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Review Article

Helicobacter pylori Eradication in the Era of Antibiotic Resistance: Challenges and Emerging Therapeutic Strategies

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Abstract

Helicobacter pylori is a persistent gastric pathogen associated with chronic gastritis, peptic ulcer disease, gastric mucosa-associated lymphoid tissue lymphoma, and non-cardia gastric cancer. Although eradication can prevent important clinical outcomes, increasing resistance to clarithromycin, metronidazole, and fluoroquinolones has undermined historically successful empirical regimens. This narrative review critically examines the biological and clinical drivers of eradication failure, current resistance-aware therapeutic approaches, and emerging diagnostic and treatment strategies. Evidence was selected from major international guidelines, systematic reviews, clinical trials, and recent translational studies, with emphasis on literature published between 2022 and 2026. Contemporary recommendations prioritize optimized 14-day bismuth quadruple therapy when susceptibility is unknown, while rifabutin-based regimens and vonoprazan-amoxicillin dual therapy offer alternatives for selected patients. Molecular resistance testing, adequate acid suppression, treatment adherence, and systematic confirmation of eradication are central to precision management. Probiotics may reduce adverse effects in some settings but cannot replace antimicrobial therapy. Antimicrobial peptides, biofilm-disrupting compounds, targeted delivery systems, bacteriophage-derived approaches, and vaccines remain largely investigational. Future progress will depend on integrating locally relevant resistance surveillance, validated susceptibility testing, antimicrobial stewardship, and equitable access to effective regimens. This review provides a practical synthesis of established strategies and emerging opportunities while emphasizing the need to distinguish clinical evidence from preclinical promise.

Keywords: Helicobacter pylori; antimicrobial resistance; eradication; bismuth quadruple therapy; vonoprazan; susceptibility-guided therapy; emerging therapeutics.

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INTRODUCTION AND BACKGROUND

Helicobacter pylori colonizes the human gastric mucosa and establishes a long-lasting inflammatory interaction with the host. Persistent infection is an established cause of chronic active gastritis and a major determinant of peptic ulcer disease and non-cardia gastric cancer. Eradication therefore has benefits extending beyond short-term symptom relief to cancer prevention in appropriately selected populations [1,2]. International initiatives increasingly recognize that the effectiveness of *H. pylori* treatment is both a clinical and a public-health issue [3].

For decades, clarithromycin-containing triple therapy was commonly used as empirical first-line treatment. However, the rise of primary and secondary antimicrobial resistance has made the success of this approach unreliable in many settings. A systematic review across World Health Organization regions documented substantial resistance to clarithromycin, metronidazole, and levofloxacin, with marked geographical heterogeneity [4]. Consequently, contemporary guidance emphasizes avoidance of empiric clarithromycin or levofloxacin regimens when susceptibility has not been established [1, 2].

The central challenge is not simply to identify another antibiotic combination. Successful eradication depends on bacterial susceptibility, sufficiently potent and sustained intragastric acid suppression, dosing and duration, adherence, access to appropriate agents, and confirmation of cure. This narrative review examines the

microbiological basis of treatment failure, evidence-based treatment selection, and the prospects and limitations of novel therapeutic approaches.

REVIEW

Scope and evidence selection

This article is a narrative review, not a systematic review or meta-analysis. It synthesizes key consensus recommendations, clinical guidelines, randomized trials, systematic reviews, and recent mechanistic literature identified through targeted consideration of PubMed-indexed and publisher-hosted sources. Priority was given to the Maastricht VI/Florence consensus, the 2024 American College of Gastroenterology (ACG) guideline, the American Gastroenterological Association (AGA) advice on refractory infection, and relevant publications from 2024–2026 [1,2,5]. Because a prespecified exhaustive search, duplicate screening, and formal risk-of-bias assessment were not undertaken, the discussion should not be interpreted as a quantitative estimate of pooled efficacy.

Why eradication fails: resistance and treatment-related factors

Antimicrobial resistance is a leading cause of eradication failure, but it operates alongside pharmacological and behavioral factors. Resistance to clarithromycin is primarily associated with point mutations in the 23S rRNA gene that reduce macrolide binding. Fluoroquinolone resistance commonly involves alterations in the quinolone resistance-determining region of gyrA. Metronidazole resistance is more heterogeneous, involving altered reductive activation and multiple genetic pathways. Resistance to amoxicillin and tetracycline is generally less frequent but may emerge through changes affecting penicillin-binding proteins or ribosomal targets. Molecular markers vary in predictive value across drugs; the absence of a single resistance marker cannot be equated with proven phenotypic susceptibility [4,6].

Biofilm formation, bacterial heterogeneity within the stomach, coccoid or low-metabolic states, and intragastric pH may further impair antibiotic activity. Inadequate acid suppression is particularly consequential for acid-sensitive antibiotics and regimens relying on active bacterial replication. Poor adherence, medication intolerance, insufficient treatment duration, and previous exposure to macrolides or fluoroquinolones also influence success. A careful antibiotic history should therefore precede selection of first-line or rescue treatment [5].

Resistance rates differ among regions, institutions, and patient groups. Broad global estimates cannot substitute for contemporary local susceptibility data. Clinicians should avoid interpreting a single-center resistance series as nationally representative and should distinguish resistance among untreated patients from resistance among those with previous eradication failure [4].

Contemporary first-line eradication regimens

When antibiotic susceptibility is unknown, the 2024 ACG guideline recommends optimized bismuth quadruple therapy for 14 days as the preferred empirical regimen for treatment-naive adults. The regimen includes a proton pump inhibitor, bismuth, tetracycline, and metronidazole. Its efficacy is less dependent on clarithromycin and fluoroquinolone susceptibility, although adherence and correct administration remain essential. Substituting doxycycline for tetracycline should not be assumed equivalent without supportive evidence [1].

For patients without penicillin allergy, 14-day rifabutin-based triple therapy or a potassium-competitive acid blocker (PCAB)-amoxicillin dual regimen can be appropriate empirical alternatives under guideline-defined conditions and subject to local availability. Vonoprazan provides potent acid suppression, potentially simplifying treatment and supporting the activity of amoxicillin. However, outcomes depend on the exact dose, schedule, adherence, population, and local availability; not all PCAB-based combinations are interchangeable [1,7].

Clarithromycin triple therapy should be reserved for situations where clarithromycin susceptibility is confirmed. Likewise, levofloxacin-containing salvage regimens should not be prescribed empirically when susceptibility is unknown. The selection of a regimen should also account for prior antibiotic exposure, true penicillin allergy, drug interactions, pregnancy status, and patient-specific contraindications [1,2].

Diagnostic stewardship and susceptibility-guided therapy

Noninvasive urea breath testing and stool antigen testing are central to diagnosis and confirmation of cure; endoscopic biopsy-based tests are appropriate when endoscopy is otherwise indicated. Molecular methods applied to gastric biopsies or, where validated, stool specimens can detect H. pylori and selected resistance-associated mutations. Polymerase chain reaction and sequencing may shorten the time to actionable clarithromycin or fluoroquinolone resistance information compared with culture, but analytical coverage, specimen quality, and interpretation vary between assays [2,6].

Culture-based susceptibility testing remains valuable because it can assess multiple drugs and identify phenotypic resistance not captured by targeted molecular panels. Its implementation is limited by specialized sampling, transport, cultivation, and

laboratory expertise. The clinical benefit of susceptibility-guided therapy is likely greatest when prior regimens have failed or when resistance patterns make empiric options uncertain; however, the availability and cost-effectiveness of routine testing differ by health system [2,5].

Every treated patient should undergo a test of cure with a validated non-serological method. As recommended by the ACG, testing should be performed at least four weeks after completion of antibiotics and after withholding proton pump inhibitors or PCABs for approximately two weeks, while observing relevant bismuth and antibiotic washout periods. Serology should not be used to document eradication because antibodies may persist after successful treatment [1].

Management after treatment failure

Persistent infection requires reassessment rather than blind repetition of the same regimen. Clinicians should first verify that infection remains present and examine the previous regimen, adherence, adverse effects, acid suppression, and exposure to macrolides or fluoroquinolones. For patients who have not previously received optimized bismuth quadruple therapy, the ACG guideline favors a 14-day optimized course when susceptibility is unknown. Following prior optimized bismuth quadruple therapy, rifabutin triple therapy is an empirical option in suitable patients without penicillin allergy [1].

After multiple failures, susceptibility testing should be considered whenever feasible, particularly when two adequately administered regimens have failed. Treatment choices should avoid reuse of antibiotics likely to have selected resistance, and specialist consultation may be warranted. Rifabutin-based therapy requires attention to potential adverse effects and interactions, while fluoroquinolone-based rescue therapy should be susceptibility-confirmed. No rescue regimen is universally optimal across all regions and prior-treatment histories [1,5].

Adjuvant approaches: probiotics and microbiome considerations

Eradication regimens can transiently alter intestinal and gastric microbial communities, with potential consequences for tolerability and the antimicrobial resistome. Probiotics have therefore been evaluated as adjuncts, especially for antibiotic-associated diarrhea and other gastrointestinal adverse events. A recent meta-analysis of randomized trials suggested that adding selected probiotics to bismuth quadruple therapy may improve tolerability and modestly increase eradication success, although findings depend on strain, formulation, trial setting, and study quality [8].

These observations should not be interpreted as evidence that probiotics can eradicate H. pylori independently. Evidence remains insufficient to recommend a universal probiotic preparation or to replace optimized antibiotic regimens. Moreover, earlier AGA advice considered proposed adjunctive therapies of unproven value in refractory infection, emphasizing the need to differentiate evolving evidence for supportive care from validated rescue therapy [5,8].

Emerging nonconventional therapeutic strategies

Antimicrobial peptides are being investigated for direct bacterial membrane disruption and possible activity against biofilm-associated organisms. Plant-derived compounds and natural products have shown inhibitory or immunomodulatory effects in experimental systems, but variability in composition, bioavailability, and toxicity limits clinical translation. Nanoparticles and other targeted drug-delivery platforms may improve mucosal retention or protect acid-labile compounds; nevertheless, favorable in vitro outcomes do not establish clinical efficacy or safety [6,9].

Biofilm-disrupting agents, urease-targeted compounds, and engineered bacteriophage or phage-derived approaches represent additional research directions. Phage-based strategies face obstacles including gastric delivery, strain coverage, manufacturing standardization, and demonstration of benefit in controlled human studies. Candidate vaccines seek to prevent acquisition or persistence, but immune correlates of protection, antigenic diversity, and durable efficacy remain unresolved. At present, these approaches should be described as experimental rather than routine alternatives to guideline-supported eradication therapy [6,9].

An important translational priority is to develop interventions that retain efficacy against resistant strains without imposing unnecessary selection pressure on commensal microbiota. Comparative clinical trials should report intention-to-treat and per-protocol eradication rates, adverse events, resistance phenotypes, and long-term safety.

Gastric cancer prevention and population-level implications

Because *H. pylori* is a major causal factor in gastric carcinogenesis, improving eradication has implications for cancer prevention. The International Agency for Research on Cancer published implementation guidance in 2025 for population-based screen-and-treat strategies, emphasizing that program design should reflect local gastric cancer burden, health-system capacity, benefits, harms, and cost-effectiveness [3]. More recent international consensus also supports eradication as a cancer-preventive intervention, while recognizing that benefits are greatest before advanced premalignant mucosal changes develop [10].

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Population strategies require dependable diagnostics, access to effective therapy, follow-up confirmation, and systems for tracking adverse events and treatment failures. Indiscriminate prescribing without resistance surveillance could undermine program effectiveness. Local laboratories can contribute by developing culture or molecular testing capacity, monitoring resistance trends, and linking microbiological findings to clinical eradication outcomes.

Epidemiological variation and surveillance gaps

H. pylori treatment decisions should be interpreted against substantial variability in antibiotic consumption, diagnostic access, previous treatment exposure, and local resistance surveillance. An international assessment covering 31 countries reported clarithromycin resistance above 15% in 24 countries and levofloxacin resistance above 15% in 18 countries. Such findings reinforce the need to avoid extrapolating from pooled worldwide estimates to a specific clinic or country [11].

Resistance reporting should stratify treatment-naive and previously treated individuals, identify the denominator of successfully tested isolates, document testing methods and breakpoints, and distinguish individual-drug from multidrug resistance. Linking microbiology results to actual eradication outcomes provides more clinically useful information than resistance prevalence alone. Surveillance networks should also record drug availability and treatment affordability, because a theoretically effective regimen is not a practical option when essential components cannot be obtained [2,11].

Comparative treatment selection and strength of evidence

Optimized bismuth quadruple therapy, rifabutin-based triple therapy, and vonoprazan-amoxicillin dual therapy differ in antibiotic exposure, administration complexity, tolerability, regulatory availability, and the populations in which supporting trials were conducted. The ACG preference for a 14-day optimized bismuth regimen when susceptibility is unknown reflects a guideline framework, not proof that one regimen performs best in every geographical context [1].

In a 2025 multicenter randomized rescue-treatment trial involving 240 previously treated adults, vonoprazan-amoxicillin dual therapy achieved an intention-to-treat eradication rate of 87.5%, compared with 83.3% for individualized susceptibility-based treatment; the authors reported noninferiority and fewer adverse effects in the dual-therapy group. The findings are encouraging, but regional context, trial design, local susceptibility patterns, and product availability restrict universal extrapolation [7].

Direct comparison of studies requires checking treatment duration, proton pump inhibitor or PCAB intensity, antibiotic dose and frequency, definitions of penicillin allergy, prior antibiotic exposure, and the timing and method of post-treatment confirmation. Studies should report both intention-to-treat and per-protocol results and should account transparently for losses to follow-up [1,2,7].

Special populations and implementation barriers

Treatment in pregnancy, childhood, patients with major drug interactions, and individuals reporting penicillin allergy requires separate evaluation rather than routine application of adult empirical algorithms. Particularly relevant limitations include tetracycline-related restrictions in pregnancy and young children, rifabutin-related hematologic toxicity concerns, and practical challenges of high pill burden. A history of penicillin allergy should be clarified because an inaccurate label can unnecessarily remove amoxicillin-containing options [1,5].

Care pathways in resource-constrained settings should prioritize reliable detection of active infection, provision of complete regimens, counseling to support adherence, and test-of-cure access. Molecular testing can support clarithromycin and fluoroquinolone resistance prediction, but assays only identify the mutations included in their design. Negative targeted molecular results do not exclude other mechanisms or replace phenotypic testing when broader evaluation is needed [2,6].

Gastric cancer prevention: translating evidence into programs

Population screen-and-treat programs should not be equated with indiscriminate population-wide antibiotic prescribing. The 2025 IARC implementation report emphasizes assessment of local cancer burden, delivery infrastructure, treatment selection, antibiotic stewardship, quality measures, and equity before program rollout [3]. In 2026, an IARC working-group summary in the New England Journal of Medicine further highlighted program-level considerations for gastric cancer prevention [10].

A robust program should track the number tested, proportion with active infection, treatment initiation and completion, proportion completing confirmation of cure, confirmed eradication, adverse events, and retreatment. These indicators can identify inequities and operational barriers that are invisible when success is summarized only among patients who return for follow-up [3,10].

Practical implementation priorities

A resistance-aware clinical pathway should begin with confirmation of active infection and review of previous antibiotic use. Treatment-naive patients with

unknown susceptibility should receive an effective locally available guideline-supported regimen, with optimized 14-day bismuth quadruple therapy as a key default under the ACG framework. Clinicians should provide clear counseling on administration and adverse effects and schedule a test of cure at treatment initiation. Persistent infection should trigger assessment of adherence and prior drug exposure, selection of a non-overlapping rescue regimen, and susceptibility testing when feasible [1,2,5].

At the institutional level, antimicrobial stewardship should discourage empirical clarithromycin and levofloxacin regimens without susceptibility evidence, promote standardized reporting of *H. pylori* susceptibility, and collect regimen-specific eradication outcomes. In lower-resource settings, investments in reliable testing, bismuth and tetracycline availability, and follow-up infrastructure may provide more immediate benefit than unvalidated experimental therapies.

Limitations of this review

This narrative synthesis does not use a registered protocol, exhaustive search strategy, formal risk-of-bias scoring, or pooled effect estimates. Consequently, study selection may be incomplete and comparisons among therapeutic strategies are qualitative. Recommendations are drawn mainly from international guidance and may not apply identically to every country. Local resistance surveillance, regulatory approvals, formulary availability, and patient characteristics must inform implementation. Emerging strategies are discussed primarily as research opportunities because clinical validation is limited.

CONCLUSIONS

Antibiotic resistance has fundamentally changed the management of *H. pylori* infection, making historical empirical regimens increasingly unreliable. Successful eradication now requires resistance-aware regimen selection, adequate acid suppression, patient-centered adherence support, and universal confirmation of cure. Optimized bismuth quadruple therapy remains a central empirical option, while rifabutin-based treatment, PCAB-amoxicillin dual therapy, and susceptibility-guided approaches broaden the therapeutic armamentarium in selected settings.

New antimicrobial peptides, targeted delivery systems, biofilm-directed agents, and vaccine platforms are scientifically promising but remain largely investigational. Future progress will depend less on replacing antibiotics with a single novel intervention than on integrating validated diagnostics, high-quality clinical trials, local resistance surveillance, and equitable implementation of effective treatments.

Author Contributions

E.B. conceived the review topic, conducted the literature appraisal, and drafted the initial manuscript. Y.B. and N.H. provided scientific supervision, contributed to the interpretation of the literature, and critically reviewed the content. M.C. contributed to manuscript preparation and critically revised the manuscript for important intellectual content. All authors are requested to review and approve the final version before submission. (Confirm the contribution statements and final approval with every author.)

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