Proceedings of the 16th International Scientific and Practical Conference «Challenges in Science of Nowadays»

(April 26-28, 2026). Washington, USA

No 292

MEDICINE AND PHARMACY

Novel Approaches to the Treatment of Helicobacter Pylori Infection in the Era of Antibiotic Resistance

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Abstract. Helicobacter pylori infection remains one of the most prevalent chronic bacterial diseases worldwide and a key etiological factor in peptic ulcer disease, gastric adenocarcinoma, and mucosa-associated lymphoid tissue lymphoma. Despite the availability of established eradication regimens, the effectiveness of standard therapies has declined in recent years, primarily due to the growing prevalence of antibiotic-resistant strains, particularly to clarithromycin, metronidazole, and levofloxacin. This review analyzes contemporary treatment strategies for H. pylori infection with a focus on approaches that address antibiotic resistance. Current evidence supports the transition from empiric standard triple therapy to optimized regimens, including bismuth-based quadruple therapy, concomitant therapy, and tailored treatment guided by antimicrobial susceptibility testing where available. The role of novel acid suppression strategies, such as potassium-competitive acid blockers, is also considered, given their potential to enhance eradication rates by improving intragastric pH control. In addition, emerging therapeutic directions are discussed, including the use of rifabutin-based regimens, high-dose dual therapy, and adjunctive approaches aimed at improving treatment adherence and microbiological outcomes. The clinical implications of regional resistance patterns and the importance of individualized treatment selection are emphasized. A shift toward resistance-adapted and patient-specific strategies appears essential to maintain high eradication success rates. Future treatment algorithms should integrate local epidemiological data, optimize pharmacological combinations, and reduce unnecessary antibiotic exposure to limit further resistance development.

Keywords: *Helicobacter pylori, antibiotic resistance, eradication therapy, clarithromycin resistance, bismuth quadruple therapy, tailored therapy, potassium-competitive acid blockers.*

Introduction. *Helicobacter pylori* infection remains one

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of the most widespread chronic bacterial infections globally, affecting more than half of the world's population, with particularly high prevalence in developing regions [1]. Its clinical significance extends beyond chronic gastritis to include peptic ulcer disease, gastric adenocarcinoma, and mucosa-associated lymphoid tissue lymphoma, making eradication a key component of both treatment and cancer prevention strategies [2,3].

Over the past decade, a steady decline in the effectiveness of standard eradication regimens has been observed. The classical triple therapy, once considered the cornerstone of treatment, has demonstrated progressively lower success rates in many regions, often falling below the acceptable threshold of 80% eradication [4]. This trend is primarily driven by increasing resistance to commonly used antibiotics, particularly clarithromycin, metronidazole, and levofloxacin, which directly compromises treatment efficacy [5].

Antibiotic resistance in *H. pylori* has evolved into a global clinical challenge with significant regional variability. In areas with high clarithromycin resistance, empiric use of standard triple therapy is no longer recommended, prompting a shift toward alternative regimens such as bismuth-containing quadruple therapy or non-bismuth concomitant therapy [6]. At the same time, the limited availability of routine antimicrobial susceptibility testing in many clinical settings continues to constrain the implementation of truly individualized treatment strategies [7].

Another important aspect influencing eradication success is the level of gastric acid suppression. Adequate intragastric pH is critical for enhancing antibiotic stability and bacterial susceptibility. In this context, potassium-competitive acid blockers, particularly vonoprazan, have emerged as a promising alternative to proton pump inhibitors, demonstrating improved eradication rates in several studies, including in populations with antibiotic resistance [8].

Taken together, these factors highlight the need for a reassessment of traditional treatment algorithms. The current approach to *H. pylori* management is shifting from empiric, uniform regimens toward strategies that consider resistance patterns, pharmacological optimization, and patient-specific factors, aiming to restore high eradication rates in the face

of growing antimicrobial resistance.

Materials and Methods. This study was conducted as a systematic literature review on contemporary treatment strategies for *Helicobacter pylori* infection, with a focus on antibiotic resistance and optimization of eradication regimens. A structured search was performed in PubMed/MEDLINE, Scopus, and Web of Science for studies published between January 2015 and December 2025, along with relevant international guidelines and consensus statements. Search terms included *Helicobacter pylori*, eradication therapy, antibiotic resistance, clarithromycin resistance, bismuth quadruple therapy, concomitant therapy, tailored therapy, vonoprazan, and rifabutin-based therapy, using Boolean operators (AND, OR).

Randomized controlled trials, cohort studies, systematic reviews, meta-analyses, and clinical guidelines reporting treatment outcomes and resistance patterns were included. Studies lacking methodological detail, case reports, conference abstracts, and duplicates were excluded. Study selection was based on title/abstract screening followed by full-text review. Extracted data included study design, population characteristics, resistance profiles, treatment regimens, and eradication rates. A qualitative analysis was performed focusing on comparative effectiveness, the impact of antibiotic resistance, and emerging therapeutic strategies.

Results. Across the analyzed studies, a consistent decline in the efficacy of standard triple therapy (proton pump inhibitor, clarithromycin, and amoxicillin) was observed. In regions with high clarithromycin resistance, eradication rates decreased to 60-75%, falling well below the acceptable clinical threshold [9,10]. Even in areas with moderate resistance, outcomes rarely exceeded 80%, indicating reduced reliability of empiric use. This trend reflects the direct impact of clarithromycin resistance on treatment success and supports current recommendations to avoid triple therapy in high-resistance settings.

Bismuth-containing quadruple therapy demonstrated more consistent and reproducible outcomes across different geographic regions and resistance profiles. Reported eradication rates ranged from 85% to 92%, with relatively stable performance even in the presence of clarithromycin resistance [11,12]. The inclusion of bismuth and tetracycline contributes to a reduced dependence on macrolide

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susceptibility. However, some studies noted challenges related to treatment complexity, pill burden, and gastrointestinal side effects, which may affect adherence in routine clinical practice.

Concomitant therapy, combining a proton pump inhibitor with clarithromycin, amoxicillin, and metronidazole, achieved eradication rates of approximately 85-90% in several studies [13]. Its effectiveness was higher than standard triple therapy but showed variability depending on local resistance patterns. Dual resistance to clarithromycin and metronidazole significantly reduced treatment success, highlighting the limitation of empiric use in high-resistance regions [14].

Personalized treatment strategies guided by antimicrobial susceptibility testing showed the highest eradication rates among all approaches analyzed. In multiple studies, tailored therapy achieved success rates exceeding 90-95%, significantly outperforming empiric regimens [15]. This approach allows for the selection of antibiotics based on resistance profiles, minimizing treatment failure. However, its implementation remains limited by the availability, cost, and turnaround time of susceptibility testing, particularly in routine clinical settings [16].

The level of gastric acid suppression emerged as a critical determinant of eradication success. Potassium-competitive acid blockers (PCABs), particularly vonoprazan, demonstrated superior acid inhibition compared to conventional proton pump inhibitors. Vonoprazan-based regimens consistently achieved eradication rates of 90-95%, including in populations with clarithromycin-resistant *H. pylori* strains [17,18]. Improved intragastric pH control enhances antibiotic stability and bacterial susceptibility, contributing to these outcomes. These findings support the growing role of PCAB-based therapy as a preferred option in optimized treatment protocols.

In cases of treatment failure, rifabutin-based therapy was identified as an effective rescue option, with eradication rates ranging from 70% to 85% [19]. Although useful in refractory infection, it concerns regarding adverse effects, cost, and the risk of resistance development limit its use as a first-line strategy.

High-dose dual therapy, combining intensive acid suppression with high-dose amoxicillin, has also gained attention. Reported eradication rates ranged from 85% to 92%, with the advantage of reduced antibiotic exposure and

simplified dosing [20]. This regimen appears particularly promising in settings with high resistance to multiple antibiotics.

Beyond the choice of regimen, several factors consistently influenced eradication outcomes. Regional antibiotic resistance patterns were identified as the primary determinant of success, followed by patient adherence and adequacy of acid suppression [21]. Studies emphasized that insufficient acid inhibition and poor compliance significantly reduce treatment effectiveness, even with optimized regimens.

Overall, the data analyzed indicates a clear transition from empiric, uniform treatment approaches to resistance-adapted and optimized strategies. Bismuth quadruple therapy, tailored regimens, and vonoprazan-based approaches demonstrated the most reliable and reproducible results across diverse clinical settings [22,23]. This shift reflects the need to address the growing challenge of antibiotic resistance while maintaining high eradication rates.

Discussion. The findings of this review reflect a clear shift in the paradigm of *Helicobacter pylori* management, driven primarily by the global rise in antibiotic resistance. One of the most debated issues remains the role of standard triple therapy in current clinical practice. While historically considered the cornerstone of eradication, its effectiveness has become highly inconsistent. In regions with elevated clarithromycin resistance, eradication rates frequently fall below acceptable thresholds, making empiric use difficult to justify [9,10]. Nevertheless, some studies suggest that triple therapy may still retain clinical value in carefully selected populations with confirmed low resistance rates or when guided by susceptibility testing [24]. This creates a persistent tension between traditional simplicity and the need for resistance-adapted strategies.

In contrast, bismuth-based quadruple therapy has emerged as a more robust first-line option, largely due to its reduced dependence on clarithromycin susceptibility. Its relatively stable eradication rates across different resistance settings support its broader applicability [11,12]. However, this approach is not without limitations. Increased pill burden, more complex dosing schedules, and a higher incidence of adverse effects may compromise adherence, particularly in real-world settings. As a result, the theoretical superiority of quadruple therapy does not always translate into

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consistently better outcomes in routine clinical practice, highlighting the importance of patient-centered considerations.

Another critical question concerns the role of tailored therapy based on antimicrobial susceptibility testing. From a purely efficacy-driven perspective, this approach offers the highest eradication rates, often exceeding 90-95% [15]. It aligns well with the principles of precision medicine, allowing for targeted antibiotic selection and avoidance of ineffective regimens. However, the widespread implementation of tailored therapy remains limited by practical constraints, including cost, accessibility, and the need for specialized laboratory infrastructure [16]. In many regions, empiric therapy continues to dominate clinical practice, raising the question of whether tailored strategies should be reserved for rescue treatment rather than used universally as first-line therapy [25].

The emergence of potassium-competitive acid blockers, particularly vonoprazan, represents one of the most significant recent advances in *H. pylori* treatment. Unlike proton pump inhibitors, PCABs provide rapid, stable, and profound acid suppression, which enhances antibiotic activity and bacterial susceptibility [17,18]. Several studies have demonstrated that vonoprazan-based regimens achieve higher eradication rates compared to conventional PPI-based therapies, including in patients with clarithromycin-resistant strains. This has led to the perception of PCABs as a potential "game changer" in eradication therapy [26]. However, questions remain regarding their long-term safety, cost-effectiveness, and generalizability beyond regions where they are widely available.

The issue of suboptimal treatment selection is further complicated by the risk of both overtreatment and undertreatment. On one hand, the use of broad-spectrum or multiple antibiotics in empiric regimens may contribute to further resistance development and disrupt the gut microbiome [27]. On the other, inadequate initial therapy increases the likelihood of treatment failure, necessitating multiple subsequent regimens and cumulative antibiotic exposure. This underscores the importance of optimizing first-line therapy rather than relying on sequential rescue strategies.

An additional layer of complexity is introduced by regional variability in resistance patterns. Evidence consistently shows that treatment success is closely linked

to local epidemiology, yet in many settings, up-to-date resistance data are lacking or not routinely integrated into clinical decision-making [21]. This gap limits the effectiveness of guideline-based recommendations and reinforces the need for more region-specific treatment algorithms.

Taken together, these findings suggest that no single strategy can be universally applied to all patients. Instead, the optimal approach to *H. pylori* eradication should balance efficacy, resistance patterns, patient adherence, and resource availability. Bismuth quadruple therapy and vonoprazan-based regimens currently offer the most reliable empiric options, while tailored therapy represents the ideal but not yet universally feasible standard [22,23,28].

The future of *H. pylori* management is likely to depend on the integration of resistance surveillance, improved diagnostic tools, and pharmacological innovation. Moving away from uniform treatment models toward more adaptive and individualized strategies appears essential to sustain high eradication rates in the era of increasing antibiotic resistance.

CONCLUSION

The management of *Helicobacter pylori* infection has entered a phase where empiric, uniform regimens are no longer sufficient to ensure reliable eradication. Declining efficacy of standard therapies, driven by antibiotic resistance, necessitates a transition toward optimized and resistance-aware strategies. Bismuth-based quadruple therapy and vonoprazan-containing regimens currently provide the most consistent outcomes in first-line treatment, while susceptibility-guided approaches represent the most effective, albeit not universally accessible, option. Achieving durable eradication will depend on integrating local resistance patterns, improving treatment selection, and minimizing unnecessary antibiotic exposure.

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