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Helicobacter Pylori: Factors Related to Therapeutic Resistance and Current Approaches

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Methodology: Original works published from 2019 to 2023, available in total, and presenting experimental and clinical studies were included.

Results: After the selection considering the inclusion and exclusion criteria, 17 articles fulfilled the defined criteria. The selected references were mainly from Brazil, Vietnam, Chile, China, Thailand, the United States, and Europe.

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Abstract- ***Introduction:*** **Helicobacter pylori (*H. pylori*), a Gram-negative bacterium, poses a global health threat linked to chronic gastritis, gastric ulcers, and adenocarcinoma. This literature review addresses *H. pylori* challenges, emphasizing therapeutic resistance and modern treatment strategies.**

Methodology: **Original works published from 2019 to 2023, available in total, and presenting experimental and clinical studies were included.**

Results: **After the selection considering the inclusion and exclusion criteria, 17 articles fulfilled the defined criteria. The selected references were mainly from Brazil, Vietnam, Chile, China, Thailand, the United States, and Europe. They highlight the growing antimicrobial resistance, particularly against the first-line antibiotic, clarithromycin. Traditional triple therapies face growing compromise, necessitating alternative approaches. Vonoprazan (VPZ)-amoxicillin dual therapy stands out for acceptable eradication rates, reduced resistance risk, and enhanced safety. Effective regimens include bismuth-free quadruple therapies and VPZ-based triple therapy, proving efficacy even in high-resistance regions. Clarithromycin resistance, particularly in gastric remnants, raises concerns about traditional triple therapy. Resistance rates to metronidazole and clarithromycin underscore the importance of considering local resistance profiles when selecting treatments. More research into the actions of drugs against *H. pylori* is needed to help reduce future levels of antimicrobial resistance and minimize the significant impact on the gut microbiota.**

Keywords: antibacterial resistance; bacterial disease; chronic gastritis; dual therapy for H. pylori.

Therapeutic resistance of Helicobacter pylori

I. Introduction

The *Helicobacter pylori* (*H. pylori*) is a spiral, rod-shaped, microaerophilic, Gram-negative bacterium. This microorganism has exceptional adherence capacity and is adapted to the harsh conditions of the stomach, and can cause, in infected individuals, chronic gastritis, gastric ulcers, lymphoma of the lymphoid tissue associated with the gastric mucosa and, in some cases, distal gastric adenocarcinoma.[1-3]

Hooi et al.[4] determined that around 4.4 billion people would be infected by *H. pylori* by the end of 2015. Among the regions studied, the highest infection rates were recorded in Africa and Latin America/ Caribbean. Oceania had the lowest prevalence, illustrating an inversely proportional relationship between urbanization and infection prevalence. On the other hand, Switzerland, with one of the areas of lowest global prevalence, has around 1.6 million people remaining infected, thus highlighting *H. pylori* as a global public health challenge.[4,5]

Therapeutic success is influenced by various environmental and host-related factors, such as non-adherence to treatment and polymorphisms in interleukin 1B (IL-1B) and enzymes involved in drug metabolism (CYP2C19 and CYP3A4). However, the primary cause of treatment failure, especially in the case of bacteria, is bacterial resistance.[6] As such, in February 2017, the World Health Organization (WHO) added *H. pylori* to the list of 16 microorganisms that threaten humanity and called for urgent implementation of control measures. *H. pylori* has been prioritized due to the progression of antibiotic resistance and the emergence of multidrug-resistant strains.[7]

Currently, the success rates for most therapies for *H. pylori* are relatively low. The increase in antimicrobial resistance has rendered empirical triple therapies [a proton pump inhibitor (PPI) + amoxicillin + clarithromycin or metronidazole or levofloxacin] ineffective.[8] The prevalence of resistance to these antibiotics has been increasing, resulting in reduced effectiveness of eradication therapies.[9-11] Other factors include poor patient adherence to treatment regimens, low gastric pH, high bacterial load, and rapid metabolism of proton pump inhibitor drugs. Additionally, the presence of genetic polymorphisms in CYP2C19 can influence treatment outcomes. In view of all this, it is clear that when selecting the drug therapy to be used, the local resistance profiles and the success rates of the eradication therapy to be used must be considered.[9,10,12]

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Other treatment recommendations for *H. pylori* include the prescription of at least one antibiotic that does not contribute to the treatment outcome. This practice contributes to the overall resistance to antibiotics. Examples include popular four-drug regimens known as simultaneous, sequential, or hybrid therapies. For example, concurrent therapy involves combining triple therapies with clarithromycin and metronidazole in a regimen that includes amoxicillin, clarithromycin, and metronidazole along with a PPI, hoping that the *H. pylori* may be susceptible to either clarithromycin or metronidazole. This practice of using double, triple or quadruple medications to treat *H. pylori* can result in the production of 14,000 kilograms of unnecessary antibiotics for every 1 million successful treatments and 28,000 kilograms for every 1 million treatment failures.[8]

Considering the clinical-epidemiological significance of *H. pylori* infection globally, including its status as a WHO intervention priority, and the need to discuss the pharmacological management of the disease, this study aimed to identify current drug therapies in treating *H. pylori* about antimicrobial resistance.

II. Materials and Methods

A literature review was conducted involving the search for scientific articles in the following databases: Medical Literature Analysis and Retrieval System Online (MEDLINE), US National Library of Medicine (PubMed), Virtual Health Library (BVS), and Scientific Electronic Library Online (SciELO). The following descriptors were used in combination with the Boolean operator "AND": "*Helicobacter pylori*", "*H. pylori*", "drug treatment", "bacterial pharmacoresistance" and "drug resistance".

National and international articles published between 2019 and 2023 were examined. The inclusion criteria established for article selection were: language (Portuguese, English or Spanish); publication time (only the last five years); and availability of full articles for download. The articles excluded from the study addressed the presence of multiple infectious agents, duplicate articles in the databases, not accessible in full to researchers, or without discussion related to bacterial resistance to drugs in the treatment of H. pylori infection.

The process of studying the selected references included compiling relevant texts, creating detailed notes, analyzing and interpreting the data and, finally, consolidating the results. The purchased articles were organized into a general summary table, including the publication titles, authorship/year, study type, objectives, and results. This table was designed to summarize information during the data collection phase, simplifying the analysis, comparison, and discussion of the information from the chosen articles.

The current study analyzed thirty-six (36) articles published within five years to create a literature review on the therapeutic resistance of *H. pylori*. However, relevance criteria were applied, leading to the exclusion of fourteen (14) articles due to content repetition, and five (5) articles were excluded for deviating from the specific theme of the review.

Each article was scrutinized, focusing on extracting the most relevant information related to bacterial resistance and therapy descriptors concerning *H. pylori*, emphasizing up-to-date treatment methodologies.

III. Results

Most of the articles used in this study (16) were obtained from the PubMed database and one from Medline. Table 1 shows the results of the characterization of the reviewed articles. The studies were conducted in different countries, most frequently in Brazil, Vietnam, Chile, China, Thailand, the United States, and Europe. Regarding treating *H. pylori* infection, studies have indicated that the most commonly used regimen was a combination therapy of vonoprazan (VPZ) and amoxicillin.

Table 1: Methodological characteristics of selected studies on drug therapies used in treating *H. pylori* about antibacterial resistance.

Title	Author/ year	Type of Study	Study objective	Results	Database
Effectiveness and safety of high-dose esomeprazole-amoxicillin dual therapy as a rescue treatment for *Helicobacter pylori* infection: a multicenter, prospective, randomized, and controlled trial	Bi et al.[10]	Randomized controlled trial	To compare the effectiveness and safety of high-dose PPI-amoxicillin dual therapy versus bismuth-containing quadruple therapy for the rescue treatment of *H. pylori* infection	The 14-day high-dose dual therapy (HDDT), which includes esomeprazole (40 mg) and amoxicillin (1000 mg) taken thrice daily, is not less effective than the traditional quadruple therapy that contains bismuth for eradicating *H. pylori*. Additionally, HDDT has fewer side effects and good patient adherence, making it a promising alternative rescue treatment *for H. pylori* in the local region.	PubMed

Quadruple therapy with vonoprazan 20 mg daily as a first-line treatment for Helicobacter infection. pylori: A single-center, open-label, randomized, controlled, non-inferiority trial	Lu et al.[13]	Randomized controlled trial	To assess the effectiveness, tolerability, and cost-effectiveness of quadruple therapy with 20 mg of VPZ per day as first-line treatment for the eradication of *H. pylori.*	Quadruple therapy with VPZ at 20 mg per day was not inferior to the esomeprazole-based regimen	PubMed
The effectiveness of quadruple therapy with bismuth, sequential therapy, and hybrid therapy as first-line treatments for *Helicobacter pylori* infection compared to standard triple therapy	Koroglu et al.[14]	Retrospective study	To compare the effectiveness *of H. pylori* treatment regimens.	In terms of eradication, the TH regimen (esomeprazole 40 mg orally twice daily and amoxicillin 1000 mg orally daily; in the second week, esomeprazole 40 mg orally twice daily, amoxicillin 1000 mg orally twice daily, clarithromycin 500 mg orally twice daily, and metronidazole 500 mg orally twice daily were used) had the highest success rate. In contrast, the lowest success rate was observed in the sTT treatment group (lansoprazole 30 mg twice daily, amoxicillin 1000 mg twice daily, and clarithromycin 500 mg twice daily for 2 weeks). This study does not recommend the use of sTT due to the low eradication rates. This study recommends HT to overcome antibiotic resistance and achieve better outcomes.	PubMed
Surveillance of antibiotic resistance in *Helicobacter pylori* in the Biobío region (Chile) over a decade.	Parra-Sepúlveda et al.[15]	Surveillance study	To report on 10 years of surveillance of primary antibiotic resistance in clinical isolates of *H. pylori* from the Biobío region in Chile, examining the changes in resistance to amoxicillin, clarithromycin, levofloxacin, metronidazole, and tetracycline among the species.	Clinical isolates of *H. pylori* are mostly susceptible to amoxicillin and tetracycline but less susceptible to levofloxacin. Conversely, metronidazole continues to show the highest score of resistant isolates. Clarithromycin has an increased frequency of isolated resistant strains. Data suggests that isolates resistant to amoxicillin, clarithromycin, and metronidazole were more commonly found in females.	PubMed
Triple and dual therapy with vonoprazan for *Helicobacter pylori* infection in the United States and Europe. Randomized clinical trial	Chey et al.[16]	Clinical trial	To assess the effectiveness of VPZ, a potassium-competitive acid blocker, compared to standard treatment in eradicating *H. pylori* in the United States and Europe.	Eradication rates were as follows for non-resistant strains: triple therapy with VPZ, 84.7%; dual therapy, 78.5%; triple therapy with lansoprazole, 78.8%. Eradication rates were as follows for clarithromycin-resistant infections: triple therapy with VPZ, 65.8%; dual therapy, 69.6%; triple therapy with lansoprazole, 31.9%. In all patients, both triple and dual VPZ therapy were more effective than triple lansoprazole therapy	Pubmed
Vonoprazan and amoxicillin at low or high doses for fourteen days as a dual therapy to eradicate *Helicobacter pylori* infection: A prospective, open-label, randomized, non-inferiority clinical trial.	Hu et al.[17]	Randomized controlled trial	To explore the effectiveness of 14-day dual therapy with VA as a first-line treatment for *H. pylori* infection.	A total of 154 patients were evaluated, and 110 individuals were randomized. The eradication rates of VPZ with amoxicillin twice daily or thrice daily for 14 days were 89.1% and 87.3%, respectively, according to the intention-to-treat analysis, and 94.1% and 95.9%, respectively, according to the per-protocol analysis.	PubMed
Tegoprazan-based triple therapy, a new potassium-competitive acid blocker as a first-line treatment for *Helicobacter pylori* infection: a phase III randomized, double-blind, clinical trial	Choi et al.[18]	Clinical trial	To assess the effectiveness and safety of tegoprazan as a component of the first-line triple therapy for eradicating *Helicobacter pylori*.	TPZ (Tegoprazan-based triple therapy 50 mg) is as effective and safe as PPI-based triple therapy for first-line eradication therapy for *H. pylori*. However, it does not overcome clarithromycin resistance in *H. pylori* in Korea.	PubMed

Tetracycline-levofloxacin versus amoxicillin-levofloxacin as second-line quadruple therapies for treating *Helicobacter pylori* infection.	Hsu et al.[19]	Randomized controlled trial	To investigate the effectiveness of quadruple tetracycline-levofloxacin (TL) therapy and quadruple amoxicillin-levofloxacin (AL) therapy as second-line treatments for *H. pylori* infection.	TL quadruple therapy achieved a significantly higher eradication rate than AL quadruple therapy. A detailed analysis showed that TL quadruple therapy achieved a high eradication rate for both levofloxacin-susceptible and resistant strains (100% and 88.9%). In contrast, AL quadruple therapy achieved a high eradication rate for levofloxacin-susceptible strains (90.9%) but exhibited poor effectiveness in eradicating levofloxacin-resistant strains (50.0%). The two therapies had similar rates of adverse events (37.5% vs 21.4%) and treatment adherence (98.2% vs 94.6%).	PubMed
Assessment of the safety and pharmacokinetics of quadruple therapy containing bismuth with vonoprazan or lansoprazole for eradicating *Helicobacter pylori*	HUH et al.[9]	Randomized controlled trial	To compare the safety and pharmacokinetics (PK) of bismuth when used in quadruple therapy with either VPZ or lansoprazole in *H. pylori*-positive individuals	A total of 30 individuals were randomized, and 26 completed the study (12 and 14 in the VPZ and lansoprazole groups, respectively). Systemic exposure to bismuth in the two treatments was comparable (~5% difference). All individuals tested negative for *H. pylori* at the follow-up visit. Systemic exposure to bismuth was similar between the quadruple therapy containing VPZ and lansoprazole. Quadruple therapy containing VPZ was safe and well-tolerated.	PubMed
Antibiotic resistance profile of *Helicobacter pylori* to 14 antibiotics: a multicenter study in Fujian, China.	Huang et al.[20]	Clinical trial	To investigate the antibiotic resistance of *H. pylori* in Fujian, China.	In Fujian, there was a high prevalence of *H. pylori* resistance to azithromycin, clarithromycin, and levofloxacin, while resistance to amoxicillin, amoxicillin-clavulanate, and gentamicin was relatively low. The main patterns of dual resistance were exhibited by clarithromycin plus metronidazole (10/205, 5%) and clarithromycin plus levofloxacin (9/205, 4%). The main triple resistance pattern was toward clarithromycin+metronidazole+levofloxacin (15/205, 7%).	MEDLINE
High rates of resistance to clarithromycin and levofloxacin in *Helicobacter pylori* among patients with chronic gastritis in Southeast Vietnam.	Dang et al.[21]	Clinical trial	To determine the rates of clarithromycin and levofloxacin-resistant *H. pylori* strains using the E-test method and to assess the risk factors for antibiotic resistance among patients with chronic gastritis in the southeastern region of Vietnam.	The resistance rates of *H. pylori* to CLR and levofloxacin were 72.6% and 40.5%, respectively. *H. pylori* with dual resistance (to both clarithromycin and LVX) accounted for 30.7% of patients. The high-level resistance rates for clarithromycin and levofloxacin were 18.9% and 83.9%, respectively.	PubMed
Emergence of amoxicillin resistance and identification of new mutations in the *pbp1A* gene in *Helicobacter pylori* in Vietnam.	Tran et al.[22]	Clinical trial	To explore the prevalence of primary resistance of *H. pylori* to amoxicillin and to assess its association with point mutations in the *pbp1A* gene in Vietnamese patients.	The E test was used to determine the susceptibility to amoxicillin (minimum inhibitory concentration [MIC]≧ 0.125 μg/ml) in 101 isolates, among which the rate of strains primarily resistant to amoxicillin was 25.7%.	PubMed

Fourteen-day high-dose triple therapy with amoxicillin and metronidazole, with or without bismuth, as a first-line treatment for *Helicobacter pylori*	Luo et al.[23]	Randomized clinical trial	To identify the additional benefit/role of bismuth in amoxicillin, metronidazole, PPI, and bismuth quadruple therapy for the treatment of *Helicobacter pylori* (*H. pylori*).	Both therapies achieved high eradication rates (triple therapy involving amoxicillin and metronidazole for 14 days, consisting of 20 mg esomeprazole twice daily, 1 g amoxicillin, and 400 mg metronidazole both taken thrice daily, with or without 220 mg of bismuth twice daily). Resistance to metronidazole did not affect the effectiveness of any of the therapies. Neither the presence nor absence of resistance to bismuth or metronidazole reduced the effectiveness of the triple therapy containing 20 mg esomeprazole twice daily, 1 g amoxicillin, and 400 mg metronidazole thrice daily in this population.	PubMed
A "new" option in eradicating *Helicobacter pylori*: high-dose amoxicillin dual therapy outperforms bismuth quadruple therapy in settings with high dual resistance	Macedo Silva et al.[24]	Prospective randomized study	To compare the effectiveness of quadruple therapy with bismuth and high-dose amoxicillin dual therapy in eradicating *H. pylori*.	When compared to BQT (bismuth 140 mg + metronidazole 125 mg + tetracycline 125 mg, taken four times a day for 10 days), the treatment involving HDADT (alternating amoxicillin 1000 mg with amoxicillin 500 mg, taken four times a day for 14 days), both combined with esomeprazole 40 mg, showed superior effectiveness, nearly 100% in eradicating *H. pylori*. There were no reported differences in side effects or patient adherence between the two treatments. This treatment is an important alternative for populations experiencing increasing resistance to the currently recommended antibiotic regimens.	PubMed
Bismuth-based quadruple therapy versus high-dose metronidazole triple therapy as a first-line treatment for clarithromycin-resistant *Helicobacter pylori* infection: a randomized, multicenter controlled trial.	Seo et al.[25]	Clinical trial	To compare the effectiveness and cost-effectiveness of 14-day bismuth-based quadruple therapy versus 14-day intensified triple therapy with metronidazole for clarithromycin-resistant *H. pylori* infection with genotypic resistance.	The 14-day bismuth-based quadruple therapy was as effective as the intensified 14-day triple therapy with metronidazole and was more cost-effective in treating clarithromycin-resistant *H. pylori* infection.	PubMed
Pilot studies on *Helicobacter pylori* eradication therapy that includes vonoprazan indicate that Thailand might have more in common with the United States than with Japan in this regard	Ratana-Amornpin et al.[26]	Clinical trial	To examine VPZ therapies in the treatment of *H. pylori* in Thailand.	Triple therapy with high doses of VPZ and triple therapy with VPZ plus bismuth can be used as first-line treatments in certain regions showing high effectiveness, regardless of CYP3A4/5 genotype and clarithromycin resistance.	PubMed
Primary *H. pylori* strains resistant to clarithromycin and virulence genotypes in the Northeast region of Brazil.	BENIGNO et al.[27]	Clinical trial	To assess the prevalence of the primary resistance of *H. pylori* to clarithromycin and its association with virulence factors in adult patients with dyspepsia and asymptomatic children.	Primary resistance to clarithromycin was lower than that reported in Southeast Brazil. The positive *H. pylori* samples have few point mutations suggesting that individuals infected with virulent strains may be more susceptible to anti-*H. pylori* treatment.	PubMed

IV. Discussion

Research has shown that VPZ-amoxicillin (VA) dual therapy offers acceptable eradication rates, improves safety and tolerability, and reduces the potential for increased antimicrobial resistance or an imbalance in the gut microbiota.[18,28,29] Quadruple therapy with VPZ was found to be safe and well-tolerated.[9,10,22,30]

High-dose dual therapy consisting of amoxicillin and a PPI has also been suggested as an effective and safe first-line or rescue treatment, showing eradication

rates that are comparable to or better than traditional triple therapy.[10,22,24,30] Therefore, the choice of therapy depends on factors such as antibiotic resistance rates and individual patient characteristics.[10,22]

Other recommended treatment regimens include 10-14 days of bismuth-free quadruple therapies and a 7-day VPZ-based triple therapy, which have shown high eradication rates even in areas with high antimicrobial-resistant strains.[16,26,31] Quadruple therapy with bismuth has been confirmed as an effective treatment, particularly against antibiotic-resistant strains.[25]

Recently, Ko et al.[32] conducted a systematic review and meta-analysis to assess the effectiveness of non-antibiotic supplements (bismuth) as a first-line treatment for eradicating *H. pylori*. In total, 25 randomized trials (3,990 patients) were included for analysis. According to the per-protocol (PP) analysis, the *H. pylori* eradication rate was significantly higher in the BQT regimen group (85.8%) than in the non-BQT regimen group (74.2%).[32]

The most commonly prescribed therapy worldwide for *H. pylori*, known as triple therapy, combines PPIs, amoxicillin, and clarithromycin.[18] However, the effectiveness of triple therapy can be impacted by antibiotic resistance, particularly to clarithromycin.[17] In patients with gastric remnants, *H. pylori* strains showed resistance rates to metronidazole, clarithromycin, levofloxacin, amoxicillin, and furazolidone of 100%, 20.63%, 22.22%, 0%, and 0%, respectively.[33]

Clarithromycin is a bacteriostatic macrolide antibiotic that inhibits bacterial growth by restricting protein synthesis. Macrolides bind to the 50S ribosomal subunit (through 23S rRNA) and prevent proliferation. The resistance to clarithromycin has been increasing, possibly due to the use of macrolides for other community-acquired infections.[34,35] Resistance to metronidazole is linked to mutations in the RdxA and FrxA genes, which reduce the effectiveness of its reductase activity. Mutations—such as frameshifts, missense mutations, and premature termination in the rdxA and frxA genes—have been reported in metronidazole-resistant *H. pylori*.[36]

In Brazil, the Fourth consensus on *H. pylori* infection, organized by the Brazilian Nucleus for the Study of *H. pylori* and Microbiota in 2017, indicates that despite increasing resistance to clarithromycin and fluoroquinolones in Brazil, their use is still recommended for treating *H. pylori*. The recommended first-line treatment is triple therapy consisting of a PPI, amoxicillin, and clarithromycin for 14 days. Alternatives include 10 to 14-day quadruple therapy with bismuth and 14-day concomitant treatment. If triple therapy with clarithromycin or concomitant quadruple treatment fails, the recommended strategies are triple therapy with levofloxacin or quadruple therapy with bismuth for 10 to 14 days. After three therapeutic failures, further treatment should be limited to exceptional cases and guided by phenotypic and genotypic tests for antimicrobial susceptibility.[5,37]

V. Conclusions

This literature review describes current standards for treating *H. pylori* through a global analysis of research in this area. Various medications—metronidazole, clarithromycin, levofloxacin, amoxicillin, furazolidone, and clavulanate—were analyzed for their effectiveness against *H. pylori*.

Studies show that the VPZ-amoxicillin dual therapy has acceptable eradication rates, improved safety and tolerability, and reduced risk of antimicrobial resistance. Quadruple therapy with VPZ is also safe. Other options, such as bismuth-free quadruple therapies and VPZ-based triple therapy, are effective even in areas with high antimicrobial resistance. Traditional triple treatment with PPIs, amoxicillin, and clarithromycin, while commonly prescribed, is facing challenges due to drug resistance, particularly to clarithromycin. The choice of treatment should consider local antibiotic resistance and individual patient characteristics.

More research into the actions of drugs against *H. pylori* is needed to help reduce future levels of antimicrobial resistance and minimize the significant impact on the gut microbiota.

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