Iranian Journal of Microbiology

Volume 17 Number 4 (August 2025) 593-599
DOI: http://doi.org/10.18502/ijm.v17i4.19248

ORIGINAL ARTICLE

Eradication of *Helicobacter pylori*: challenges and advances

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Received: November 2024**, Accepted:** May 2025

ABSTRACT

Background and Objectives: *Helicobacter pylori*, identified in 1982, remains a major cause of gastric infections. Despite extensive research, an ideal treatment regimen for its eradication is yet to be determined, with antibiotic resistance posing a significant challenge. This study, conducted at Mohammed VI University Hospital, aimed to evaluate and compare the effectiveness of different therapeutic protocols for *H. pylori* eradication.

Materials and Methods: This 13-month retrospective descriptive study was conducted at the Microbiology Laboratory of Mohammed VI University Hospital in Oujda, Morocco, to evaluate patients suspected of *H. pylori* infection using the urea breath test.

Results: A total of 190 patients were included, with an overall eradication rate of 73%. Three therapeutic protocols were tested, and bismuth concomitant therapy showed the highest eradication rate at 82%, outperforming the other regimens.

Conclusion: These findings highlight the importance of combining antimicrobial agents with antisecretory treatments to enhance eradication outcomes. The study also emphasizes the need for novel treatment strategies, particularly in light of rising antibiotic resistance. Vonoprazan-based regimens appear to offer a promising alternative, especially in the absence of antibiotic sensitivity testing. Future research should focus on optimizing treatment protocols while preserving beneficial gut flora.

Keywords: *Helicobacter pylori*; Urea breath test; Antibiotic resistance; Eradication; Antimicrobial therapy; Treatment protocols

INTRODUCTION

The gastric infection caused by *Helicobacter pylori*, a 1982 discovery, remains a topical issue given, the evolving scientific data concerning its pathophysiology, the diseases and pathologies now involved beyond the gastric or digestive sphere, and the therapeutic modalities confronted by the development of antibiotic resistance (1). This Gram-negative, spiral-shaped, microaerophilic bacterium primarily

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colonizes the human gastric mucosa, which is considered as its only known natural reservoir. Its pathogenicity is largely attributed to urease production, its ability to disrupt the mucosal barrier, and the chronic inflammatory response contributing to the development of gastritis, peptic ulcers, and gastric malignancies (2).

The ideal treatment to ensure eradication of the bacterium is not yet in place, that's why various comparative studies are still underway (3). The evaluation of *H. pylori* eradication uses both invasive and non-invasive techniques. The urea breath test is still the best non-invasive tool (4).

Over the last 5 years major shifts have been seen in defining whom to test and how to treat *H. pylori* infection (5). The predominant obstacle in addressing *H. pylori* infection lies in antibiotic resistance, significantly impacting the effectiveness of eradication therapies (6). A recent systematic review and meta-analysis revealed that primary and secondary resistance rates to clarithromycin, metronidazole, and levofloxacin have surpassed 15% globally across all World Health Organization (WHO) regions, indicating alarming levels of resistance (7). The rise in antimicrobial resistance has led to a general decline in treatment success, prompting a rethink of the therapeutic approach to develop good antimicrobial stewardship (5).

This study aims to evaluate the effectiveness of various therapeutic protocols and the role of the urea breath test in the context of rising antibiotic resistance.

MATERIALS AND METHODS

Study design. This is a 13-month retrospective descriptive study between April 2022 and May 2023, carried out at the Microbiology Laboratory of the Mohammed VI University Hospital of Oujda Morocco.

Study population. The study included specimens (breath) from patients consulting at our hospital. The patients were received by the doctor, who carried out the interview, accompanied the patients through all stages of the test, and performed the test on the HELIFAN PLUS automated system; Single-beam infrared analyzer. The test was carried out according to the required specifications outlined by the French Society for Microbiology (8). All patients fasted for at least 6 hours, had stopped antibiotic treatment for at least 4 weeks, and had stopped proton pump inhibitor treatment for at least 2 weeks. At the beginning of the protocol, patients were given citric acid to create a favorable environment for bacterial activation, if present. Then, after 10 minutes, patients exhaled air into the bag marked T0. Patients ingested the 13C-labelled urea solution: a 75 mg tablet dissolved in 30 ml of water. 30 minutes later, patients breathed air into a second bag marked T30. The samples were delivered without delay to the laboratory under optimum conditions. The doctor's vigilance at all stages ensures that test non-conformities are avoided.

Inclusion and exclusion criteria. Patients were eligible for inclusion if they presented suspected *H. pylori* infection and were referred for a diagnostic urea breath test (UBT). All included patients had fasted for a minimum of six hours prior to testing and had discontinued antibiotic therapy for at least four weeks, as well as proton pump inhibitors (PPIs) for at least two weeks.

Patients were excluded from the study if they did not meet these pre-test requirements, had a known history of partial gastrectomy or other forms of gastric surgery, or were unable to comply with the procedure or provide informed cooperation.

RESULTS

Our study series included 190 patients, ranging in age from 12 to 90 years, the median age was 42. The sex ratio M/F was 0.26, with a clear female predominance. Among all patients included in the study, 10% (n = 20) consulted for initial diagnosis of *H. pylori* infection, while the remaining 90% (n = 170) were evaluated post-treatment to assess the efficacy of eradication therapy.

The patients were assigned to one of three probabilistic therapeutic protocols for the eradication of *H. pylori* (Table 1). These protocols were designed based on current treatment guidelines, with each regimen combining antimicrobial agents with antisecretory treatments, including bitherapy, sequential therapy and bismuth-concomitant therapies, depending on the patient's clinical presentation and prior treatment history.

The total sample size of 190 patients was considered sufficient to provide reliable results based on similar

Table 1. The different therapeutic regimens included in our study.

Protocol	PPI	Antibiotics	Eradication rates
Bitherapy N= 13	Esomeprazole or omeprazole 20 mg 2 times per day (4 weeks)	Amoxicillin 1000 mg 2 times per day (14 days)	54% N= 7
Sequential therapy N = 140	Esomeprazole or omeprazole 20 mg 2 times per day (4 weeks)	Amoxicillin 1000 mg 2 times per day for 5 days followed by clarithromycine 500mg and metronidazole 500mg 2 times per day for 5 days	74% N= 104
Bismuth Concomitant Therapy N= 17	Esomeprazole or omeprazole 20 mg 2 times per day (4weeks)	Bismuth subcitrate 140mg + Tetracycline 125 mg + Metronidazole 125 mg 3 capsules taken 4 times a day for 10 days	82% N= 14

studies in the literature. The overall eradication rate following medical treatment was 73% (n = 125). The eradication success rate varied across the different treatment protocols, with bismuth concomitant therapy showing the highest eradication rate of 82%.

DISCUSSION

Diagnosis of infection has two inseparable components: bacterial identification and identification of the endoscopic and histological lesions induced by the bacteria.

There are non-invasive tests (serology, urea-13C breath test, stool testing for *H. pylori* Ag) and invasive tests (endoscopic biopsies of the gastric mucosa for anatomopathological and bacteriological purposes (*H. pylori* cultures or PCR) (9). The urea breath test is used to monitor bacterial eradication, provided that it is carried out after antibiotics (4 weeks) and PPIs (2 weeks) have been discontinued. The sensitivity and specificity of this test exceed 95%.

The treatment for *H. pylori* infection involves a combination of antimicrobial agents and antisecretory agents. To ensure the bactericidal effectiveness of antimicrobial agents, gastric pH needs to be elevated with antisecretory agents. Due to the propensity for antibiotic resistance when used in isolation, the recommended approach involves a combination of multiple antibiotics in treatment of *H. pylori* (10). Many antimicrobial agents are used in the treatment protocol for *H. pylori*, including clarithromycin, amoxicillin, levofloxacin, metronidazole, tetracycline, and rifabutin, as well as antisecretory agents, proton pump inhibitors and bismuth-containing compounds (11, 12). The bismuth compound inhibits pepsin activity, increases mucus secretion, and interacts with proteins present in the ulcer crater, presumably forming a barrier to acid diffusion. Bismuth penetrates the mucosa and is incorporated into *H. pylori*, thereby reducing the ability of bacterial cells to adhere to the gastric epithelium. The *H. pylori* eradication regimens currently used worldwide and their eradication rates are presented in Figs. 1 and 2.

It is not easy to compare the results of our study with the various treatments described, as the protocols used are not identical and this is due to the availability of drugs and medical coverage, which vary from one country to another and from one region to another.

In a meta-analysis published in 2021, the effects of various treatment regimens for *H. pylori* infection were compared. The study examined 68 randomized clinical trials, encompassing 22,975 patients. The focus was on evaluating *H. pylori* eradication rates for nine different empirical first-line treatment regimens, including bismuth quadritherapy, concomitant quadritherapy, sequential therapy, reverse hybrid therapy, levofloxacin-containing therapy, and high-dose PPI-amoxicillin dual therapy (13). The study determined that vonoprazan-based triple therapy had the best eradication performance, followed by concomitant quadruple therapy and reverse hybrid therapy, in the comparative efficacy rankings. Ac-

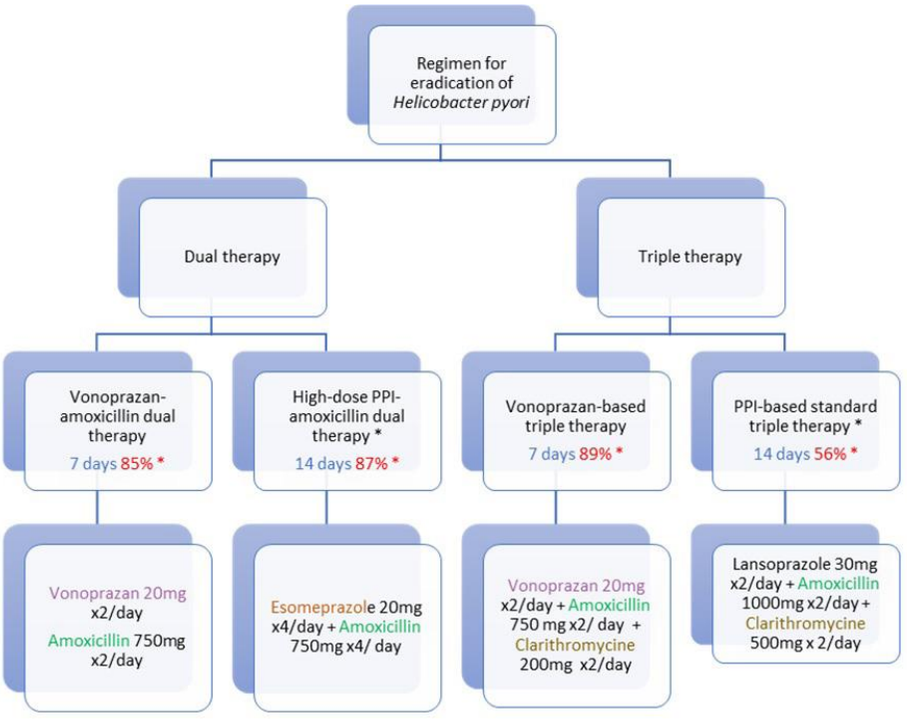

Fig. 1. Different protocols described in the literature for *H. pylori* eradication

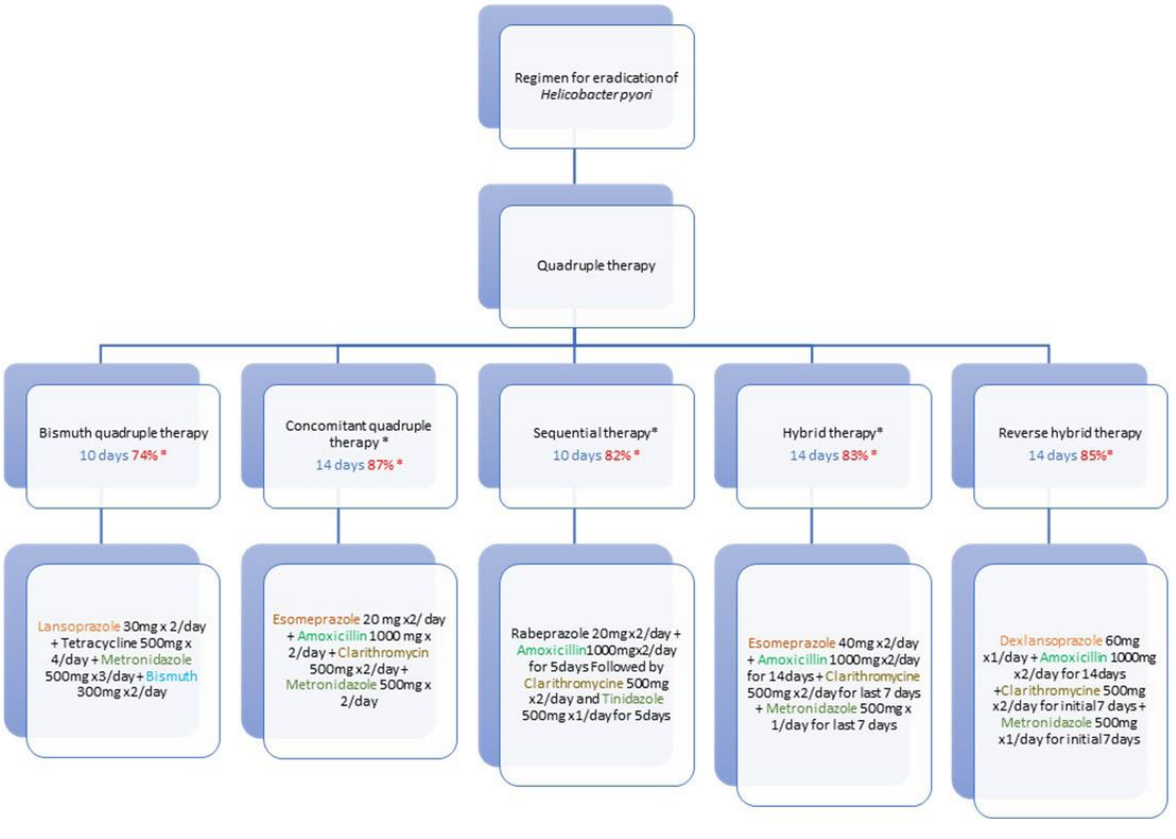

Fig. 2. Different protocols described in the literature for *H. pylori* eradication (quadruple therapy)

* Treatments available in Morocco.

* Treatment protocol eradication rate.

cording to the study's findings, vonoprazan-based triple therapy demonstrated the highest eradication performance, followed by concomitant quadruple therapy and reverse hybrid therapy, as per the comparative efficacy rankings. Consequently, the study recommends vonoprazan-based triple therapy as the preferred first-line treatment in regions where vonoprazan is accessible. In areas where vonoprazan is not available, bismuth quadruple therapy, comprising concomitant quadruple therapy or reverse hybrid therapy, is suggested as the primary treatment option. In our study, the predominant treatment was sequential therapy comprising esomeprazole or omeprazole 20mg 2 times per day for 4 weeks and amoxicillin 1000mg 2 times per day for 5 days followed by clarithromycin 500mg and metronidazole 500mg 2 times per day for 5 days, which showed an eradication rate of 74%, different from and lower than the sequential protocol in the meta-analysis. The dual therapy described in our study showed a rate approaching PPI-based standard triple therapy comprising lansoprazole 30mg ×2/day, amoxicillin 1000mg ×2/day, and clarithromycin 500mg × 2/day for 14 days. The concomitant treatment included in our work indicated a satisfactory eradication rate of 82%, and it was the best of the three protocols which showed a higher rate than that described in the literature Bismuth quadruple therapy showing a rate of 74%. The generalization of this protocol in our country has not been possible due to the absence of the capsule in pharmacies. Bismuth-based quadruple therapy (BQT) is widely used for *H. pylori* eradication due to its proven efficacy; however, it is often associated with adverse effects such as nausea, diarrhea, abdominal pain, and dark stools. These effects are generally mild and transient but may impact patient adherence to the treatment regimen (14). A recent meta-analysis demonstrated a significantly higher incidence of adverse events in patients receiving BQT compared to other regimens (RR = 1.64; 95% CI: 1.11–2.44) (15). While the overall safety profile of BQT remains acceptable, proper patient counseling and monitoring are essential for successful treatment outcomes.

The various treatments described in the literature, as well as those included in our study, present limitations for the eradication of *H. pylori* (16). The main challenge in *H. pylori* eradication treatment stems from the escalating prevalence of antimicrobial-resistant strains. Widespread and indiscriminate antibiotic usage in many countries contributes to resistance across various bacterial species, including *H. pylori* (17). In the updated 2024 WHO Bacterial Priority Pathogens List, clarithromycin-resistant *H. pylori* has been removed from the high-priority category. This decision was based on evidence and expert consensus, reflecting a reassessment of the global threat posed by this pathogen and its resistance patterns (18).

A recent systematic review and meta-analysis published in 2024 indicated that primary resistance rates to clarithromycin have reached alarming levels worldwide, exceeding 15% in all WHO regions. This surge in resistance has significant implications for the efficacy of standard eradication therapies (19).

Despite the removal from the high-priority list, the escalating resistance rates underscore the necessity for continued surveillance and the development of alternative treatment strategies to effectively manage *H. pylori* infections.

Susceptibility testing faces limitations in becoming a routine clinical practice primarily due to the invasive nature of endoscopy. Furthermore, it is time-consuming and necessitates access to suitable laboratory culture facilities, thereby escalating costs. Recent studies have explored the feasibility of non-invasive methods such as PCR-based detection of resistance mutations in stool samples. Although promising, these approaches are not yet widely standardized or adopted in clinical practice and remain primarily investigations (20).

Eradication of *H. pylori* is a medical necessity, as the bacterium is a type I carcinogen and is implicated in the majority of gastric cancers. Gastric cancer is the fifth most prevalent cancer and the third most common cause of death in developed countries (21). The eradication of *H. pylori* also impacts the metabolic aspect. Several studies have highlighted that diabetic patients with active *H. pylori* infection require more intensive glycemic treatment to attain comparable glycemia levels. Additionally, the eradication of *H. pylori* leads to a reduction in HbA1C levels, thereby enhancing glycemic control (22). However, treatment of infection with antibiotics and antisecretory agents has a major impact on the intestinal microbiota. The human microbiota is crucial for human health as it contributes significantly to energy metabolism, immune modulation, and host defense mechanisms (23). Disturbances resulting from treatment of *H. pylori* vary from one protocol to another. Some studies have shown that triple-therapy treatment compared

with quadruple-therapy was much better in terms of side effects on the intestinal microbiota (24). These studies remain insufficient, and further studies are needed to draw definitive conclusions.

In the future, the primary objective should be to develop personalized treatment strategies that achieve complete *H. pylori* eradication while avoiding the selection of resistant strains and limiting the development of antimicrobial resistance. These approaches should also take into account the side effects of therapy, particularly its impact on the intestinal microbiota, in order to preserve gut health and ensure long-term treatment success.

A compelling option is to substitute traditional PPIs with vonoprazan in dual therapies. Employing vonoprazan in combination with amoxicillin as a dual therapy presents an alternative for *H. pylori* eradication with minimal impact on the intestinal microbiota (25).

CONCLUSION

H. pylori is a major human pathogen, and its failure to respond to treatment involves several factors: patient compliance, the therapeutic protocol chosen by the clinician, the availability of pharmaceutical molecules, and the emergence of bacterial resistance to the various antibiotics. The therapeutic objective is to find the most effective treatment while protecting the bacterial flora. Vonoprazan-based treatments seem promising in the absence of antibiotic sensitivity studies, a technique which is difficult to implement in routine practice. Morocco's drug sovereignty strategy will enable the use of various therapeutic protocols described in the literature, and significantly improve patient care.

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