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A REVIEW ON PREVALENCE AND GENETIC ELEMENTS ASSOCIATED WITH ANTIBIOTIC RESISTANCE OF H. PYLORI: A NARRATIVE REVIEW

Narrative Review

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ABSTRACT

Background: The management of *Helicobacter pylori* infection has become increasingly complex due to the global rise in antibiotic resistance, which undermines the effectiveness of conventional eradication regimens. This resistance is largely driven by inappropriate antibiotic use and regional variations in prescribing practices. Understanding the mechanisms and trends of resistance is crucial to designing effective, locally adapted treatment strategies.

Objective: This review aimed to analyze global trends in *H. pylori* antibiotic resistance and identify genetic determinants associated with antimicrobial resistance to commonly used antibiotics, including amoxicillin, metronidazole, clarithromycin, levofloxacin, and tetracycline.

Main Discussion Points: Evidence from multiple countries indicates a significant rise in resistance to several antibiotics, with metronidazole resistance reaching up to 100% in India and clarithromycin and tetracycline resistance rates exceeding 90% in some regions. Levofloxacin resistance remained relatively lower but showed a progressive increase in East Asia. Multidrug resistance, particularly the combination of metronidazole and clarithromycin, was notably high in Korea (40.3%). Genetic studies revealed key mutations responsible for resistance: A2143G in the 23S rRNA gene for clarithromycin, amino acid substitutions in the PBP1A gene for amoxicillin, mutations in the 16S rRNA gene for tetracycline, gyrA/gyrB substitutions for levofloxacin, and nucleotide alterations in the *rdxA* gene for metronidazole.

Conclusion: There is marked geographic and temporal variation in *H. pylori* resistance patterns. Continuous antimicrobial surveillance and genotype-based diagnostic approaches are essential to guide region-specific therapy and curb resistance development.

Keywords: *Helicobacter pylori*, Antibiotic resistance, Global trends, Genetic mutations, Multidrug resistance, Narrative review.

INTRODUCTION

Helicobacter pylori is a spiral-shaped, flagellated, Gram-negative, and microaerophilic bacterium that colonizes the gastric mucosa and has been implicated in several gastrointestinal disorders, including gastritis, peptic ulcer disease, mucosa-associated lymphoid tissue (MALT) lymphoma, and primary B-cell gastric lymphoma (1). It was first identified by Warren and Marshall in Australia in 1988 through stomach biopsies, revolutionizing the understanding of gastric pathology by linking microbial infection with peptic ulceration (2). Over time, this discovery reshaped clinical perspectives on chronic gastritis and ulcer disease, establishing H. pylori as a key etiological factor in gastric malignancy. Beyond its well-documented gastrointestinal effects, emerging evidence suggests that H. pylori may also contribute to various extra-intestinal manifestations such as vitamin B12 deficiency, immune thrombocytopenic purpura, and refractory iron deficiency anemia (3-5). The transmission dynamics of H. pylori remain incompletely understood; however, epidemiological studies indicate that infection is often acquired during childhood, predominantly through fecal–oral or gastro–oral routes, particularly in areas with poor sanitation or contaminated food and water (6). Once acquired, the bacterium tends to persist for life unless effectively eradicated, with approximately 80% of infected individuals remaining asymptomatic while others develop clinically significant disease.

The World Health Organization has classified H. pylori as a Group I carcinogen due to its established role in gastric carcinoma development (7). Its ability to survive and colonize the acidic gastric environment is attributed to a range of virulence factors that enable adhesion, motility, and immune evasion, causing chronic inflammation and gastric mucosal damage. The complete genome sequencing of H. pylori in 1997 revealed that its genome is roughly one-third the size of Escherichia coli, a finding that provided crucial insights into its molecular biology, immunopathogenesis, and mechanisms of host interaction (8-10). Among these mechanisms, bacterial adhesins—surface-expressed proteins facilitating attachment to gastric epithelial cells—play a central role in the organism's persistence and chronic infection (6). Despite decades of research, the epidemiology, molecular pathogenesis, and host–pathogen interactions of H. pylori remain incompletely elucidated, warranting continued scientific exploration. Therefore, the present study aims to investigate the pathogenic mechanisms and clinical associations of H. pylori infection, emphasizing its role in both gastrointestinal and extra-intestinal diseases to enhance understanding and guide improved diagnostic and therapeutic strategies.

ANTIBIOTIC RESISTANCE OF H.PYLORI AGAINST DIFFERENT ANTIBIOTICS

Antibiotic resistance in Helicobacter pylori has emerged as the principal determinant of eradication failure, reshaping first-line and rescue therapy choices across regions and health systems (7). Resistance prevalence varies markedly by geography and appears tightly linked to patterns of community antibiotic consumption, stewardship practices, and over-the-counter availability (8,9). While contemporary regimens still rely on a limited armamentarium—clarithromycin, amoxicillin, metronidazole, levofloxacin, rifabutin, and tetracycline—empirical "one-size-fits-all" strategies have become increasingly untenable, prompting region-tailored protocols and, where feasible, susceptibility-guided therapy (10). The collective evidence synthesized below integrates country-level resistance rates, temporal trends, and resistance genotypes to highlight converging themes, divergences, and persistent uncertainties that bear directly on therapeutic decision-making.

AMOXICILLIN RESISTANCE

Amoxicillin resistance remains generally low worldwide but displays striking outliers that caution against complacency. Low resistance was documented in China (0.1%) and Pakistan (2.2%), consistent with amoxicillin's preserved activity in many Asian settings, whereas Egypt (18%), Mongolia (11.9%), and Cuba (10%) illustrate intermediate pressures, and India reported an exceptional 80% based on E-test MICs up to 256 µg/mL, underscoring potential local drivers such as antibiotic access and stewardship gaps (Table 1) (11-14). Temporal signals are notable: Korea maintained 0% in earlier cohorts but later reported 20% by 2017–2019, and Iran showed an apparent rise from 1.5% to ~30% across successive series, patterns plausibly attributed to non-prescription use and bystander selection in the community (9,10). Together, these findings support amoxicillin's continued role in standard regimens in many regions while reinforcing the value of up-to-date local surveillance to detect emergent hotspots (10,11).

LEVOFLOXACIN RESISTANCE

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Fluoroquinolone resistance exhibits pronounced heterogeneity and temporal escalation. Korea's levofloxacin resistance increased from 26.8% (2011–2012) to 42.9% (2017–2019), mirroring broader quinolone exposure trends, whereas Iran reported very low levels in some cohorts (1.5%), highlighting intra-regional variability that complicates empiric use (15,16). High resistance was recorded in Mongolia (41.3%), with intermediate rates in China (20.6%), Cuba (22.5%), and Pakistan (16.2%); several European and Chilean series reported <10%, illustrating a north–south and east–west mosaic that likely reflects distinct prescribing ecologies and travel-related strain flow (13–18). These data collectively argue for caution with empiric levofloxacin-based regimens in settings surpassing 15–20% resistance, reserving them for susceptibility-guided or rescue therapy where surveillance supports efficacy (10,17).

CLARITHROMYCIN RESISTANCE

Clarithromycin resistance remains the pivotal predictor of triple-therapy failure. Exceptionally high rates were reported in Egypt (93%) and India (76%), while Iran demonstrated lower levels in select cohorts (4.5%) but rising trends across years, and Korea increased from 16.0% to 28.6% over sequential surveys, indicating ongoing macrolide selection pressure from respiratory and outpatient indications (16,19). China and European aggregates hover around ~20%, whereas Chile, Pakistan, and early Korean data were lower, albeit with upward drift over time (11–13). Consistent with current guidance, classic PPI-clarithromycin-amoxicillin triple therapy should be confined to locales where clarithromycin resistance is demonstrably <15% or guided by susceptibility testing, otherwise supplanted by bismuth quadruple or non-clarithromycin regimens (18-20).

METRONIDAZOLE RESISTANCE

Metronidazole resistance is both common and labile across settings, with rates often exceeding 50% and reaching near-fixation in parts of South and East Asia. India reported 100%, China ~95%, and Pakistan ~98%, while Iran hovered between ~50–83% across contemporaneous series and Korea demonstrated a decline from ~56% to ~27% by 2017–2019, possibly reflecting shifting prescribing patterns and evolving gut-microbiome dynamics (21–24). Given the high baseline resistance yet partial reversibility under optimized dosing, bismuth-based quadruple therapy can retain effectiveness despite metronidazole resistance by leveraging dose and duration effects; nonetheless, local resistance ecology remains central to regimen design (23-25).

TETRACYCLINE RESISTANCE

Tetracycline resistance is generally rare, preserving its value in bismuth quadruple therapy, but outliers exist. Egypt reported 98% resistance, a sharp contrast to 0% in Korea, Poland, and Cuba, and intermediate signals in India (4%) and later Iranian cohorts (up to 50%), suggesting that even "heritage" agents are not immune to local selection pressures and potential clonal expansion events (26,27). These inconsistencies justify ongoing phenotypic and genotypic surveillance, especially where tetracycline anchors first-line therapy (23,26).

MULTI DRUG RESISTANCE

Multidrug resistance (MDR) patterns crystallize the clinical challenge by eroding multiple empiric options simultaneously. Dual resistance to clarithromycin+metronidazole reached 40.3% in a Korean 2017–2018 cohort, whereas Bulgaria reported 6% and Pakistan 5.4%, illustrating wide gradients within and across regions (28). Metronidazole+levofloxacin resistance peaked at 18% in Mongolia but was as low as 2% in Bulgaria, while metronidazole+amoxicillin resistance exceeded 7% in Iran but was <0.1% in China, patterns that directly influence the viability of quinolone- or amoxicillin-containing salvage regimens (28-30). Triple resistance (MTZ+CLA+LEV) reached 7.4% in China, with intermediate values in Korea and ≤2–3% in parts of Europe and Mongolia; triple resistance involving amoxicillin (CLA+AMO+MTZ) was as high as 11.2% in Korea yet around ~1–3% elsewhere, underscoring the strategic importance of bismuth-based quadruple therapy and tailored salvage sequences in high-MDR settings (23–28). These data collectively argue for incorporating local MDR matrices alongside single-drug resistance rates when constructing treatment pathways (15–28).

MUTATIONS IN RESISTANCE ASSOCIATED GENE OF HELICOBACTER PYLORI

Mechanistically, H. pylori leverages diverse genetic routes to withstand antibiotic exposure. Agents such as levofloxacin, rifampicin, and metronidazole target nucleic-acid synthesis; macrolides and tetracycline disrupt ribosomal function; and amoxicillin impairs peptidoglycan cross-linking via PBPs, meaning that resistance can arise through target-site mutations, enzymatic inactivation, efflux, or altered permeability (29–31). Mutations in gyrA/gyrB diminish quinolone binding; in rdxA/frxA/fdxB they curtail prodrug activation of nitroimidazoles; in 23S rRNA they reduce macrolide affinity; in 16S rRNA they impair tetracycline binding; and in PBP1A they

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decrease β-lactam susceptibility, often in concert with efflux upregulation, forming a multifactorial, strain-specific resistance landscape (29–32).

CLARITHROMYCIN-RELATED RESISTANCE GENOTYPE

Clarithromycin resistance is predominantly mediated by point mutations in the peptidyl-transferase region (domain V) of the 23S rRNA gene, most commonly A2143G, with A2142G and less frequently A2144G also implicated (30-33). In Nanchang, 23S rRNA mutations were detected in ~40% of biopsies with A2143G predominance, whereas Iranian and Brazilian cohorts similarly highlighted A2143G as the dominant event, with variable representation of A2142G/A2144G and near-absence of A2142C/A2143C in some series, aligning molecular epidemiology with the observed escalation in phenotypic macrolide resistance across regions and time (33,34). These data reinforce the utility of molecular assays detecting A2143G/A2142G as rapid proxies for clarithromycin resistance in clinical algorithms (34).

GENOTYPE OF LEVOFLOXACIN RELATED RESISTANCE

Quinolone resistance maps chiefly to quinolone-resistance–determining regions in gyrA, with recurrent substitutions at Asn-87 and Asp-91 abrogating drug-enzyme interactions; gyrB mutations are less consistently implicated and may be secondary or compensatory (27–30). Across Nepalese, Chinese, and Japanese datasets, Asp-91 and Asn-87 substitutions dominate resistant isolates, with occasional additional variants (e.g., Val150Ala, Arg140Lys) whose individual contributions remain less certain, and sporadic gyrB changes with unclear phenotypic weight, collectively mirroring the stepwise rise in levofloxacin resistance observed epidemiologically (27–30). These findings support gyrA-focused molecular screening as a pragmatic adjunct where culture-based testing is limited (27–30).

GENOTYPE OF METRONIDAZOLE RELATED RESISTANCE

Metronidazole requires intracellular reduction to exert bactericidal activity, rendering loss-of-function mutations in nitroreductase pathways a principal resistance route. Inactivation of rdxA via deletions, insertions, or missense/nonsense substitutions is repeatedly linked to high-level resistance, with frxA/fdxB alterations contributing variably across strains (31,32). Chinese and Iranian studies report clustered rdxA mutations—including T184G, G47A, and a ~200 bp deletion—correlating with phenotypic resistance, while broader sequencing reveals a dense mosaic of missense and frameshift events, consistent with multiple mutational paths converging on impaired prodrug activation and variable cross-talk with redox homeostasis (31-33). This genetic plasticity likely underpins the wide, sometimes reversible, metronidazole resistance spectrum observed in vitro and in vivo (21,23).

GENOTYPE OF AMOXICILLIN RELATED RESISTANCE

Amoxicillin targets PBP1A, and resistance frequently tracks with amino-acid substitutions within or near transpeptidase motifs, compounded by increased efflux activity (13–16). Korean analyses identified recurrent substitutions—including Ala599→Ser, Gly595→Ser, Thr593→Ala, Asn562→Tyr, Ser414→Arg, Val45→Ile, Val16→Ile, and Glu406→Ala—with functional studies highlighting Ser413/414 region changes as particularly influential on MIC shifts (15,16). Although amoxicillin resistance remains uncommon in many locales, the presence of convergent PBP1A mutations across distinct lineages warrants vigilance, especially where rising phenotypic resistance has been documented (21,26).

GENOTYPE OF TETRACYCLINE RELATED RESISTANCE

Tetracycline binds the 30S subunit, and resistance commonly stems from base substitutions at positions 926–928 in 16S rRNA that diminish ribosomal affinity, sometimes accompanied by altered membrane permeability that reduces intracellular drug accumulation (17–19). Sequencing studies reveal single or double substitutions at AGA965–967 and positions 926–928 (e.g., A928C, AG926–927GT, A926G), with subsets of resistant isolates showing no canonical binding-site changes but evidence of reduced uptake, supporting a multifactorial model integrating ribosomal and membrane mechanisms (17–19). These molecular patterns align with generally low global resistance yet explain the sporadic high-resistance pockets reported in specific cohorts (16,21).

Synthesis, gaps, and practice implications: Across regions, clarithromycin and metronidazole resistance—alone and in combination—pose the most immediate threat to legacy triple therapy, while levofloxacin resistance curtails the utility of quinolone-based rescue regimens in several high-use settings (10–13). Amoxicillin and tetracycline largely retain activity but exhibit notable regional exceptions, emphasizing that local antibiograms and, where feasible, molecular resistance testing should anchor regimen selection rather than historical assumptions (11,15,16). Methodological diversity—varying breakpoints, testing platforms, and sampling frames—remains a key limitation that complicates direct inter-study comparisons, and the clinical correlates of some genotypes, particularly rare gyrB or

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non-canonical 16S variants, warrant further prospective validation (31–34). In aggregate, the evidence supports a tiered strategy: prioritize bismuth-based quadruple therapy or susceptibility-guided regimens in areas with high macrolide/nitroimidazole resistance, reserve levofloxacin for documented susceptibility or later-line use, and continually update local resistance maps to sustain eradication efficacy (26–28).

Mechanism–phenotype map (summary): Clarithromycin—A2143G/A2142G/A2144G in 23S rRNA; Amoxicillin—PBP1A substitutions with potential efflux upregulation; Tetracycline—16S rRNA substitutions at 926–928 and reduced permeability; Levofloxacin—gyrA substitutions at Asn-87/Asp-91 (± ancillary variants), infrequent gyrB; Metronidazole—rdxA loss-of-function and allied redox-pathway alterations, often heterogeneous (33,34). These convergent lines of evidence provide a mechanistic rationale for the regional resistance patterns summarized in Table 1 and the MDR constellations in Table 2, and they motivate integration of molecular assays into clinical pathways where culture-based testing is not readily available (15–18).

Table 1: Antibiotic resistance rates in different countries

Country	Year	No of isolate-s	Patients (n)	CLA %	MTZ %	TET %	AMO %	LEV %	Ref
Korea	1994-1999	652	456	5.9%	40.5%	5.3%	0%	ND	[1]
European countries	1999-2000	1233	1233	(1999-2022) 20%	(233/1024) 23%	ND	(6/1037) 0.6%	ND	[2]
Southern Chile	2010	88	240	5.3%	26.3%	ND	5.3%	6.3%	[3]
India	2012	100	100	76%	100%	4%	80%	3%	[4]
Poland	2008-2011	50	178	24%	42%	0%	0%	8%	[5]
Egypt	2015-2017	60	60	93%	25%	98%	18%	ND	[6]
Cuba	2005	46	70	10%	85%	0%	10%	22.5%	[7]
Magnolia	2014-2016	361	361	29.9%	78.7%	ND	11.9%	41.3%	[8]
Iran	2016-2017	68	160	4.5%	34%	ND	1.5%	1.5%	[9]
Poland	2016	62	132	14.3%	31.4%	ND	ND	11.4%	[10]
Iran	2010-2017	218	985	34.4%	79.4%	38.5%	27.1%	27.1%	[11]
Iran	2018	140	450	35.6%	82.7%	50%	29.9%	ND	[12]
Korea	2017-2018	349	590	17.8%	29.5%	37.0%	0%	ND	[13]
Korea	2011-2012	94	94	16.0%	56.3%	0%	2.1%	26.8%	[14]
Balgaria	2012-2013	50	50	22.0%	34.0%	2.0%	ND	18.0%	[15]
Korea	2017-2019	70	174	28.6%	27.1%	18.6%	20%	42.9%	[16]
China	2010-2012	17731	51891	21.5%	95.4%	ND	0.1%	20.6%	[17]
Pakistan	2008-2013	254	889	5.4%	97.8%	4.3%	2.2%	16.2%	[18]

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Table 2: Multi drug resistance in different countries

Country	CLA+MTZ	MTZ+LEV	MTZ+CLA +LEV	MTZ+TET	CLA+AMO +MET	MET+AMX	Ref
Korea	40.3%				11.2%		[13]
Poland	20%	4%	2%				[5]
Mangolia	9%	18%	2.8%		2.8%	2.5%	[8]
Iran		3%				7.5%	[9]
Egypt	5%				1.6%	1.6%	[6]
Iran		5%		2.8%			[11]
Korea	3.2%	8.5%	6.4%			2.1%	[14]
Bulgaria	6.0%	2.0%	2.0%				[15]
Korea	3%				1%		[16]
China	13.0%	12.0%	7.4%	4		<0.1%	[17]
Pakistan	5.4%			4.3%		2.1%	[18]

Table 3: Mechanisms and Genetic Mutations Associated with Antibiotic Resistance in *Helicobacter pylori*

Drug	Mechanism of AMR	Major antibiotic resistance mutation	Reference
CLA	23SrRNA gene mutation	A2143G, A2142G, A2144G point mutation	[19], [20], [21]
AMX	Increased activity of efflux pumps, Amino acid substitutions in PBP1A gene	Amino acid substitutions i.e., Ala599→Ser, Gly595→Ser, Thr593→Ala, Asn562→Tyr, Ser414→Arg, Val45→Ile, Val16→Ile, Glu406→Ala and Ser413→Arg	[28], [29] , [30] , [31]
TET	mutations in 16SrRNA genes, Changes in membrane permeability	Single bp substitutions (AGT, AGC, TGA, GGA, CGA) Single and double bp substitution (A928C, AG926-927GT, A926G and A928C)	[32], [33], [34]
LEV	amino acid variation at gyrA and gyrB subunit,	Asp-91 substitution, Asn-87 and Glu-483 substitutions, Val150 Ala and Arg140Lys, Asn87Lys mutation	[22], [23], [24], [25]
MET	rdxA gene inactivation, 200bP deletion in rdxA gene, Nucleotide insertion and substitutions	mutations at T184G and G47A, 200bP deletion in rdxA gene, insertion of A at position 141, substitution of T for G in 523 position, T for G in position 223, and T for C in position 148	[23], [26], [27]

CRITICAL ANALYSIS AND LIMITATIONS

The body of evidence on Helicobacter pylori antibiotic resistance is substantial yet uneven, and several methodological features limit how confidently findings can be translated into clinical policy across settings. Much of the literature synthesizes observational cohorts and laboratory surveillance rather than randomized therapeutic trials designed a priori to compare resistance-informed regimens with

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empiric strategies, which constrains causal inference about the benefits of susceptibility-guided care in routine practice (11,12). Sample sizes vary widely, with numerous single-center studies underpowered for temporal or subgroup analyses; pediatric data in particular remain sparse relative to adults despite clear epidemiologic importance, creating uncertainty about age-specific resistance trajectories and treatment effects (13). Follow-up horizons are often short and geared toward eradication at 4–8 weeks rather than longer-term clinical outcomes such as ulcer recurrence or gastric neoplasia risk reduction, limiting the ability to connect microbiologic success with durable health benefits at scale (14,15). Methodological bias also permeates several domains. Selection bias is common when isolates derive from referral endoscopy populations, retreatment cases, or urban tertiary hospitals, each of which may inflate resistance estimates compared with community-based presentations (13,26). In therapeutic effectiveness studies, performance bias arises from heterogeneous background acid suppression (standard vs high-dose PPIs vs PCABs), variable bismuth use, and inconsistent adherence support, all of which modulate apparent efficacy independent of resistance patterns (14). Blinding is rarely feasible in multi-drug regimens, and intention-to-treat analyses are not uniformly reported; per-protocol reporting without parallel ITT estimates may exaggerate effectiveness and obscure the real-world impact of intolerance or non-adherence (1,14). Confounding by prior antibiotic exposure—especially macrolides prescribed for respiratory infections and fluoroquinolones for urinary or enteric indications—is incompletely captured, yet strongly linked to resistance emergence and treatment failure, making between-study comparisons precarious when community antibiotic consumption is not quantified (2,6,7).

Publication bias likely shapes the evidence base. Registries and multicountry syntheses suggest declining effectiveness of legacy clarithromycin- or levofloxacin-containing regimens in many regions, but negative or inconclusive single-center reports may be underrepresented in the literature, while industry-sponsored trials of newer options (e.g., rifabutin-based combinations or PCAB-anchored regimens) are more visible, potentially skewing perceptions of comparative benefits (1,5). Systematic reviews increasingly attempt to address this through funnel plots and meta-regression, yet heterogeneity remains high and small-study effects persist, particularly for macrolide resistance estimates with wide regional variance (13,18). Outcome measurement varies substantially, complicating cross-study synthesis. Diagnostic confirmation and test-of-cure differ—^13C-urea breath test, monoclonal stool antigen testing, histology/culture, or PCR-based assays—with variable timing post-therapy and inconsistent withdrawal windows for PPIs or antibiotics, each of which alters sensitivity and specificity and can misclassify true eradication (12). Susceptibility testing methods—agar dilution, E-test, or genotypic assays—use differing breakpoints (EUCAST vs CLSI), and genotypic panels target non-identical mutations (e.g., 23S rRNA A2143G/A2142G for clarithromycin; gyrA Asn-87/Asp-91 for fluoroquinolones), generating discordant phenotype–genotype correlations that hinder pooled estimates (18). Even within phenotypic testing, laboratory protocols and quality controls are not uniformly reported, and mixed-strain infections may be missed, underestimating minority resistant subpopulations that carry clinical relevance (26).

Generalizability remains limited by geography, health-system context, and antimicrobial stewardship maturity. Global meta-analyses reveal resistance mosaics with macrolide and nitroimidazole resistance exceeding 15% in many countries, but the gradients within nations—urban vs rural, public vs private sectors, and migrant vs non-migrant populations—are rarely disaggregated, reducing the utility of national means for local decision-making (12,16). European registries offer valuable real-world insights, yet the external validity to low- and middle-income settings—where over-the-counter antibiotic access, diagnostic capacity, and adherence barriers differ—remains uncertain (14). Likewise, promising performance of PCAB-based regimens and rifabutin-anchored therapy in high-income contexts may not translate where drug availability or cost is prohibitive, and where stewardship frameworks are still evolving (15). There are also thematic gaps and controversies. While consensus statements urge avoidance of clarithromycin- or levofloxacin-containing empiric regimens when resistance likely exceeds 15%, the operational threshold is debated, and many regions lack current antibiograms to make evidence-based choices (26). Molecular testing shows clear value for detecting canonical mutations rapidly, yet standardized panels for metronidazole resistance remain elusive because nitroreductase gene alterations are heterogeneous and context-dependent, leading to poor predictive performance compared with macrolide or quinolone markers (28). Finally, the field still lacks adequately powered, pragmatic randomized trials comparing susceptibility-guided therapy to best-available empiric regimens across diverse health systems, with standardized diagnostics, adherence support, and cost-effectiveness end points; without these, treatment algorithms will continue to lean on indirect evidence and expert consensus (24–26). In sum, contemporary literature convincingly documents the rise and clinical impact of H. pylori antibiotic resistance, but its interpretability is tempered by design limitations, bias, heterogeneous methods, and patchy generalizability. Future work should prioritize multicenter, adequately powered trials with harmonized diagnostics and breakpoints; robust capture of prior antibiotic exposure and adherence; routine reporting of ITT and per-protocol outcomes; and integration of phenotype–genotype data within surveillance systems to enable timely, region-specific regimen selection and stewardship (14–18).

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IMPLICATIONS AND FUTURE DIRECTIONS

The evidence synthesized in this review carries significant implications for both clinical management and public health strategy. The rising prevalence of *Helicobacter pylori* antibiotic resistance underscores the urgent need for personalized and regionally informed therapeutic approaches. From a clinical perspective, the findings strongly advocate for abandoning uniform empiric triple therapy in favor of susceptibility-guided or locally tailored regimens that reflect current resistance trends (12). In regions where clarithromycin or metronidazole resistance exceeds 15%, bismuth-based quadruple therapy or concomitant regimens should be prioritized as first-line options. The review also highlights the utility of incorporating molecular diagnostics, particularly genotypic detection of key resistance mutations—such as 23S rRNA (A2143G/A2142G) and gyrA (Asp-91/Asn-87)—to inform rapid, point-of-care treatment decisions when culture-based testing is unavailable (34). Clinicians must also emphasize patient adherence, dosing optimization, and acid suppression strength, as these factors critically modulate eradication outcomes independent of resistance profiles (25). For policymakers and guideline developers, the current findings emphasize the necessity of dynamic surveillance systems that continuously update local and national resistance maps. Integration of resistance monitoring into national antimicrobial stewardship programs could help inform rational antibiotic prescribing and prevent unnecessary macrolide or fluoroquinolone exposure that accelerates resistance selection (26). Existing consensus statements such as Maastricht VI and ACG 2024 should be adapted locally to reflect resistance data from low- and middle-income countries, where empiric strategies often persist due to cost and diagnostic constraints (17). The establishment of centralized resistance registries, similar to the European Hp-EuReg model, would enhance comparability, encourage standardized reporting, and facilitate timely updates to treatment guidelines (25,27).

Despite extensive documentation of resistance trends, key uncertainties persist. There remains incomplete understanding of the genetic diversity underlying metronidazole resistance, the role of mixed-strain infections, and the impact of emerging antibiotic classes or host genetic factors on eradication success (23,24). Longitudinal data connecting specific genotypes to treatment outcomes across diverse populations are still lacking, as are cost-effectiveness analyses comparing phenotypic versus genotypic susceptibility testing in routine care (25). Furthermore, much of the current evidence originates from hospital-based or urban samples, leaving gaps in rural, pediatric, and immunocompromised cohorts where infection dynamics may differ significantly (16,18). Future research should move beyond descriptive resistance surveys toward methodologically robust, multicenter, randomized controlled trials that evaluate the comparative effectiveness of susceptibility-guided versus empiric regimens under real-world conditions. These studies should incorporate adequate sample sizes, standardized diagnostic methods, and longer follow-up intervals to capture recurrence and reinfection rates (11,24). Future investigations should also explore pharmacogenomic determinants of therapy response, the clinical utility of next-generation sequencing (NGS)–based resistance profiling, and the potential role of non-antibiotic adjuncts such as probiotics or antimicrobial peptides (23,25). Interdisciplinary collaboration among microbiologists, clinicians, and public health authorities will be vital to create predictive resistance models that inform region-specific clinical algorithms. In conclusion, this review reinforces that *H. pylori* management must evolve from empiric, population-level strategies toward precision medicine approaches grounded in surveillance data and molecular diagnostics. Strengthening diagnostic infrastructure, harmonizing resistance testing standards, and expanding multicenter collaboration are pivotal steps to sustain eradication success and mitigate the growing threat of antibiotic resistance worldwide (15,16).

CONCLUSION

The collective evidence demonstrates that *Helicobacter pylori* has developed substantial resistance to multiple antibiotics, with the highest rates observed for metronidazole, followed by tetracycline, clarithromycin, amoxicillin, and levofloxacin. These resistance patterns vary considerably across regions, reflecting differences in antibiotic consumption and stewardship practices. Molecular analyses consistently associate point mutations in the 23S rRNA gene with clarithromycin resistance, amino acid substitutions in the PBP1A gene with amoxicillin resistance, mutations in 16S rRNA with tetracycline resistance, alterations in gyrA and gyrB subunits with levofloxacin resistance, and diverse nucleotide changes in the *rdxA* gene with metronidazole resistance. The emergence of multidrug-resistant strains, particularly in East Asia, signals a growing global threat to eradication efficacy. Although the reviewed studies provide valuable insights, variability in methodology and limited sample representativeness constrain the generalizability of their findings. Clinically, these data emphasize the need for region-specific treatment strategies, integration of molecular resistance testing into routine practice, and stringent antibiotic stewardship to preserve therapeutic options. Continued large-scale, multicenter studies using standardized susceptibility testing and genomic surveillance are urgently required to refine evidence-based treatment protocols and mitigate the accelerating trend of antimicrobial resistance in *H. pylori*.

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AUTHOR CONTRIBUTION

Author	Contribution
Sharista	Substantial Contribution to study design, analysis, acquisition of Data Manuscript Writing Has given Final Approval of the version to be published
Maissor Ahmed Nafees	Substantial Contribution to study design, acquisition and interpretation of Data Critical Review and Manuscript Writing Has given Final Approval of the version to be published
Saif-Ud-Din*	Substantial Contribution to acquisition and interpretation of Data Has given Final Approval of the version to be published
Shan Alam	Contributed to Data Collection and Analysis Has given Final Approval of the version to be published
Imraan	Contributed to Data Collection and Analysis Has given Final Approval of the version to be published

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