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H. pylori treatment in a resistant world: Regional strategies for effective eradication: A narrative review

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Abstract

The transmission of *Helicobacter pylori* (*H. pylori*) is still a major global health concern. As antibiotic resistance increases, the efficacy of traditional treatment plans—which are mostly dependent on proton pump inhibitors and antibiotics—is being gradually undermined. This review examines the regional variations in *H. pylori* treatment guidelines, shaped by local resistance patterns, healthcare infrastructure, and available therapies. In regions with high resistance, such as South Asia, bismuth quadruple therapy has become the preferred first-line option, offering higher eradication rates. In contrast, countries like Japan and South Korea have seen improved outcomes with the introduction of potassium-competitive acid blockers (P-CABs) and high dose amoxicillin-based regimens respectively. These regional disparities highlight the significance of tailoring *H. pylori* treatment to local resistance trends in order to tackle the growing threat of antibiotic resistance. The purpose of this review is to investigate geographical variations in *Helicobacter pylori* antibiotic resistance patterns and their impact on treatment methods. By highlighting how resistance trends impact therapeutic outcomes, this review seeks to guide clinicians in selecting the most effective, region-specific therapies for *H. pylori* eradication. Additionally, it underscores the critical need for ongoing research to better understand resistance dynamics and inform updated treatment guidelines, ensuring improved patient outcomes and combating the global rise of antimicrobial resistance.

Keywords: *Helicobacter pylori*; Antibiotic Resistance; Eradication; Alternative therapy; Clinical Practice

1. Introduction

Helicobacter pylori (*H. pylori*) is a spiral-shaped, gram-negative bacteria that often lives in the human stomach mucosa. Globally, it is regarded as one of the most frequently observed chronic infections. A multitude gastrointestinal disorders have been reported to involve *H. pylori* as the initial triggering pathogen Because of its distinct immune evasion strategies and capacity to cause inflammation and damage to the gastric mucosa, *H. pylori* can survive for decades in the stomach's acidic environment. *H. pylori* communally transmitted by oral-oral or fecal-oral mode, and acquisition usually takes place in childhood which could involve stomach cancer, peptic ulcer disease (PUD), and chronic gastritis. The average incidence of *H. pylori* developing an infection in adolescents and kids throughout the world is 35.1%, per the most recently published Studie [1]. The diagnosis of *H. pylori* infection has historically been verified using a number of techniques, such as stool antigen testing, serology, breath testing, and gastroscopy with biopsy and for the eradication of this infection Proton Pump Inhibitors (PPIs) in conjunction with antibiotic therapy have been the mainstay of treatment for *H. pylori* infections over the past few decades. The ultimate objective of this review is to examine the worldwide problem of antibiotic resistance in the treatment of *Helicobacter pylori*, with an emphasis on how it affects therapeutic results in various nations. The frequency and trends of antibiotic resistance to widely used medications will be investigated in this article.

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1.1. Antibiotic Resistance: A Global Challenge

Antibiotics have been recognized as the most wonderful technological breakthrough of the 20th century and are the "magic bullets" for eradicating bacteria. Without a doubt, antibiotics have been a blessing to humanity but the expanding adoption and misuse of antimicrobial drugs has led to the establishment of antimicrobial resistance (AMR) in bacteria. The resistance to antibiotics is a new far and wide issue that could jeopardize decades of advancement in medicine. Antibiotics need to be utilized to treat a variety of bacterial infections, from common illnesses to critical illnesses. Treatment for infections brought on by these resistant organisms is more difficult, and the risk of serious health problems and, frequently, death is increased due to infection as antibiotic have no ability to kill bacteria [2,3,4].

1.2. Cause of antibiotic resistance:

The primary drivers of resistance of antibiotic are the overuse and misuse of antibiotics in both human healthcare and agricultural practices. Antibiotic overprescription, self-medication, and unfinished treatment regimens all play a major role in the emergence and spread of resistant microorganisms with poor sanitation and irrelevant protocols for controlling infections making the issue more deteriorating. Two significant drivers of the broadly rise of resistant bacteria are the contamination of the environment by pharmaceutical waste and the rapid dissemination of resistance through horizontal gene transfer. Moreover, the problem is made worse by the dearth of novel antibiotics in the medical research pipe line [5,6]. Healthcare practitioners have few alternatives for treating resistant infections because of the slow rate of antibiotic development and the absence of financial incentives for pharmaceutical corporations to invest in novel antibiotics. In conclusion, antibiotic resistance is not just a healthcare problem, but a complex, global issue that requires urgent, collective action [7,8]. Only through coordinated efforts across sectors—healthcare, agriculture, environment, and policy—can we hope to slow the progress of antibiotic resistance and protect the effectiveness of antibiotics for future generations. Timely action and sustained commitment to addressing this crisis are essential for safeguarding public health and ensuring that antibiotics remain a viable treatment option in the years to come.

1.3. Current Treatment guideline of *H. pylori* Infection:

Treatment recommendations for *H. pylori* infections are always changing due to new developments in medicine, rising worries about antibiotic resistance, and the constant need to enhance patient outcomes and treatment effectiveness. The primary goal of preventing an *H. pylori* infection is to completely get rid of the bacteria [9,10] Treatment for *H. pylori* eradication usually consists of a mix of drugs such as Combinations of proton pump inhibitors, which lower the production of stomach acid, and antibiotics, which attack the bacteria directly, are the most commonly used regimens [10,11]. It consists of First line therapy, second line therapy, and salvage therapy to eradicate the *H. pylori* infection. The details are shown in the Table-1 to help you better comprehend this treatment [11-14]. :

Table 1 Overview of *H. pylori* Treatment Regimen

Name of medicine with Dose	**Duration**	**Condition**	**Comments**
FIRST LINE THRAPY			
Clarithromycin Triple Therapy:			
PPI + AC Amoxicillin 1 gm BD Clarithromycin 500mg BD	7 – 14 days	Used in region when CR rate is <15-20 %.	Most commonly used first line therapy with Eradication rate – 70 to 85 %.
PPI + MC Metronidazole 500mg TDS Clarithromycin 500mg BD	14 days	Used as a substituted when the patient is allergic to penicillin class of drug.	-
Bismuth Quadruple Therapy:			
PPI +BMT Bismuth Subsalicylate 120 mg QIDS	7 days or 10 to 14 days	Used in region when CR rate is high First line therapy	FDA approved treatment regimen PYLERA a fixed dose capsule is taken with PPI for 10 days.

Metronidazole 250 mg QIDS or 400-500 mg TDS Tetracycline hydrochloride 500 mg QIDS		For who are allergic to Penicillin class of drug.	
Sequential therapy:			
PPI+AMC Amoxicillin 1g BD Metronidazole 500mg BD Clarithromycin 500mg BD	PPI+ Amoxicillin 7 days followed by PPI +AMC 7 days	-	Several Interational studies support using this therapy as alternative to clarithromycin triple therapy.
SECOND LINE THERAPY			
Bismuth Quadruple Therapy:			
PPI +BMT Bismuth Subsalicylate 120 mg QIDS Metronidazole 250 mg QIDS Tetracycline hydrochloride 500 mg QIDS	14 days	After failure of clarithromycin containing regimen.	Used as second-line treatment therapy if the first-line medication has been taken earlier.
Levofloxacin triple therapy:			
PPI + AL Amoxicillin 750mg BD Levofloxacin 500 mg OD or 250 mg BD	10-14 days	Used when <15% LR rate.	Used after failure of quadruple therapy.
High dose dual therapy:			
PPI + Amoxicillin Amoxicillin 750mg QIDS or 1 gm TDS	14 days	Used when both CR and LR.	In one trial, 95.3% of patients receiving the high-dose dual therapy regimen had their infections completely eliminated [15].
SALVAGE THERAPY			
PPI+AR Amoxicillin 750mg TDS Rifabutin 300mg OD	7-14 days	Consider as Third line or forth line therapy.	Risk of significant neutropenia, which tends to limits its use.

Abbreviation: AC: Amoxicillin + Clarithromycin, CR: clarithromycin Resistance, MC: Metronidazole + Clarithromycin, BMT: Bismuth Subsalicylate + Metronidazole+ Tetracycline, AMC: Amoxicillin + Metronidazole+ Clarithromycin, AL: Amoxicillin + Levofloxacin, LR: Levofloxacin Resistance AR: Amoxicillin + Rifabutin.

1.4. Antibiotic Resistance in *H. pylori*: A Regional Comparison

The resistance rates of antibiotics of *H. pylori* are varied significantly between regions influenced by factors that already mention above such as healthcare practices, antimicrobial stewardship, regulatory measures, socioeconomic status, and the use of antibiotics in agriculture. There are now major obstacles in treating *Helicobacter pylori* infections worldwide due to the rising incidence of antibiotic resistance in this infection [10]. In order to improve eradication rates and customize appropriate treatment regimens, it is essential to comprehend local resistance data because resistance patterns differ greatly between regions. Based on recent study, The Table-2 provides some antibiotic resistance patterns

in various different regions that help to clinicians for optimize treatment outcomes, avoid therapeutic failures, and limit the development of resistance [16-18]:

Table 2 Regional Antibiotic Resistance Profiles for *H. pylori*

Name of antibiotic	Name of region	Antibiotic Resistance Rate
Amoxicillin	India	70%
	Pakistan	38%
	Africa	30%
	America	8%
Clarithromycin	India	60%
	Pakistan	43%
	Europe	32%
	Bangladesh	24%
Metronidazole	Africa	91%
	India	80%
	Bangladesh	63%
	Europe	38%
Tetracycline	Pakistan	55%
	India	50%
	Africa	13%
	Bangladesh	7%
Levofloxacin	India	61%
	Pakistan	40%
	Bangladesh	34%
	America	14%

1.5. Regional Approaches to *H. pylori* Treatment

Different regions have different guidelines for therapy for *H. pylori* associated with variability in antibiotic resistance patterns, healthcare systems, and testing approaches. In many parts of the world, especially in areas with high resistance rates, tailored therapy which considers local resistance patterns is becoming more advised. This has increased the demand for customized treatment for *H. pylori* infections. Tailored therapy is modifying the course of treatment in accordance with the patient's particular strain of *H. pylori*'s antibiotic susceptibility. By tailoring the treatment to increase eradication rates, decrease the needless use of broad-spectrum antibiotics, and limit side effects or adverse reactions, this strategy aims to address the growing problem of antibiotic resistance. Instead, depending on a set course of treatment, customized therapy selects the best antibiotics based on clinical parameters such past treatment history, geographical resistance patterns, and susceptibility test findings.

- **China** In China, *Helicobacter pylori* infection is widespread, with an estimated prevalence of 44.2%. The most commonly used first-line antibiotics, clarithromycin and metronidazole, exhibit resistance rates of 37% and 77%, respectively. Due to these high resistance rates, there has been a shift in treatment recommendations. Bismuth-based quadruple therapy is now advocated as the preferred first-line treatment in China, especially in areas with significant resistance to clarithromycin and metronidazole. This therapy is considered more effective in China to overcoming the challenges of resistance and ensuring better eradication of the infection [19,20].
- **Japan** In Japan, the prevalence of *H. pylori* infection ranges between 37.6% and 43.2%. A significant advancement in the treatment of this infection has been the introduction of potassium-competitive acid

blockers (P-CABs), particularly Vonoprazan. These medications have transformed the approach to *H. pylori* treatment by providing superior acid suppression compared to traditional proton pump inhibitors (PPIs) [20]. which significantly improves the effectiveness of combination therapies, particularly in overcoming challenges posed by antibiotic resistance. This enhanced acid control reduces the need for more complex and prolonged treatment regimens, improving patient adherence by shortening therapy duration. Studies indicate that P-CAB-based regimens, when combined with antibiotics, lead to higher eradication rates compared to PPI-based therapies in Japan. Overall, the success of treating *H. pylori* has been significantly impacted by the introduction of P-CABs in Japan, which has established it as a viable first-line treatment option [20-25].

- **South Korea** In South Korea, the prevalence rate of *Helicobacter pylori* (*H. pylori*) infection is reported to be around 51.0%, indicating a significant public health concern. The resistance rates to amoxicillin for *Helicobacter pylori* are relatively low, especially compared to other antibiotics like clarithromycin and metronidazole, which tend to have higher resistance rates [26]. A significant breakthrough in the management of *H. pylori* infections was made in 1989 with the launch of PPI-Amoxicillin dual therapy, which provided a low resistance rate, well-tolerated alternative, and an effective treatment. Even if antibiotic resistance has increased over time, amoxicillin plus a PPI remains a crucial first-line treatment for *H. pylori* eradication in south Korea [20,27]. The 2015 study by Yang et al. introduced a modified 14-day dual therapy regimen, which increased the dosage and frequency of administration of the drugs in order to enhance the eradication rate [28].
- **Bangladesh, India and Pakistan** In regions like Bangladesh, India, and Pakistan, where clarithromycin resistance to *Helicobacter pylori* exceeds 15%, bismuth quadruple therapy emerges as the preferred first-line treatment for *H. pylori* eradication. This approach is crucial for overcoming the limitations posed by antibiotic resistance, ensuring higher success rates, and reducing the risk of treatment failure. The four-drug regimen (PPI, bismuth, tetracycline, and metronidazole) offers a broad-spectrum, multi-targeted solution that effectively addresses the challenges posed by resistance to clarithromycin and metronidazole, which are common in these regions. The therapy's proven high eradication rates (often exceeding 85%) make it a reliable choice, offering a significant improvement over traditional regimen. Ultimately, bismuth quadruple therapy represents a crucial step forward in the fight against *H. pylori* infections in regions with high antibiotic resistance, contributing to improved treatment success, better patient outcomes, and more sustainable management [29,30].
- **Nepal and Bhutan** In Nepal and Bhutan, both clarithromycin-containing triple therapy and bismuth quadruple therapy are viable options for treating *H. pylori* infections. Triple therapy remains effective in areas with low resistance to clarithromycin, but in regions with higher resistance rates, bismuth quadruple therapy offers a more reliable alternative. Clinicians should consider local resistance patterns, patient health status, and availability of medications when selecting the most appropriate regimen to ensure optimal treatment outcomes for *H. pylori* eradication [29].

2. Conclusion

The treatment of *Helicobacter pylori* infections is becoming increasingly complex due to the rising global issue of antibiotic resistance, which presents unique challenges across different regions. The global prevalence of *H. pylori* and its associated diseases. However, the rising resistance to commonly used antibiotics like clarithromycin and metronidazole complicates the effectiveness of standard therapies. As a result, many countries have adapted their treatment guidelines based on local antibiotic resistance patterns, healthcare infrastructure, and available medications. In countries like China, where resistance to clarithromycin and metronidazole is high, bismuth-based quadruple therapy has become the preferred first-line treatment. This therapy has shown improved eradication rates and offers an effective solution in regions with significant resistance. Similarly, in South Korea, despite increasing resistance to other antibiotics, high dose amoxicillin combined with a proton pump inhibitor remains a first-line therapy, with modifications to treatment duration and dosage helping to improve outcomes. In Japan, the introduction of potassium-competitive acid blockers (P-CABs), such as Vonoprazan, has revolutionized *H. pylori* treatment by providing superior acid control and higher eradication rates compared to traditional PPIs, helping to address antibiotic resistance more effectively. In regions like Bangladesh, India, and Pakistan, where clarithromycin resistance exceeds 15%, bismuth quadruple therapy is becoming the preferred treatment to overcome resistance challenges. Similarly, in Nepal and Bhutan, where resistance rates vary, clinicians must consider local resistance data to choose the best treatment option, with both triple and quadruple therapies being effective depending on the resistance patterns. As antibiotic resistance continues to rise, the global medical community must commit to ongoing research, regional surveillance, and the development of new therapies to ensure the continued effectiveness of *H. pylori* eradication treatments. By tailoring therapy to local resistance patterns and individual patient needs, the medical community can improve treatment success, minimize the risk of resistance development, and ensure better long-term outcomes for patients worldwide.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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