



Review Article

Minimizing the Impact of Antibiotic Resistance on *Helicobacter pylori* Eradication: From Mechanisms to Clinical Application



Xiaoying Zhou^{1,2#}, Zizhuang Wang^{1,2#}, Hui Yang^{1,2}, Yan Wang^{1,2}, Colm A. O'Morain^{3,4*}  and Harry Hua-Xiang Xia^{5*} 

¹Department of Gastroenterology, the First Affiliated Hospital with Nanjing Medical University, Nanjing, Jiangsu, China; ²First Clinical Medical College of Nanjing Medical University, Nanjing, Jiangsu, China; ³Beacon Hospital Research Institute, Beacon Hospital, Dublin, Ireland; ⁴School of Medicine, Trinity College Dublin, Dublin, Ireland; ⁵Department of Gastroenterology, the First Affiliated Hospital of Guangdong Pharmaceutical University, Guangzhou, Guangdong, China

[#]These authors contributed equally to this work.

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Abstract

Rising resistance in *Helicobacter pylori* to metronidazole, clarithromycin, and fluoroquinolones has significantly reduced eradication efficacy. This narrative review explores evidence-based strategies that minimize the impact of antibiotic resistance. Current practical approaches include empirical therapy (EMT), in which regimens are selected without individual susceptibility testing based on local or regional resistance patterns, previous antibiotic exposure, guideline recommendations, and expected effectiveness, and susceptibility-guided therapy (SGT), which avoids antibiotics to which the infecting strain is resistant. EMT does not simply exclude every antibiotic with a high resistance prevalence because regimen-level efficacy may remain high despite resistance to one component. When susceptibility testing is unavailable, optimized 14-day bismuth quadruple therapy is a guideline-preferred empirical regimen and can remain effective despite metronidazole resistance with adequate dosing and treatment duration. Rifabutin-based triple therapy provides an additional empirical or rescue option for selected patients without penicillin allergy. SGT is not universally superior to well-selected EMT, but may improve eradication rates in selected populations, particularly in settings with high clarithromycin resistance or where rapid molecular testing is available. However, susceptibility testing may be time-consuming, costly, and limited to only a few antibiotics. Emerging approaches include potassium-competitive acid blockers (PCABs), antimicrobial stewardship, probiotics, N-acetylcysteine, nanomaterial-based drug delivery, and vaccination. Among these, vonoprazan-based regimens are the most clinically mature. Vonoprazan-amoxicillin dual therapy can reduce exposure to resistance-prone antibiotics, although its use should reflect regional effectiveness, availability, and cost. Other non-antibiotic approaches remain investigational. In conclusion, management should move from undifferentiated empirical regimen selection toward risk-stratified precision treatment. Locally validated EMT remains appropriate when susceptibility testing is unavailable, whereas SGT should be prioritized after treatment failure or in patients at high risk of resistance. Rifabutin-based and vonoprazan-amoxicillin therapies provide additional options according to treatment history, penicillin allergy, regional evidence, and accessibility.

Keywords: *Helicobacter pylori*; antibiotic resistance; eradication therapy; clarithromycin resistance; vonoprazan; potassium-competitive acid blocker; susceptibility-guided therapy.

***Correspondence to:** Colm A. O'Morain, Beacon Hospital Research Institute, Beacon Hospital, Dublin 18, D18 AK68, Ireland; School of Medicine, Trinity College Dublin, Dublin 2, D02 PN40, Ireland. ORCID: <https://orcid.org/0000-0002-1847-6782>. Tel: +353-87-2581282, E-mail: colmomorain@gmail.com; Harry Hua-Xiang Xia, Department of Gastroenterology, The First Affiliated Hospital of Guangdong Pharmaceutical University, Guangzhou, Guangdong 510080, China. ORCID: <https://orcid.org/0000-0002-7952-9200>. Tel: +86-020-61321457, E-mail: xiaharry@hotmail.com

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Introduction

Helicobacter pylori infection, present in approximately 50% of the global population,¹ is a major cause of chronic gastritis, peptic ulcer disease, gastric mucosa-associated lymphoid tissue lymphoma, and gastric cancer.² Over the past three decades, highly effective regimens have been established for the eradication of *H. pylori* infection. Historically, proton pump inhibitor (PPI)-based clarithromycin triple therapy, consisting of a PPI plus clarithromycin and amoxicillin or metronidazole, was widely used as a first-line regimen.² However, increasing clarithromycin resistance has substantially reduced its efficacy, and current guidelines no longer recommend empirical PPI-clarithromycin triple therapy when clarithromycin susceptibility is unknown.^{2,3} Instead, optimized bismuth quadruple therapy (BQT) is recommended as an important empirical first-line option, while rifabutin-based therapy and potassium-competitive acid blocker (PCAB)-amoxicillin dual therapy are additional options in appropriate clinical settings.³ Initially, these regimens achieved eradication rates exceeding 85% in general populations. However, following widespread clinical application, acquired antibiotic resistance has emerged, and the prevalence of clarithromycin and metronidazole resistance in *H. pylori* has increased substantially. From the 1990s to the 2020s, the prevalence of antibiotic resistance in *H. pylori* increased substantially.^{4–9} Specifically, metronidazole resistance is extremely high worldwide, exceeding 50–90% in many regions, and clarithromycin resistance rates surpass 20–30% in many European, Asian, and American populations, having exceeded 40% in some Middle Eastern and East Asian countries by the early 2020s.¹⁰ Levofloxacin resistance has exceeded 15–20% in most countries and 40% in parts of Asia and Africa.¹⁰ Amoxicillin resistance remains low in most regions (typically <2%), making it a reliable antibiotic for eradication. However, substantially higher resistance has been reported in some African settings.^{10,11} Most importantly, antibiotic resistance is the major determinant of eradication efficacy.^{6,12} As early as 1993, Xia *et al.*¹³ reported that *H. pylori* was eradicated by a 1-week triple regimen of colloidal bismuth subcitrate, metronidazole, and tetracycline in 92.3% (60 out of 65) of patients with metronidazole-sensitive strains and in 62.5% (15 out of 24) with metronidazole-resistant strains ($P < 0.001$), indicating that resistance to metronidazole reduces the efficacy of the triple regimen. This finding has been confirmed by later observations.¹⁴ The global rise in metronidazole resistance (42.1%–90.0%) and clarithromycin resistance (22.2%–51.7%) has rendered conventional triple regimens ineffective, resulting in

eradication failure.^{15–17}

The European *Helicobacter* and Microbiota Study Group recommends that first-line *H. pylori* treatment should achieve eradication rates of $\geq 90\%$.² However, achieving this goal in the era of rising antibiotic resistance is challenging. Besides antibiotic resistance, inadequate acid suppression, inappropriate regimen selection, and poor patient compliance also contribute to eradication failure.^{18,19} Therefore, the central argument of this review is that management of *H. pylori* infection should move from undifferentiated empirical regimen selection toward risk-stratified precision treatment. This transition does not mean replacing empirical therapy with susceptibility-guided therapy (SGT) in every patient. Rather, it requires matching the intensity of diagnostic support and regimen selection to the probability and consequences of resistance by integrating local resistance surveillance, previous antibiotic exposure and treatment history, access to susceptibility testing, and the capacity to provide potent and sustained acid suppression.^{2,3}

Current practical antibiotic approaches

Antibiotic resistance in *H. pylori* is primarily attributed to point mutations in specific genes.^{2,20–22} For example, clarithromycin resistance arises primarily from point mutations in the 23S rRNA gene (e.g., A2142G, A2143G), which reduce macrolide binding to the ribosome, and fluoroquinolone resistance results from mutations in the quinolone resistance-determining region of *gyrA* and *gyrB*. Metronidazole resistance is linked to inactivation or reduced expression of nitroreductases (e.g., *rdxA*, *frxA*), impairing conversion of the prodrug into its active form. Amoxicillin resistance is associated with alterations in penicillin-binding proteins and less commonly, changes in outer membrane permeability; although these mechanisms usually confer low-level resistance, they may still reduce eradication rates under suboptimal conditions. In addition, multidrug resistance occurs from efflux pump overexpression or multiple genetic mutations.^{23,24}

Antibiotic resistance in *H. pylori* mediated by genetic mutations is generally persistent and may compromise subsequent eradication regimens.^{3,25,26} Once these mutations are present, the bacteria typically remain resistant even after the antibiotic is stopped. Thus, it is not easy to “restore” susceptibility in *H. pylori*, and current management focuses on selecting effective regimens based on avoiding resistance, not reversing resistance. Empirical therapy (EMT) refers to the selection of an eradication regimen without individual-level susceptibility testing, based on the best available evidence regarding local or regional resistance patterns, previous antibiotic exposure, guideline recommendations, and expected regimen efficacy. EMT does not necessarily require avoidance of every antibiotic with a high resistance prevalence, because some regimens can retain substantial activity despite resistance to an individual component.^{2,3} For example, optimized BQT remains effective in many settings despite high prevalence of metronidazole resistance, particularly when appropriate dosing and treatment duration are used. Accordingly, the key principle of EMT is not simply to avoid all resistance-prone antibiotics, but to select regimens with a sufficiently high probability of achieving successful eradication in the relevant population.^{2,3,14,27} SGT provides a rational means of avoiding antibiotics to which an individual *H. pylori* strain is resistant. However, current evidence does

not demonstrate that SGT is universally superior to EMT. Earlier studies and meta-analyses found no consistent overall advantage of SGT,^{28,29} whereas more recent randomized trials have reported improved eradication rates in selected populations, particularly in settings with high clarithromycin resistance and when molecular susceptibility testing can be performed rapidly, compared with EMT regimens (Table 1).³⁰⁻³³ SGT is recommended by various guidelines.^{2,3,27,34,35}

Rifabutin-based triple therapy represents an additional option for both initial and rescue treatment. The 2024 ACG guideline conditionally suggests 14-day rifabutin triple therapy as an empirical first-line alternative in treatment-naïve patients without penicillin allergy.³ In a phase 3 randomized trial, rifabutin-based triple therapy achieved an eradication rate of 83.8% in treatment-naïve patients, with efficacy unaffected by clarithromycin or metronidazole resistance.³⁶ Rifabutin-based therapy may also be considered in patients with previous eradication failures or limited treatment alternatives, as rifabutin resistance remains relatively uncommon compared with resistance to clarithromycin or fluoroquinolones.³⁷ Two multicenter randomized non-inferiority trials involving patients with at least two previous eradication failures showed that PPI- or vonoprazan-based rifabutin triple therapy was non-inferior to BQT, supporting its use as an alternative rescue regimen.^{37,38} However, rifabutin should not be regarded as a resistance-independent strategy, and its use should be balanced against hematologic toxicity and the potential selection of rifamycin resistance. Non-bismuth concomitant therapy, consisting of a PPI plus clarithromycin, amoxicillin, and metronidazole, remains an option for first-line eradication in selected settings. Its efficacy, however, depends on local clarithromycin and metronidazole resistance and treatment duration. Recent randomized trials support 14-day concomitant therapy, while susceptibility-guided approaches may provide additional benefit in selected high-resistance populations. Therefore, concomitant therapy should be considered according to regional resistance patterns rather than as a universally preferred regimen.^{2,30,39,40}

For SGT, susceptibility testing is required before eradication therapy. At present, culture-based susceptibility testing is the reference standard; however, it is limited by its availability, time-consuming procedures, and technical complexity, restricting its routine use.² Polymerase chain reaction-based susceptibility testing, mainly for clarithromycin and fluoroquinolone resistance mutations from gastric biopsies or stool samples, enables rapid, non-culture-based guidance of therapy.^{22,41-43} In addition, whole-genome sequencing has been applied to provide a comprehensive resistance profile.^{17,44} However, it is expensive and may not be available in resource-limited settings. Moreover, patients need an additional visit to the hospital to start the eradication therapy, which incurs additional costs, including transportation and lost productivity. Therefore, a balance between clinical efficacy and cost also needs to be considered when SGT is implemented.⁴⁵⁻⁴⁷

Many non-antibiotic factors, such as patient compliance, gastric acid suppression, CYP2C19 genotype, bacterial load and distribution, and host immune response, influence the clinical efficacy of antibiotic-containing eradication therapy, and optimization of these factors may improve *H. pylori* eradication rates, including in antibiotic-resistant strains, as described later. Moreover, several non-antibiotic agents possessing anti-*H. pylori*

properties have been recently reported to be effective against both antibiotic-susceptible and antibiotic-resistant strains, when used alone or in combination with antibiotics, as described later. Therefore, SGT may no longer be the only optimal option for overcoming antibiotic resistance in *H. pylori*.

Emerging antibiotic and non-antibiotic approaches

The rising prevalence of antibiotic resistance in *H. pylori* has stimulated interest in searching for approaches that bypass classical antibiotic targets, i.e., emerging antibiotic or non-antibiotic approaches. The underlying mechanisms for these approaches include optimization of the microenvironment to overcome resistance, reduction of the selective pressure for resistance, disruption of bacterial survival, enhancement of localized drug delivery, and vaccination.

Optimizing the microenvironment to overcome resistance

Adequate acid suppression enhances antibiotic stability, promotes bacterial replication, and improves antimicrobial activity, particularly that of amoxicillin, and is therefore an important determinant of eradication efficacy in amoxicillin-containing regimens.^{2,3,19}

PPIs, including omeprazole and esomeprazole, have been widely used to achieve sustained gastric acid suppression in *H. pylori* eradication therapy. However, interindividual variability in PPI metabolism, influenced by CYP2C19 polymorphisms, contributes to inconsistent acid suppression and consequently treatment failure in some patients treated with PPI-based regimens.^{19,35,48} Vonoprazan and other PCABs, including tegoprazan and keverprazan, provide rapid and sustained acid suppression and are less dependent on CYP2C19 metabolism.⁴⁸⁻⁵⁵ Randomized trials and large real-world studies, particularly from East Asia, have demonstrated that vonoprazan-based regimens, used as first-line or rescue treatment, achieve higher eradication rates than PPI-based therapy for *H. pylori*, including in clarithromycin-resistant strains, with improved compliance (Table 2).^{56-68,70-80}

Building on potent acid suppression, vonoprazan-containing dual therapy (vonoprazan plus high-dose amoxicillin) has emerged as a leading antibiotic-minimizing strategy. Recent studies (2022–2024) report intention-to-treat eradication rates of approximately 85–91% and per-protocol rates exceeding 90%, particularly in treatment-naïve patients and in those harboring clarithromycin-resistant *H. pylori*.^{59,60,62} Treatment duration and amoxicillin dose vary across studies, and the optimal vonoprazan-amoxicillin dual regimen remains uncertain. Appropriately extended treatment duration may improve efficacy, while lower-dose amoxicillin regimens have also achieved acceptable eradication rates (Table 2).^{62,67} Moreover, this approach also minimizes the exposure to resistance-prone antibiotics and aligns with principles of antimicrobial stewardship, as described later. Although vonoprazan-based dual, triple, and quadruple regimens have demonstrated high eradication efficacy in Asian populations,^{71,81} their efficacy varies across populations and treatment settings. The US/European phase 3 trial confirmed clinically meaningful efficacy, particularly against clarithromycin-resistant *H. pylori*, although overall eradication rates were lower than those reported in some Asian studies.⁸²⁻⁸⁵ High efficacy in Asia does not establish that PCAB-

Table 1. Comparisons of clinical efficacy between susceptibility-guided therapies (SGT) and empirical therapies (EMT) for *Helicobacter pylori* eradication

First authors	Year	Country	Study design	Antibiotic susceptibility test	Antibiotics tested	Eradication regimen		Eradication rate*(ITT/mITT)	
						SGT	EMT	SGT	EMT
Lee ³⁰	2024	Republic of Korea	RCT	Culture-based susceptibility guided	CLR, MTZ	CLR-s & MTZ-s: LCA, 10D	LCAM, 10D	84.2%	83.3%
						CLR-s & MTZ-r: LCA, 10D			
						CLR-r & MTZ-s: LMA, 10D			
						CLR-r & MTZ-r: LTBM, 10D			
Cho ³¹	2025	Republic of Korea	RCT	DPO-PCR	CLR	CLR-s: LCA, 10D	LCAM, 10D	92.0%*	85.0%*
						CLR-r: LTBM, 10D			
Yu ³²	2025	China	RCT	RT-PCR	CLR	CLR-s: RBAC, 14D	RBAC, 14D	87.4%	82.0%
						CLR-r: RBAF, 14D			
Suo ³³	2025	China	RCT	PCR coupled CYP2C19 polymorphism test	CLR, LEV	CLR-s: EACB, 7D	EACB, 14D	87.7%	80.8%
						LEV-s & CLR-r: EALB, 7D			
						CLR-r & LEV-r: EAMB, 14D			

Eradication rates are based on intention-to-treat analyses, except for Cho *et al.*,³¹ for whom modified intention-to-treat results are reported. Regimen abbreviations were standardized by the authors for consistency across studies. In Lee’s study³⁰: LCA: lansoprazole 30 mg b.i.d + clarithromycin 500 mg b.i.d + amoxicillin 1000 mg b.i.d; LMA: lansoprazole 30 mg b.i.d + metronidazole 500 mg b.i.d + amoxicillin 1000 mg b.i.d; LTBM: lansoprazole 30 mg b.i.d + tetracycline 500 mg q.i.d + bismuth potassium citrate 300 mg q.i.d + metronidazole 500 mg t.i.d; and LCAM: lansoprazole 30 mg b.i.d + clarithromycin 500 mg b.i.d + amoxicillin 1000 mg b.i.d + metronidazole 500 mg b.i.d. In Cho’s study³¹: LCA: lansoprazole 30 mg b.i.d + clarithromycin 500 mg b.i.d + amoxicillin 1000 mg b.i.d; LTBM: lansoprazole 30 mg b.i.d + oxytetracycline 500 mg t.i.d + potassium bismuth citrate 300 mg t.i.d + metronidazole 500 mg q.i.d; and LCAM: lansoprazole 30 mg b.i.d + clarithromycin 500 mg b.i.d + amoxicillin 1000 mg b.i.d + metronidazole 500 mg b.i.d. In Yu’s study³²: RBAC: rabeprazole 10 mg b.i.d + colloidal bismuth 200 mg b.i.d + amoxicillin 1000 mg b.i.d + clarithromycin 500 mg b.i.d; and RBAF: rabeprazole 10 mg b.i.d + colloidal bismuth 200 mg b.i.d + amoxicillin 1000 mg b.i.d + furazolidone 100 mg b.i.d. In Suo’s study³³: EACB: esomeprazole 20 mg b.i.d + amoxicillin 1000 mg b.i.d + clarithromycin 500 mg b.i.d + bismuth potassium citrate 220 mg b.i.d; EALB: esomeprazole 20 mg b.i.d + amoxicillin 1000 mg b.i.d + levofloxacin 500 mg q.d + bismuth potassium citrate 220 mg b.i.d; and EAMB: esomeprazole 20 mg b.i.d + amoxicillin 1000 mg b.i.d + metronidazole 400 mg q.i.d + bismuth potassium citrate 220 mg b.i.d. *, as evaluated in the intention-to-treat (ITT) or modified ITT analysis. mITT, modified intention-to-treat analysis; SGT, susceptibility-guided therapies; EMT, empirical therapies; RCT, randomized controlled trial; DPO-PCR, dual priming oligonucleotide polymerase chain reaction; RT-PCR, real time polymerase chain reaction; CLR, clarithromycin; MTZ, metronidazole; LEV, levofloxacin; CLR-r, clarithromycin-resistant; CLR-s, clarithromycin-sensitive; MTZ-r, metronidazole-resistant; MTZ-s, metronidazole-sensitive; LEV-r, levofloxacin-resistant; LEV-s, levofloxacin-sensitive; D, days.

based regimens are uniformly superior to optimized high-dose PPI regimens. In some Asian studies, high-dose esomeprazole-amoxicillin dual therapy achieved broadly comparable efficacy, suggesting that the incremental benefit of PCABs may depend on the comparator regimen and clinical setting.⁶⁸ Conversely, the European Registry on *H. pylori* Management reported poor efficacy of high-dose PPI-amoxicillin dual therapy, with eradication rates of approximately 51% by modified intention-to-treat analysis and 52% per protocol, indicating that dual-therapy outcomes cannot be directly extrapolated across regions.⁶⁹ PCAB availability remains geographically uneven, with limited routine

availability in Europe, and higher acquisition costs may further limit widespread use. Therefore, region-specific comparative efficacy and cost-effectiveness studies are needed. In addition, the clinical efficacy of another PCAB, tegoprazan, in *H. pylori* eradication also needs to be further confirmed.^{75,86}

Reduction of the selective pressure for resistance

Current guidelines emphasize principles of antimicrobial stewardship in *H. pylori* management, including avoidance of ineffective empiric regimens, consideration of the regional prevalence of antibiotic resistance in *H. pylori* and an individual’s previous antibi-

Table 2. Vonoprazan-based regimens for *Helicobacter pylori* eradication

Regimen	Duration	Eradication rate*	Clinical features	Limitations
Vonoprazan-based dual therapy ^{56-62,64-68,70-72}	7–14 days	approximately 85–96%	Clinically ready; minimizes resistance selection; favorable safety & tolerability	Limited Western data
Vonoprazan-based triple therapy ^{57,63,65,70,71,73-78}	7–14 days	approximately 80–96%	Robust acid suppression; simplified dosing; high patient compliance	Resistance-dependent; higher adverse event risk
Vonoprazan-based quadruple therapy ^{71,78-80}	14 days	approximately 85–95%	Simplified dosing; broad clinical applicability	Limited Western data; higher adverse event risk

* represent the approximate range reported in the cited studies, primarily based on intention-to-treat (ITT) or modified intention-to-treat (mITT) analyses.

otic exposure, and use of SGT to minimize resistance selection and optimize eradication rates.^{2,3} Therefore, empirical regimens should be selected according to local resistance patterns and expected regimen-level efficacy, rather than by simply avoiding any antibiotic with a high population-level resistance rate. For example, dual therapy with vonoprazan and high-dose amoxicillin has been shown to be highly effective in eradicating *H. pylori* infection.⁶²

Disruption of bacterial survival

The density of *H. pylori* colonizing the gastric mucosa not only affects the eradication efficacy but is also associated with acquired antibiotic resistance.⁸⁷ Interventions that reduce bacterial burden or improve treatment tolerance may therefore have adjunctive effects in increasing the efficacy and preventing acquired resistance.⁸⁸ Probiotics and prebiotics have been extensively evaluated for their potential roles in *H. pylori* eradication.⁸⁹⁻⁹¹ It has been reported that the selected *Lactobacillus reuteri* strains inhibited the binding of *H. pylori* to the putative glycolipid receptors asialo-GM1 and sulfatide *in vitro*, suggesting a strain-specific mechanism of competitive interference with bacterial adhesion.⁹² Similarly, *Saccharomyces boulardii* may reduce *H. pylori* adhesion to host cells through neuraminidase activity.⁹³ In addition, *Lactobacillus acidophilus* and *Lactobacillus rhamnosus* have been reported to reduce the bacterial load of *H. pylori*, although probiotic treatment alone did not achieve eradication.⁹⁴ Thus, the proposed mechanisms for adjunctive effects of probiotics include interference with epithelial adhesion, production of bacteriocins or organic acids, and modulation of the gastric and intestinal microbiota.⁹⁰⁻⁹⁴ Probiotics do not directly overcome established antibiotic resistance or replace an optimized eradication regimen. They should therefore be regarded as optional adjuncts for improving treatment tolerance in selected patients rather than as a core resistance-overcoming strategy. More recently, fecal or washed microbiota transplantation has also been explored as an adjunctive approach, potentially boosting eradication rates and reducing antibiotic adverse events, but evidence remains preliminary and insufficient for routine eradication practice.^{95,96}

Formation of *H. pylori* biofilms, which confer up to 1000-fold increased antibiotic tolerance via reduced penetration and slow-growing cell populations, is one of the causes of eradication failure.⁹⁷ It has been reported that N-acetylcysteine (NAC) cleaves disulfide bonds in the exopolysaccharide matrix of *H. pylori* biofilms.⁹⁸ NAC possesses a mucolytic effect, which reduces gastric mucus viscosity, thereby enhancing drug access, and the

capacity to disrupt BabA adhesin-mediated epithelial attachment via thiol-based disulfide reduction at the adhesin binding site.⁹⁹ In a small randomized trial of resistant/refractory *H. pylori* infection, pretreatment with NAC 600 mg once daily for 7 days before culture-guided therapy increased eradication rates from 20% to 65%.¹⁰⁰

Enhancement of localized drug delivery

Nanomaterial-based therapies have emerged in recent years. First, metallic (e.g., silver or bismuth) and metal-oxide (e.g., zinc oxide)-based nanoparticles exhibit direct bactericidal activity against *H. pylori*, including antibiotic-resistant strains, through membrane disruption, reactive oxygen species generation, and inhibition of urease activity.¹⁰¹ *In vitro* and animal studies have demonstrated that bismuth-based nanoparticles possess improved mucosal adhesion and potential dose-sparing effects compared with conventional bismuth salts¹⁰²; however, long-term safety and toxicity remain key barriers to clinical translation. In addition, polymer-based and targeted nano-delivery systems have also been reported.¹⁰³ Polymeric nanoparticles, such as chitosan-based formulations, possess mucoadhesive properties that prolong gastric residence time and enhance local drug concentrations.¹⁰⁴ pH-responsive nanoplateforms that exploit the acidic gastric environment have been developed to achieve localized or targeted antimicrobial activity.¹⁰⁵ Preclinical studies suggest that polymeric, lipid-based, and pH-responsive nanocarriers can increase local antimicrobial concentrations, improve penetration of the gastric mucus barrier, and facilitate controlled drug release. These properties may enhance antibacterial activity while potentially reducing systemic exposure; however, whether these pharmacological advantages translate into improved clinical eradication rates and clinically meaningful reductions in toxicity remains to be established in human studies.^{103,106,107} Well-designed clinical studies are required to confirm this assumption. Recently, nanozyme-based approaches targeting urease activity and photothermal nanoparticles activated by near-infrared light have also been explored.^{108,109} Table 3 summarizes some recently explored emerging nanomaterial-based approaches.^{102,105,109-116} Despite their antibiotic-resistance-independent activity in experimental models, significant technical and practical challenges currently limit the clinical applicability of these strategies.

Vaccination

Theoretically, vaccination is a promising antibiotic-independent strategy to prevent *H. pylori* acquisition. Scientists have been in-

Table 3. Emerging nanomaterial-based approaches

Strategy	Primary mechanism	Development stage	Translational barrier
<i>Nanomaterial-based approaches</i>			
Bismuth nanoparticles ^{102,110}	Urease inhibition; mucosal adhesion; disruption of <i>H. pylori</i> membranes and biofilms	Preclinical–early translational	Safety profiling
Silver / ZnO nanoparticles ^{111,112}	ROS-mediated killing	Preclinical	Cytotoxicity
Chitosan nano-delivery ^{113,114}	Mucoadhesive drug targeting	Preclinical	Manufacturing scale-up
pH-responsive nanoplatforms ^{109,115}	Targeted gastric release	Preclinical	Clinical validation
Nanozymes ^{105,116}	Microenvironment disruption	Preclinical	Delivery feasibility

ROS, reactive oxygen species.

vestigating vaccines, using various whole-cell, subunit, DNA, and live-vector candidates, against *H. pylori* infection for over three decades.¹¹⁷⁻¹¹⁹ However, vaccine development has been disappointing from a clinical-translation perspective.^{120,121} Despite encouraging animal and human studies,^{117,118,120,122} the landmark phase 3 trial by Zeng *et al.*¹²² in children demonstrated 71% efficacy strictly in preventing new *H. pylori* infections over one year; it did not demonstrate therapeutic efficacy in clearing established, chronic infections. So far, neither prophylactic nor therapeutic vaccines have been approved for clinical management of *H. pylori* infection. Major barriers include immune evasion, extensive genetic diversity among strains, uncertain correlates of protection, and the inability to induce durable and effective gastric mucosal immunity.^{119,121} Nevertheless, due to increasing concerns regarding antibiotic resistance, especially the need for *H. pylori* prevention and eradication as the primary gastric cancer prevention strategy, vaccine development is continuing.^{123,124} Following advances in mucosal immunology, novel antigen discovery, next-generation vaccine platforms, and improved adjuvant systems, vaccination should be viewed with cautious optimism; however, it remains a long-term research objective rather than a realistic near-term solution to antibiotic resistance in routine *H. pylori* management.

Future directions

From a translational gastroenterology perspective, future *H. pylori* management depends on bridging mechanistic insights with clinical solutions. The immediate priority is not to replace guideline-based therapy with experimental approaches, but to use proven regimens more judiciously. When susceptibility is unknown, an EMT approach should remain a major first-line option in settings where local antibiotic resistance data are known, while SGT is especially valuable after treatment failure or when the use of resistance-prone antibiotics is contemplated.^{2,3,27} PCAB-based regimens, particularly vonoprazan-amoxicillin dual therapy, are promising antibiotic-minimizing options in Asian populations,^{61,125} but region-specific validation is required in other populations, especially in Europe.¹²⁶ Nano-formulated bismuth and targeted antimicrobial delivery systems have shown improved gastric retention,

site-specific release, and microbiome-sparing antibacterial activity in preclinical models.^{103,107,110} Antibiotic-independent responsive biomaterials and nanozyme-based therapies are also promising, whereas vaccines remain a research priority and microbiome-directed interventions are currently better regarded as adjunctive strategies (Fig. 1).^{107,127,128} However, most of these approaches remain preclinical and require substantial translational and safety validation.^{103,107} Finally, at the population level, improvements in socioeconomic and household conditions, access to safe water and sanitation, food hygiene, and reduction of household crowding are known to be associated with lower *H. pylori* prevalence and thus are biologically plausible measures to reduce transmission of the infection.^{1,10}

Limitations

This review has several limitations. First, as a narrative review, the literature search was non-systematic and may therefore be subject to selection bias. Second, the quality and consistency of the available evidence are heterogeneous, particularly for adjunctive interventions such as probiotics and microbiota-based therapies, as well as for SGT. Third, although randomized trials increasingly support PCAB-based regimens, particularly vonoprazan-amoxicillin dual therapy, much of the available evidence remains derived from East Asian populations, and differences in treatment regimens, antimicrobial resistance patterns, host characteristics, and prescribing practices may limit direct extrapolation to other regions. Fourth, evidence for nanomaterial-based therapies, microbiome-modulating approaches, and vaccination remains predominantly preclinical or early translational, and their long-term safety and clinical efficacy have not been established. Finally, no quantitative synthesis or formal meta-analysis was performed; therefore, the eradication rates reported in this review should be interpreted descriptively rather than as pooled estimates.

Conclusions

The impact of antibiotic resistance on *H. pylori* eradication is best minimized through a risk-stratified hierarchy rather than by choosing between EMT, SGT, and PCAB-based therapy as

From Resistance Challenges to Practical and Translational Solutions

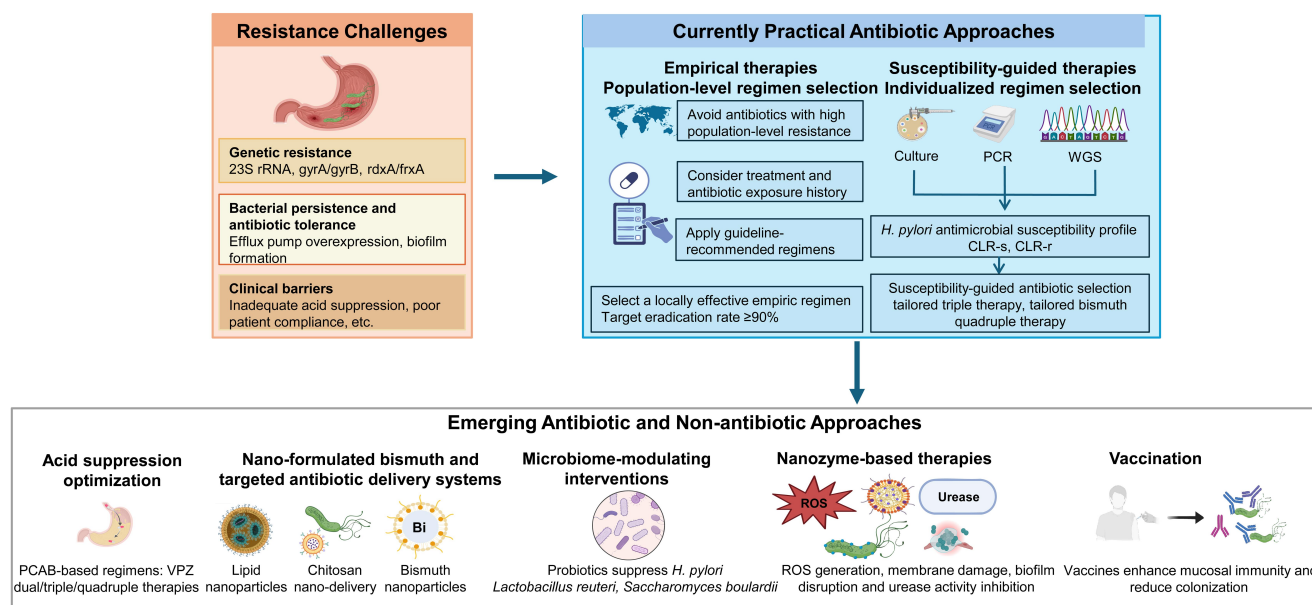


Fig. 1. A translational gastroenterology perspective on antibiotic and non-antibiotic approaches in minimizing the impact of antibiotic resistance in *Helicobacter pylori* on clinical efficacy of eradication therapy: from resistance challenges to practical and translational solutions. Resistance-related treatment failure is driven by target-gene mutations, bacterial persistence and antibiotic tolerance, and clinical barriers such as inadequate acid suppression and poor patient compliance. Current practical clinical approaches include empirical therapies (EMT), guided by local resistance prevalence, previous antibiotic exposure, and guideline recommendations, and susceptibility-guided therapies (SGT), which use culture-based susceptibility testing (Culture), polymerase chain reaction (PCR)-based resistance testing, or whole-genome sequencing (WGS), where available, to individualize antibiotic selection. Potassium-competitive acid blocker (PCAB) optimization, particularly with vonoprazan (VPZ)-based dual, triple, or quadruple regimens, is one of the emerging antibiotic and non-antibiotic approaches, of which VPZ-amoxicillin dual therapy represents the predominant PCAB-based eradication strategy. Other emerging antibiotic and non-antibiotic approaches include microbiome-modulating interventions, nano-formulated bismuth and targeted drug-delivery systems, nanozyme-based therapies, and therapeutic vaccine candidates. These approaches aim to maintain eradication efficacy while reducing antibiotic exposure and resistance selection; however, most of these approaches require further translational and clinical validation. CLR-r, clarithromycin-resistant; CLR-s, clarithromycin-sensitive; ROS, reactive oxygen species.

equivalent alternatives. When individual susceptibility is unavailable, clinicians should use a locally validated, guideline-recommended empiric regimen; in settings with high or unknown clarithromycin resistance, optimized 14-day BQT is the most broadly supported default. SGT should be prioritized after treatment failure or when a clarithromycin- or fluoroquinolone-containing regimen is contemplated, but it is not universally superior to a well-selected empiric regimen. For patients without penicillin allergy, vonoprazan-amoxicillin dual therapy provides a clinically mature antibiotic-minimizing option where amoxicillin resistance is low and regional effectiveness, availability, and affordability support its use. Its importance lies in demonstrating that potent acid suppression can reduce antibiotic burden, not in establishing universal superiority across populations. Across all pathways, adequate acid suppression, optimized dosing and treatment duration, adherence support, and confirmation of eradication remain essential. Nanomaterial-based therapies, vaccines, and other resistance-independent strategies are promising but remain investigational and should not displace validated treatment in current clinical practice. Continued integration of resistance surveillance, optimized acid suppression,

affordable SGT, and translational technologies will be essential to sustain eradication rates above the accepted thresholds and to realize the long-term clinical and population-level benefits of *H. pylori* control.

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Conflict of interest

XZ has been an Editorial Board Member of the *Journal of Translational Gastroenterology* since 2023, CAO has been Honorary Editor-in-Chief of the *Journal of Translational Gastroenterology* since 2026, and HHXX has been Editor-in-

Chief of the *Journal of Translational Gastroenterology* since 2026. The other authors declare no conflicts of interest.

Author contributions

Study design and initial drafting of the manuscript (XZ, ZW, HY); data collection and figure preparation (YW); critical revision of the manuscript for important intellectual content (CAO, HHXX). All authors critically reviewed and approved the final manuscript.

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