.7326/0003-4819-136-1-200201010-00008]

9 **Bouihat N**, Burucoa C, Benkirane A, Seddik H, Sentissi S, Al Bouzidi A, Elouennas M, Benouda A. Helicobacter pylori Primary Antibiotic Resistance in 2015 in Morocco: A Phenotypic and Genotypic Prospective and Multicenter Study. *Microb Drug Resist* 2017; **23**: 727-732 [PMID: 27996373 DOI: 10.1089/mdr.2016.0264]

10 **Liou JM**, Chen PY, Kuo YT, Wu MS; Taiwan Gastrointestinal Disease and Helicobacter Consortium. Toward population specific and personalized treatment of Helicobacter pylori infection. *J Biomed Sci* 2018; **25**: 70 [PMID: 30285834 DOI: 10.1186/s12929-018-0471-z]

11 **Gisbert JP**, McNicholl AG. Optimization strategies aimed to increase the efficacy of H. pylori eradication therapies. *Helicobacter* 2017; **22** [PMID: 28464347 DOI: 10.1111/hel.12392]

12 **Zullo A**, De Francesco V, Hassan C, Ridola L, Repici A, Bruzzese V, Vaira D. Modified sequential therapy regimens for Helicobacter pylori eradication: a systematic review. *Dig Liver Dis* 2013; **45**: 18-22 [PMID: 23022424 DOI: 10.1016/j.dld.2012.08.025]

13 **Sachs G**, Shin JM, Munson K, Vagin O, Lambrecht N, Scott DR, Weeks DL, Melchers K. Review article: the control of gastric acid and Helicobacter pylori eradication. *Aliment Pharmacol Ther* 2000; **14**: 1383-1401 [PMID: 11069309 DOI: 10.1046/j.1365-2036.2000.00837.x]

14 **Li M**, Oshima T, Horikawa T, Tozawa K, Tomita T, Fukui H, Watari J, Miwa H. Systematic review with meta-analysis: Vonoprazan, a potent acid blocker, is superior to proton-pump inhibitors for eradication of clarithromycin-resistant strains of Helicobacter pylori. *Helicobacter* 2018; **23**: e12495 [PMID: 29873436 DOI: 10.1111/hel.12495]

15 **Seddik H**, Boutallaka H, Elkoti I, Nejjari F, Berraida R, Berrag S, Loubaris K, Sentissi S, Benkirane A. Saccharomyces boulardii CNCM I-745 plus sequential therapy for Helicobacter pylori infections: a randomized, open-label trial. *Eur J Clin Pharmacol* 2019; **75**: 639-645 [PMID: 30694338 DOI: 10.1007/s00228-019-02625-0]

16 **Miner P Jr**, Katz PO, Chen Y, Sostek M. Gastric acid control with esomeprazole, lansoprazole, omeprazole, pantoprazole, and rabeprazole: a five-way crossover study. *Am J Gastroenterol* 2003; **98**: 2616-2620 [PMID: 14687806 DOI: 10.1111/j.1572-0241.2003.08783.x]

17 **Misiewicz JJ**. The Sydney System: a new classification of gastritis. Introduction. *J Gastroenterol Hepatol* 1991; **6**: 207-208 [PMID: 1912430 DOI: 10.1111/j.1440-1746.1991.tb01467.x]

18 **Wang Y**, Zhao R, Wang B, Zhao Q, Li Z, Zhu-Ge L, Yin W, Xie Y. Sequential versus concomitant therapy for treatment of Helicobacter pylori infection: an updated systematic review and meta-analysis. *Eur J Clin Pharmacol* 2018; **74**: 1-13 [PMID: 28990120 DOI: 10.1007/s00228-017-2347-7]

19 **Flores-Treviño S**, Mendoza-Olazarán S, Bocanegra-Ibarias P, Maldonado-Garza HJ, Garza-González E. Helicobacter pylori drug resistance: therapy changes and challenges. *Expert Rev Gastroenterol Hepatol* 2018; **12**: 819-827 [PMID: 29976092 DOI: 10.1080/17474124.2018.1496017]

20 **Yang JC**, Lu CW, Lin CJ. Treatment of Helicobacter pylori infection: current status and future concepts. *World J Gastroenterol* 2014; **20**: 5283-5293 [PMID: 24833858 DOI: 10.3748/wjg.v20.i18.5283]

21 **Georgopoulos SD**, Papastergiou V, Karatapanis S. Treatment of Helicobacter Pylori infection: optimization strategies in a high resistance era. *Expert Opin Pharmacother* 2015; **16**: 2307-2317 [PMID: 26330278 DOI: 10.1517/14656566.2015.1084503]

22 **Liao XM**, Nong GH, Chen MZ, Huang XP, Cong YY, Huang YY, Wu BH, Wei JQ. Modified sequential therapy vs quadruple therapy as initial therapy in patients with Helicobacter infection. *World J Gastroenterol* 2015; **21**: 6310-6316 [PMID: 26034367 DOI: 10.3748/wjg.v21.i20.6310]

23 **Zullo A**, Rinaldi V, Winn S, Meddi P, Lionetti R, Hassan C, Ripani C, Tomaselli G, Attili AF. A new highly effective short-term therapy schedule for Helicobacter pylori eradication. *Aliment Pharmacol Ther* 2000; **14**: 715-718 [PMID: 10848654 DOI: 10.1046/j.1365-2036.2000.00766.x]

24 **Seddik H**, Ahid S, El Adioui T, El Hamdi FZ, Hassar M, Abouqal R, Cherrah Y, Benkirane A. Sequential therapy versus standard triple-drug therapy for Helicobacter pylori eradication: a prospective randomized study. *Eur J Clin Pharmacol* 2013; **69**: 1709-1715 [PMID: 23695545 DOI: 10.1007/s00228-013-1524-6]

25 **Liou JM**, Chen CC, Fang YJ, Chen PY, Chang CY, Chou CK, Chen MJ, Tseng CH, Lee JY, Yang TH, Chiu MC, Yu JJ, Kuo CC, Luo JC, Hsu WF, Hu WH, Tsai MH, Lin JT, Shun CT, Twu G, Lee YC, Bair MJ, Wu MS; Members of the Taiwan Gastrointestinal Disease and Helicobacter Consortium. 14 day sequential therapy versus 10 day bismuth quadruple therapy containing high-dose esomeprazole in the first-line and second-line treatment of Helicobacter pylori: a multicentre, non-inferiority, randomized trial. *J Antimicrob Chemother* 2018; **73**: 2510-2518 [PMID: 29846605 DOI: 10.1093/jac/dky183]

26 **Liou JM**, Chen CC, Lee YC, Chang CY, Wu JY, Bair MJ, Lin JT, Chen MJ, Wu MS; Taiwan Gastrointestinal Disease and Helicobacter Consortium. Systematic review with meta-analysis: 10- or 14-day sequential therapy vs. 14-day triple therapy in the first line treatment of Helicobacter pylori infection. *Aliment Pharmacol Ther* 2016; **43**: 470-481 [PMID: 26669729 DOI: 10.1111/apt.13495]

27 **Graham DY**, Lu H, Dore MP. Relative potency of proton-pump inhibitors, Helicobacter pylori therapy cure rates, and meaning of double-dose PPI. *Helicobacter* 2019; **24**: e12554 [PMID: 30440097 DOI: 10.1111/hel.12554]

28 **Ierardi E**, Losurdo G, Fortezza RF, Principi M, Barone M, Leo AD. Optimizing proton pump inhibitors in Helicobacter pylori treatment: Old and new tricks to improve effectiveness. *World J Gastroenterol* 2019; **25**: 5097-5104 [PMID: 31558859 DOI: 10.3748/wjg.v25.i34.5097]

29 **McNicholl AG**, Linares PM, Nyssen OP, Calvet X, Gisbert JP. Meta-analysis: esomeprazole or rabeprazole vs. first-generation pump inhibitors in the treatment of Helicobacter pylori infection. *Aliment Pharmacol Ther* 2012; **36**: 414-425 [PMID: 22803691 DOI: 10.1111/j.1365-2036.2012.05211.x]

30 **Xu X**, He C, Zhu Y. Treatment of refractory Helicobacter pylori infection: A new challenge for clinicians. *Front Microbiol* 2022; **13**: 998240 [PMID: 36329840 DOI: 10.3389/fmicb.2022.998240]

31 **Kwon SB**, Lee KL, Kim JS, Lee JK, Kim W, Jung YJ, Jeong JB, Kim JW, Kim BG. Antibiotics-associated diarrhea and other gastrointestinal abnormal responses regarding Helicobacter pylori eradication. *Korean J Gastroenterol* 2010; **56**: 229-235 [PMID: 20962558 DOI: 10.4166/kjg.2010.56.4.229]

32 **Eisig JN**, Navarro-Rodriguez T, Teixeira AC, Silva FM, Mattar R, Chinzon D, Haro C, Diniz MA, Moraes-Filho JP, Fass R, Barbuti RC. Standard Triple Therapy versus Sequential Therapy in Helicobacter pylori Eradication: A Double-Blind, Randomized, and Controlled Trial. *Gastroenterol Res Pract* 2015; **2015**: 818043 [PMID: 26064098 DOI: 10.1155/2015/818043]

33 **Farhoud NS**, Ibrahim OM, Ezzat SE. Efficacy and Cost-effectiveness Comparison of 10-Day, 14-Day Sequential Versus 14-Day Triple Therapies for Treating Helicobacter pylori Infection in Egyptian Patients. *J Clin Gastroenterol* 2020; **54**: 806-812 [PMID: 31904681 DOI: 10.1097/MCG.0000000000001278]

34 **Kim JS**, Park SM, Kim BW. Sequential or concomitant therapy for eradication of Helicobacter pylori infection: A systematic review and meta-analysis. *J Gastroenterol Hepatol* 2015; **30**: 1338-1345 [PMID: 25867718 DOI: 10.1111/jgh.12984]

35 **Kate V**, Kalayarasan R, Ananthakrishnan N. Sequential therapy versus standard triple-drug therapy for Helicobacter pylori eradication: a systematic review of recent evidence. *Drugs* 2013; **73**: 815-824 [PMID: 23625272 DOI: 10.1007/s40265-013-0053-z]

36 **Valooran GJ**, Kate V, Jagdish S, Basu D. Sequential therapy versus standard triple drug therapy for eradication of Helicobacter pylori in patients with perforated duodenal ulcer following simple closure. *Scand J Gastroenterol* 2011; **46**: 1045-1050 [PMID: 21627398 DOI: 10.3109/00365521.2011.584894]

37 **Zhou YQ**, Xu L, Wang BF, Fan XM, Wu JY, Wang CY, Guo CY, Xu XF. Modified Sequential Therapy Regimen versus Conventional Triple Therapy for Helicobacter Pylori Eradication in Duodenal Ulcer Patients in China: A Multicenter Clinical Comparative Study. *Gastroenterol Res Pract* 2012; **2012**: 405425 [PMID: 22550478 DOI: 10.1155/2012/405425]

**Footnotes**

**Institutional review board statement:** An Institutional Review Board (Scientific committee at Mohammed V Military Teaching Hospital of Rabat) reviewed and approved the trial protocol. Our study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments.

**Clinical trial registration statement:** Our clinical trial has been retrospectively registered in the Pan African Clinical Trial Registry ([www.pactr.org](http://www.pactr.org)) on December 7, 2021, Registration No.: PACTR202112632957229.

**Informed consent statement:** All patients included in the study provided written informed consent before being enrolled in the trial.

**Conflict-of-interest statement:** The authors report having no relevant conflicts of interest for this article.

**Data sharing statement:** The datasets generated and/or analyzed during the study are available from the corresponding author on reasonable request.

**CONSORT 2010 statement:** The authors have read the CONSORT 2010 Statement, and the manuscript was prepared and revised according to the CONSORT 2010 Statement.

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non-Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: https://creativecommons.org/Licenses/by-nc/4.0/

**Provenance and peer review:** Unsolicited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Corresponding Author’s Membership in Professional Societies:** United European Gastroenterology; Société Marocaine Des Maladies de L'Appareil Digestif; Société Nationale Française de Gastro-Entérologie; Société Française d'endoscopie Digestive; Société Marocaine d'endoscopie Digestive.

**Peer-review started:** October 6, 2023

**First decision:** November 12, 2023

**Article in press:** December 29, 2023

**Specialty type:** Gastroenterology and hepatology

**Country/Territory of origin:** Morocco

**Peer-review report’s scientific quality classification**

Grade A (Excellent): 0

Grade B (Very good): 0

Grade C (Good): C, C

Grade D (Fair): 0

Grade E (Poor): 0

**P-Reviewer:** Bordin DS, Russia; Cheng H, China **S-Editor:** Wang JJ **L-Editor:** Filipodia **P-Editor:** Yuan YY

**Figure Legends**



**Figure 1 Flow-chart of study patients.**

**Table 1 Basic overall population and group characteristics**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Characteristic** | **Overall, *n* = 317** | **QT-14, *n* = 107** | **QT-10, *n* = 105** | **OST-14, *n* = 105** | ***P* value** |
| Age in yr, mean ± SD | 44.13 ± 15.30 | 43.37 ± 14.40 | 43.36 ± 15.9 | 45.67 ± 15.53 | 0.46 |
| Sex ratio as male/female | 0.98 | 1.03 | 1 | 0.92 | 0.91 |
| Smoking habit | 49 (14.9) | 18 (16.4) | 14 (12.7) | 17 (15.7) | 0.62 |
| Gastroduodenal ulcer | 47 (14.3) | 22 (20) | 13 (11.8) | 12 (11.1) | 0.16 |
| Gastric atrophy | 51 (15.5) | 14 (12.7) | 18 (16.4) | 19 (17.6) | 0.58 |
| Gastric metaplasia | 18 (5.5) | 7 (6.4) | 8 (7.3) | 3 (2.8) | 0.26 |
| HP antral density |  |  |  |  | 0.30 |
| + | 114 (34.9) | 37 (33.9) | 37 (33.6) | 40 (37) |  |
| ++ | 170 (52) | 58 (53.2) | 56 (50.9) | 56 (51.9) |  |
| +++ | 35 (10.7) | 11 (10.1) | 12 (10.9) | 12 (11.1) |  |
| HP fundic density |  |  |  |  | 0.74 |
| + | 147 (44.8) | 54 (49.1) | 46 (41.8) | 47 (43.5) |  |
| ++ | 62 (18.9) | 20 (18.2) | 22 (20) | 20 (18.5) |  |
| +++ | 7 (2.1) | 1 (0.9) | 2 (1.8) | 4 (3.7) |  |

All values are expressed as *n* (%) unless otherwise stated. +: Sparse; ++: Moderate; +++: Marked. HP: *Helicobacter pylori*; SD: Standard deviation.

**Table 2 Incidence of adverse effects among the study groups**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Analysis** | **QT-10** | **QT-14** | **OST-14** | ***P* value1** |
| ITT | 39% | 42.7% | 24.7% | 0.03 |
| PP | 45.1% | 49.5% | 31.3% | 0.01 |

1*P* value of *χ*2 test.

ITT: Intention to treat; PP: Per-protocol.

**Table 3 Cost-effectiveness ratio in the three protocols costs, expressed in Moroccan dirhams**

|  |  |  |  |
| --- | --- | --- | --- |
| **Therapeutic protocol** | **Overall cost of 100 patients** | **Effectiveness** | **Cost-effectiveness ratio** |
| QT-10 | 58710 | 89.5% | 655 |
| QT-14 | 69190 | 94.4% | 732 |
| OST-14 | 42710 | 98.1% | 435 |



Published by **Baishideng Publishing Group Inc**

7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA

**Telephone:** +1-925-3991568

**E-mail:** office@baishideng.com

**Help Desk:** https://www.f6publishing.com/helpdesk

https://www.wjgnet.com



**© 2024 Baishideng Publishing Group Inc. All rights reserved.**