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# Antibiotic Resistance of *Helicobacter pylori*: Mechanisms and Clinical Implications

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## ABSTRACT

*Helicobacter pylori* is a pathogenic bacterium associated with various gastrointestinal diseases, including chronic gastritis, peptic ulcers, mucosa-associated lymphoid tissue lymphoma, and gastric cancer. The increasing rates of *H. pylori* antibiotic resistance and the emergence of multidrug-resistant strains pose significant challenges to its treatment. This comprehensive review explores the mechanisms underlying the resistance of *H. pylori* to commonly used antibiotics and the clinical implications of antibiotic resistance. Additionally, potential strategies for overcoming antibiotic resistance are discussed. These approaches aim to improve the treatment outcomes of *H. pylori* infections while minimizing the development of antibiotic resistance. The continuous evolution of treatment perspectives and ongoing research in this field are crucial for effectively combating this challenging infection.

**Keywords:** *Helicobacter pylori*; Antibiotic Resistance; Multidrug Resistance; Antimicrobial Stewardship

## INTRODUCTION

*Helicobacter pylori* is a Gram-negative bacterium that colonizes and persists in the stomach.[1] It can be transmitted from an infected person to an uninfected person by direct contact via an oral-oral, fecal-oral, or both routes.[2,3] Most people become infected during their childhood, and parents and siblings appear to play a significant role in pathogen transmission.[3,4] Once infected, *H. pylori* causes lifelong chronic progressive gastric inflammation, which can lead to clinical complications in up to 10% of infected individuals.[1,5] The major clinical complications include peptic ulcer disease, chronic gastritis, gastric cancer, and mucosa-associated lymphoid tissue lymphoma.[1,2,5-7] The prevalence of *H. pylori* infection varies widely according to geographic area, age, and socioeconomic status.[6] Although the prevalence of *H. pylori* is decreasing due to improving hygiene and standard of living, it remains high, particularly in the Eastern Asian countries.[6,8-10]

A combination of two to three antibiotics (from a few antibiotics such as amoxicillin, clarithromycin, metronidazole, tetracycline, levofloxacin, and rifabutin) and an acid-suppressive agent with or without bismuth are used to eradicate *H. pylori*.[11-13] However, the successful eradication rate of *H. pylori* has decreased in the past decades, in parallel with

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increasing antibiotic resistance.[14-20] Antibiotic resistance of *H. pylori* is particularly important because this is one of the most common causes of bacterial infections worldwide, affecting millions of people every year.[1,6] Additionally, overuse or inappropriate use of antibiotics can contribute to the development of antimicrobial resistance in *H. pylori* and other bacteria, which can have serious public health implications.[21-23] Recently, the World Health Organization listed *H. pylori* as a serious threat to human health for their resistance against most available treatment regimens.[24]

The molecular mechanisms underlying antibiotic resistance in *H. pylori* infection are diverse and complex. Several mechanisms have been proposed to drive the antibiotic resistance of *H. pylori*, including genetic mutations in the bacterium itself and physiological changes that can upregulate efflux pump expression in bacterial cells.[25-30] Cellular adaptation associated with biofilm or coccoid formation, which protects drug penetration into bacterial cells, is another potential resistance mechanism.[31,32] Many of these resistance mechanisms can work in concert to confer multidrug resistance (MDR) in *H. pylori*, making eradication increasingly challenging and highlighting the need for new therapeutic strategies. In this review, the mechanism of resistance of *H. pylori* to commonly used antibiotics and their clinical implications are explored.

## MOLECULAR MECHANISMS OF ANTIBIOTIC RESISTANCE

### Mechanism of single-drug resistance

Single-drug resistance refers to a situation in which a microorganism, such as a bacterium, virus, or fungus, is resistant to only one type of drug while remaining susceptible to other drugs. Although the eradication regimen for *H. pylori* consists of a combination of antibiotics, resistance to a single antibiotic agent could result in eradication failure.[33] Antibiotic resistance in *H. pylori* is mainly from de novo genetic mutations that disrupt the activity of antibiotics by either altering the drug target or inhibiting drug activation within cells (**Table 1** and **Fig. 1**).[7] With advances in next-generation sequencing (NGS), many mutations have been observed in resistant clinical isolates.[25,26,34,35] However, the relative contribution of each mutation to phenotypic resistance and the effect of combinations of mutations remain unclear.[36]

#### *Beta-lactams*

Amoxicillin is widely used for *H. pylori* eradication in combination with acid-suppressive agents to improve drug stability and efficacy. After administration, amoxicillin is well absorbed into bloodstream and then released into the gastric juice.[37] In a favorable environment with acid-suppressive agents, amoxicillin exerts its antimicrobial effect by binding to penicillin-binding proteins (PBPs).[38,39] Binding of amoxicillin to PBPs inhibits

**Table 1.** Mechanisms of antibiotic resistance in *H. pylori*

| Antibiotics | Antibiotic resistance mechanism | Associated gene or sequence |
|---|---|---|
| Amoxicillin | Mutational change of penicillin-binding protein | *pbp1A*, *pbp2*, *pbp3*, *pbp4* |
| | Production of beta-lactamase | |
| | Outer membrane protein mutations causing decreased membrane permeability | *hefC*, *hopC*, *hofH* |
| Clarithromycin | Point mutations in 23S rRNA | 23S rRNA |
| | Increased antibiotic efflux mediated by efflux pump systems | *rplV22*, *infB* |
| Levofloxacin | Point mutations in quinolone resistance determination region of DNA gyrase gene | *gyrA*, *gyrB* |
| Metronidazole | Mutations causing reduced or abolished nitroreductase activity | *rdxA*, *frxA* |
| Tetracycline | Mutations in 16S rRNA | 16S rRNA |
| Rifabutin | Point mutations in rifampicin-resistance determining region of RNA polymerase gene | *rpoB* |


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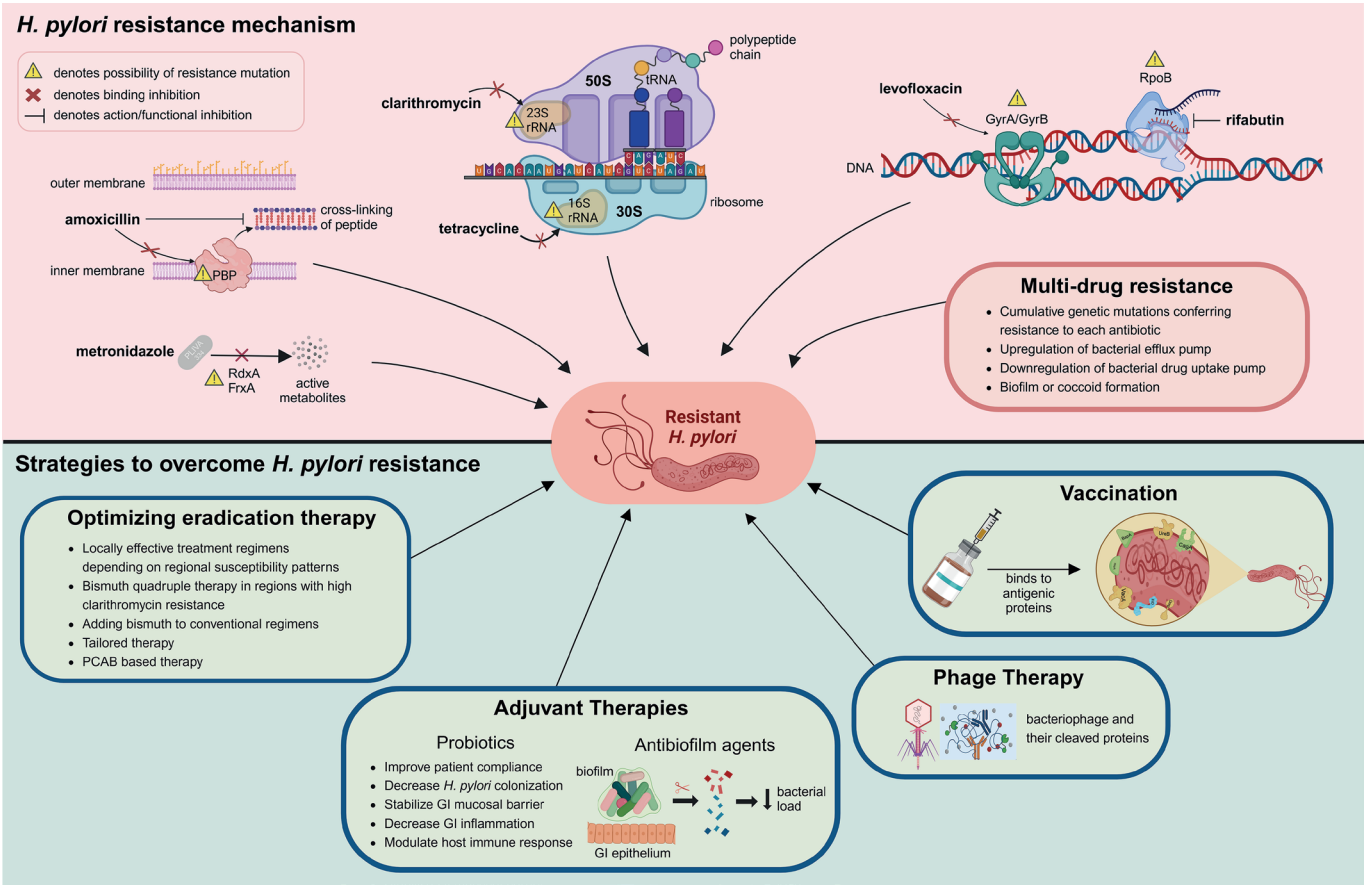


**Fig. 1.** Overview of molecular mechanism of antibiotic resistance in *H. pylori* and strategies to overcome this resistance. This image was created with BioRender.com.
FrxA = NAD(P)H flavin oxidoreductase, GI = gastrointestinal, GyrA = DNA gyrase subunit A, GyrB = DNA gyrase subunit B, PBP = penicillin-binding protein, PCAB = potassium-competitive acid blocker, RdxA = oxygen-insensitive NAD(P)H nitroreductase, RpoB = β-subunit of DNA-dependent RNA polymerase, rRNA = ribosomal RNA, tRNA = transfer RNA.

the synthesis of peptidoglycan, a major component of bacterial cell walls, resulting in cell wall lysis in replicating bacteria.[39,40] Amoxicillin generally shows a low antibiotic resistance rate.[41-44] In *H. pylori*, amoxicillin resistance is mainly due to mutational changes in PBP1A.[45-48] Mutations in other PBPs (PBP2 and PBP 3) have also reported, and multiple mutations in all three isotypes PBP1, PBP2 and PBP3 was found to confer high level of amoxicillin resistance when compared to the amoxicillin susceptible strain.[49] Beta-lactamase activity, which can hydrolyze amoxicillin to attenuate the optimum concentration needed to elicit bactericidal effect, was also found in *H. pylori*.[40,50] Furthermore, amoxicillin resistance may be contributed by mutations in *hefC*, *hopC*, and *hofH*, which are likely associated with changes in the composition of the outer membrane and membrane permeability of *H. pylori*.[51-53]

### *Macrolides*

Clarithromycin is widely used in the frontline regimen to eradicate *H. pylori*. Clarithromycin has pharmacokinetic advantages over other macrolides, including increased oral bioavailability, higher plasma concentration, and longer elimination half-life.[54] Concomitant administration with acid-suppressive agents also increases its stability in acidic environments.[55] Clarithromycin exerts antimicrobial effects by binding to the peptidyl transferase loop of domain V in the 23S ribosomal RNA (rRNA) in the bacterial ribosomal subunit 50S.


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Mutations in domain V of the 23S rRNA gene of *H. pylori*, A2142G/C and A2143G, can result in reduced binding affinity of the antibiotic agent, making it less effective at inhibiting bacterial growth.[56,57] Other point mutations are also reported in the 23S rRNA in *H. pylori* isolates.[25-27,58] In addition, studies using experimentally induced resistant phenotype for clarithromycin found that mutations in *rpl22* and *infB* genes had synergistic effects with mutations in the 23S rRNA genes, resulting in higher minimum inhibitory concentration of clarithromycin.[34,35] Another relevant mechanism for clarithromycin resistance is attributed to the efflux pump system.[29,59] However, the role of novel mutations and specific function of efflux pump system in the development of clarithromycin resistance in clinical isolates should be further clarified.

### *Fluoroquinolones*

Among the fluoroquinolones, levofloxacin, moxifloxacin, and sitafloxacin have been used for *H. pylori* eradication therapy. Due to high resistance rate, fluoroquinolones are generally used in rescue treatment after initial eradication failure.[11,60,61] Fluoroquinolones act on microbes by inhibiting bacterial topoisomerase II (DNA gyrase) and topoisomerase IV enzymes involved in bacterial synthesis of nucleic acid, a step proceeding cell division and proliferation.[28] The most common mechanism of fluoroquinolone resistance in *H. pylori* is due to a specific mutation in one or more of *gyrA* and *gyrB* genes.[62] The region where mutations arise in these genes is a short DNA sequence known as the quinolone resistance-determining region (QRDR).[63,64] Fluoroquinolone resistance of *H. pylori* is mainly due to point mutations of codon position 87 and 91 in the QRDR of *gyrA*.[65-67] These few mutations associated with most cases of phenotypic resistance indicate that molecular testing for levofloxacin can be a reliable substitute for culture and antimicrobial susceptibility testing. Mutations present outside the QRDR region of *gyrA* or in the QRDR region of *gyrB* have also been reported to be associated with levofloxacin resistance; however, the impact of these mutations requires further investigation.[26,27,58,66]

### *Nitroimidazole*

Among the nitroimidazoles, metronidazole is frequently used to eradicate *H. pylori* infections. Metronidazole is actively released into gastric juice after oral ingestion, with the acidic condition in the stomach rarely affecting its antimicrobial activity.[68] Metronidazole is a prodrug that needs to be activated by intracellular reduction of the nitro group attached to the imidazole ring.[69] Reductive activation of metronidazole causes imidazole fragmentation and nitro-anion free radicals which are cytotoxic.[69,70] The reduction of metronidazole is mainly mediated by oxygen-insensitive NAD(P)H nitroreductase (RdxA), NAD(P)H flavin oxidoreductase (FrxA), and ferredoxin-like enzymes (FdxB) in *H. pylori*. Metronidazole resistance in *H. pylori* is primarily due to decreased drug activation mediated by mutations in *RdxA* gene which encodes an oxygen-insensitive NAD(P)H nitroreductase.[70-76] Mutations involving the *FrxA* gene were also reported.[35,74,77] However, metronidazole resistance was observed in *H. pylori* isolates without the loss of functional RdxA and FrxA, suggesting that other factors are involved in metronidazole resistance.[72,78-81] Other putative mechanisms of metronidazole resistance in *H. pylori* include mutations in FdxB, ferric uptake regulator (Fur), and enhancement of efflux pump (HefA) protein.[72,82-84]

### *Tetracyclines*

Tetracycline is stable in gastric pH and acts as a topical agent on the surface of the gastric mucosa against *H. pylori*.[85] At the bacterial cytoplasm, tetracycline binds to bacterial ribosomes and interacts with a highly conserved 16S rRNA target in the 30S ribosomal subunit, arresting translation and protein synthesis.[86] Resistance mechanism of *H. pylori*


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against tetracycline is not widely studied because tetracycline resistance is not common in clinical isolates.[14,41,44,87] Among various mechanisms of tetracycline resistance, the major resistance mechanisms are related to mutations in the 16S rRNA genes.[88-90] However, tetracycline resistance without mutation in the 16S rRNA gene has been reported, suggesting that other mechanisms, such as efflux, are associated with tetracycline resistance.[84,91]

*Rifamycins*

Rifamycins are transcriptional inhibitors that specifically inhibit the activity of bacterial transcription by binding to RNA polymerase, mostly β-subunit encoded by the *rpoB* gene.[92] Among the rifamycins, rifabutin has better pharmacokinetics than rifampicin and is used for *H. pylori* eradication. Rifabutin is chemically stable at a wide range of pH values and is not inactivated by gastric acid.[93] The resistance rate of *H. pylori* against rifabutin is low, and most rifabutin-resistant strains were isolated after treatment failure.[94-96] In *H. pylori*, the molecular mechanism driving rifabutin resistance is at least one point mutation in the rifampicin resistance-determining region of the *rpoB* gene.[27,97-100] However, a previous study reported that rifabutin-resistant strains were successfully eradicated with rifabutin-based triple therapy.[101] Correlations between *rpoB* gene mutation status, phenotypic resistance, and treatment outcome need further clarification.

## MDR in *H. pylori*

The presence of *H. pylori* strains with MDR profiles poses a significant challenge for *H. pylori* eradication and complicates the management of *H. pylori*-related diseases. The MDR profile of *H. pylori* is expressed as the cumulative result of genetic mutations conferring resistance to each antibiotic agent.[7] Other putative mechanisms of *H. pylori* MDR include physiologic changes in bacterial cells (upregulation of efflux pump systems or downregulation of drug uptake proteins in the outer membrane of bacteria) and cellular adaptation properties (biofilm or coccoid formation).[59,102-105]

Bacterial biofilms are complex microbiological ecosystems where adherent aggregates of microorganisms surround themselves in multidimensional extracellular polymeric substances.[106,107] Biofilms are often associated with chronic infectious diseases as they protect the bacteria from unfavorable environments, antimicrobial exposure, and host immune system.[31,108] Biofilm formation in *H. pylori* has been observed both in vitro (environmental water body) and in vivo (gastric mucosa).[109,110] The presence of biofilm was shown to be associated with decreased susceptibility to antibiotics in *H. pylori*.[31] Previous studies showed that mutations in several genes coding for flagellar protein, outer membrane protein, cytotoxin-associated gene pathogenicity island protein, or efflux pumps were responsible for biofilm formation in *H. pylori*, which can further potentiate antibiotic resistance.[84,111,112] However, the precise mechanisms for *H. pylori* biofilm formation have yet to be determined. In addition, the clinical implications of biofilm formation on the development of antibiotic resistance in *H. pylori* and treatment outcomes should be further investigated.

An exceptional feature of *H. pylori* is the formation of a viable but non-culturable coccoid morphology. In *H. pylori*, the coccoid form becomes dominant when bacteria are exposed to environmental stress conditions, such as starvation, prolonged culture, and exposure to antibiotics.[113,114] It has been reported that this dormant state of *H. pylori* induces ultrastructural modifications in the cell membrane and metabolic pathways that contribute to antibiotic resistance.[24,107] However, the clinical relevance of coccoid formation in the development of MDR profile and treatment outcome of *H. pylori* is not fully understood.


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## Heteroresistance

Heteroresistance refers to a phenomenon where subpopulations of bacteria have different antibiotic susceptibility profiles.[115] Heteroresistance in *H. pylori* has been reported in several studies in which both susceptible and resistant bacterial strains were isolated either from the same biopsy site (intraniche) or from different sites (interniche).[87,115-122] Heteroresistance can be developed through evolutionary change in a single strain or mixed infection of multiple bacterial strains.[7] Previous studies reported that heteroresistant *H. pylori* strains had similar fingerprinting patterns, suggesting that the presence of the same strain with mixed susceptible and resistant phenotype, rather than coinfection of different strains, is associated with the development of *H. pylori* heteroresistance.[117-121] The possibility of heteroresistance should be considered during antimicrobial susceptibility testing and eradication therapy for *H. pylori* infection since underestimation of the presence of antibiotic-resistant strain may lead to treatment failure. To address this issue, multiple biopsies from different sites in the stomach or multiple bacterial colonies from the same sample should be obtained when evaluating the antimicrobial susceptibility of *H. pylori*.

## Antimicrobial susceptibility testing

With increasing antibiotic resistance, it is imperative to develop individualized therapeutic approaches based on the results of antimicrobial susceptibility tests. Common methods for antimicrobial susceptibility testing include culture-based antimicrobial susceptibility testing and molecular detection. Bacterial culture is necessary for the use of conventional antimicrobial susceptibility tests, such as E-test, disk diffusion method, and agar dilution method.[39,42,123] However, *H. pylori* culture requires specific conditions, is time-consuming, and is affected by several factors, such as transport conditions and the time interval between specimen collection and inoculation, limiting its availability in clinical practice.

Molecular methods are also used to assess antimicrobial susceptibility. Since the resistance of *H. pylori* to clarithromycin, fluoroquinolones, and tetracycline is mainly driven by specific point mutations in a small region of the responsible gene, molecular methods can be utilized for antimicrobial susceptibility testing. Polymerase chain reaction (PCR) was used to assess antibiotic resistance by detecting resistance-associated mutations. Similarly, PCR-restriction fragment length polymorphism, real-time PCR, multiplex PCR, and droplet digital PCR have been widely used to determine antibiotic resistance in *H. pylori*.[124-129] Currently, several commercial kits are available to detect clarithromycin resistance, levofloxacin resistance, or both.[130-135] Another diagnostic tool using loop-mediated isothermal amplification methods, combined PCR and quenching probe method, and single cell-based antimicrobial susceptibility test Ramanometry has been introduced.[136-139]

Compared to conventional methods, molecular detection methods have the advantages of high sensitivity, specificity, and reproducibility, and disadvantages such as high cost. Furthermore, as molecular detection methods target specific gene loci, antibiotic resistance caused by other mutations cannot be detected, leading to false-negative results.[140] In addition, as metronidazole has complex resistance mechanisms and the presence of metronidazole resistance does not necessarily lead to treatment failure, the role of molecular detection of metronidazole resistance is limited.

Recent advances in high-throughput molecular detection technology, including NGS and metagenomic analysis, have enabled the detection of *H. pylori* infection and antibiotic resistance.[25-27,34] While NGS provides comprehensive information, applying NGS results to


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clinical practice requires additional knowledge about the correlation between NGS results and phenotypic resistance as well as treatment outcomes.[141] In addition, cost-effectiveness and availability should be considered for the clinical application of NGS to predict antibiotic susceptibility profiles.

## CILNICAL IMPLICATION AND FUTURE DIRECTIONS

The main clinical implication of antibiotic resistance in *H. pylori* is significantly compromised eradication therapy efficacy. It is well-known that the eradication success rate using clarithromycin-based regimens is markedly decreased in the presence of clarithromycin resistance.[33,142,143] Accordingly, clarithromycin containing standard triple therapy is recommended only in areas with a clarithromycin resistance rate of less than 15%.[11] On the other hand, a lower decrease in eradication rates has been observed for metronidazole, and successful eradication was reported using bismuth quadruple therapy, especially with higher metronidazole dose, even in the presence of metronidazole resistance.[33,142,143] Multiple different mechanisms leading to metronidazole resistance and diversity of identified mutations may explain the relatively poor correlation between phenotypic resistance against metronidazole and treatment outcome. The increasing number of MDR *H. pylori* strains has made eradication therapy more challenging. Given that the first-line treatment regimen is usually selected empirically rather than based on antimicrobial susceptibility testing, failure of initial eradication therapy is another important cause of the emergence of MDR *H. pylori* strains.

The development of antibiotic resistance in *H. pylori* has reduced available treatment options. Eradication failure necessitates additional rounds of therapy, including alternative antibiotic combinations. With the decline in the eradication rates of standard therapies, physicians face challenges in selecting effective alternatives. However, these options are not always effective, involve higher pill burdens, and can lead to more side effects. There have been some important changes to expert recommendations for *H. pylori* eradication: more frequent use of bismuth-containing quadruple therapy as a first-line treatment instead of clarithromycin-based triple therapy is recommended.[144] The limited arsenal of effective treatments against antibiotic-resistant *H. pylori* strains underscores the need for novel treatment strategies, including non-antibiotic approaches, to address this growing problem (**Fig. 1**).

### Optimizing eradication therapy

Current treatment regimens for *H. pylori* eradication are derived from empirical approaches developed by gastroenterologists over the past few decades. A significant decrease in the eradication rate worldwide, along with an increasing trend of *H. pylori* antibiotic resistances warrants more specific approach to *H. pylori* eradication therapy, utilizing antimicrobial stewardship.[145] Given that antibiotic resistance patterns differ according to geographic regions, it is recommended to use treatment regimens that are locally effective according to regional susceptibility patterns.[87,145,146] However, many regions lack reliable data on the prevalence and characteristics of antibiotic resistance in local populations to guide the selection of empirical eradication therapy. Currently, bismuth quadruple therapy is recommended in regions with high antibiotic resistance to both clarithromycin and metronidazole.[11] In addition, adding bismuth to some triple regimens and prolonging the treatment duration to 14 days can increase eradication rates up to 30% or more, even in the presence of antibiotic resistance in some strains.[13] Recent meta-analysis also showed that bismuth supplements as the first-line regimen showed better eradication rate compared to non-bismuth containing regimens.[147]


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### *Tailored therapy*

With increasing resistance rates and MDR *H. pylori* strains, the role of antimicrobial susceptibility testing and subsequent individualized antibiotic treatment has been emphasized.[11] Tailored therapy, in which antibiotics are chosen based on the antimicrobial susceptibility profile, is an ideal therapeutic option to improve the efficacy of *H. pylori* eradication therapy while minimizing unnecessary prescription of antibiotics. Studies have reported better eradication success rates using tailored therapy than empiric therapy, especially when antimicrobial susceptibility testing was performed before treatment.[148-151] However, the benefit of tailored therapy has not been demonstrated in clinical trials comparing tailored therapy with empirical quadruple regimens as a first-line treatment or tailored therapy after previous treatment failure.[151-153] This suggests that the benefit of tailored therapy is not obvious when the empirical regimen is highly effective for *H. pylori* eradication. In addition, the limited availability of *H. pylori* cultures and antimicrobial susceptibility testing has made this approach difficult. More evidence is required to establish the generalized use of tailored therapy for *H. pylori* eradication.

### *Acid suppression with potassium-competitive acid blocker*

To increase eradication success, antibiotic resistance patterns and patient characteristics, such as compliance and cytochrome P450 2C19 genetic polymorphisms, should be considered. Potassium-competitive acid blocker provides fast and long-lasting acid suppression and is recently used for *H. pylori* eradication therapy in combination with various antibiotics.[154-157] Vonoprazan-based triple therapy showed higher eradication rate compared to proton pump inhibitor (PPI), especially in the subpopulation with clarithromycin resistance, potentially overcoming clarithromycin resistance.[158,159] Recent meta-analysis of randomized controlled trials also showed that vonoprazan-containing regimens achieved a higher eradication success rate compared to PPI-based regimens.[160] In line with this, a Japanese guideline recommends vonoprazan-based triple therapy or PPI-based triple therapy as the first-line treatment for *H. pylori* eradication.[161] Vonoprazan-based dual therapy consisting amoxicillin may be another treatment option while minimizing unnecessary antibiotic use; however, the dosage and duration of dual therapy need to be further determined.[159,162,163] Notably, most studies on vonoprazan-based regimens were conducted in Japan, and further studies are needed to confirm these promising results in different regions.[164,165]

## Adjuvant therapies

Adjuvant therapies aim to enhance the efficacy of antibiotic treatment either by overcoming the bacterial mechanisms of antibiotic resistance or by modifying the host response. These include the use of probiotics and anti-biofilm agents. As supplementary to conventional eradication therapy, probiotics can reduce gastrointestinal adverse events and thus improve patient compliance.[166,167] In a recent meta-analysis, it has been found that most probiotics added to triple therapy provided better treatment outcomes.[167] The potential mechanisms of probiotic action against *H. pylori* include direct and indirect inhibitory effects against *H. pylori* colonization, stabilization of gastric mucosal protective barrier and reduction of gastric mucosal inflammation, and modulation of host immune response to the infection.[168,169] Probiotic supplementation also reduced antibiotic-induced alteration of gut microbiota and helped the restoration of dysbiosis caused by eradication therapy.[170,171] However, further research is needed to better understand the role and mechanism of action of probiotics in *H. pylori* eradication therapy, as the species and strains, dose, and duration of investigated probiotics are heterogeneous.

An alternative therapeutic approach is to target and disrupt bacterial biofilms. Previous studies have shown that the use of N-acetylcysteine (NAC) reduces bacterial load and


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enhances eradication rate.[172,173] The effect of NAC was also found in a clinical trial, showing better clearance of *H. pylori* in patients treated with NAC before antibiotic treatment.[174] However, the exact mechanism underlying the reported therapeutic effect of NAC in the disruption of biofilms and overcoming *H. pylori* antibiotic resistance has yet to be defined. In a recent study, the combination of antibiotics and rhamnolipid, a glycolipid biosurfactant capable of disrupting biofilm and potentially inhibiting bacterial adhesion, was reported to effectively inhibit biofilm formation in vitro.[175] Although the results are promising, the roles of rhamnolipid and anti-biofilm compounds need further investigation in vitro and in vivo.

### Phage therapy

The rise in antibiotic resistance has increased interest in studying bacteriophages, particularly lytic bacteriophages. Phage therapy has various potential advantages over antibiotics because phages and their cleaved proteins are highly specific, affecting the target strain but not the microbiome.[176] Furthermore, phages exclusively replicate at the site of infection, and no secondary effects have been reported.[177] Few studies have investigated the presence of phages in *H. pylori* strains, including prophages and lytic phages.[178-181] However, the exact function and properties of phages to be used therapeutically are yet to be determined. Although phage therapy appears to be a promising approach for future treatment options for *H. pylori* infection, further investigations are required to improve our understanding of phage and *H. pylori* interactions, which are still in the exploratory stage.

### Vaccination

Developing an effective vaccine against *H. pylori* could be a game-changer in preventing infections and reducing the reliance on antibiotic treatment. Several vaccine candidates are currently under investigation, aiming to elicit a protective immune response against *H. pylori*; however, few have shown a protective effect.[182-194] In a randomized, double-blind, placebo-controlled, phase 3 clinical trial, three doses of oral recombinant *H pylori* vaccine were introduced in children and were followed up for the next three years.[194] The vaccine was effective against *H. pylori* in 71.8% of subjects without any serious adverse events. However, the authors suggested a longer follow-up period to confirm protective effects against *H. pylori*-associated diseases. The search for an effective vaccine is in the exploratory stage and needs further investigations, considering better design of vaccine strategies, optimal combination of antigens, selection of suitable adjuvants, and proper delivery carriers. Additionally, given that *H. pylori* infection usually occurs in early childhood, the optimal timing of vaccination and subsequent follow-up strategies to ensure the protective effects of vaccination should be further elucidated.

## CONCLUSIONS

The increasing rates of *H. pylori* antibiotic resistance and MDR strains pose significant challenges for eradication therapy. Substantial progress has been made in understanding the fundamental mechanisms underlying antibiotic resistance in *H. pylori*, including genetic mutations, efflux pump systems, and biofilm formation. To overcome antibiotic resistance of *H. pylori*, antibiotic stewardship and tailored therapy based on antimicrobial susceptibility testing are recommended. Strategies such as adjuvant treatment, phage therapy, and vaccine development are currently being explored. In addition to optimizing currently available treatment options, continuous monitoring of local resistance profiles, ongoing research, and the development of innovative therapies are required to effectively manage antibiotic-resistant *H. pylori* infections and associated gastrointestinal diseases.


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