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REVIEW ARTICLE

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Helicobacter pylori resistome analysis in Colombia

Análisis del resistoma de Helicobacter pylori en Colombia

Análise do resistoma de *Helicobacter pylori* na Colômbia

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ABSTRACT

Introduction: *Helicobacter pylori* is a bacterium closely associated with chronic gastritis and gastric cancer. In Colombia, its high prevalence, along with marked geographical differences in gastric cancer incidence, has prompted studies focused on the antimicrobial resistance of this bacterium. **Objective:** To characterize the resistome of *Helicobacter pylori* in Colombia through the analysis of phenotypic and genotypic studies, in order to evaluate resistance patterns. **Materials and methods:** A systematic review was conducted in scientific databases, selecting 21 original studies. Mutations in resistance-associated genes were evaluated, and a descriptive statistical analysis was performed using R software. **Results:** High resistance to metronidazole was identified, along with variable resistance to clarithromycin and tetracycline, moderate resistance to amoxicillin and levofloxacin, and low resistance to furazolidone and rifampicin. **Conclusion:** The high resistance to metronidazole excludes it as a reliable first-line option. The variable resistance to clarithromycin and tetracycline requires regional susceptibility testing. Amoxicillin and levofloxacin retain moderate efficacy, while furazolidone and rifampicin stand out as promising alternatives. It is essential to implement phenotypic or genotypic susceptibility testing prior to treatment and to update empirical guidelines based on local resistance surveillance.

Keywords: Antibiotic resistance; *Helicobacter pylori*; gastric cancer; Colombia. (Source: DeCS, Bireme).

Sustainable development goals: Good health and well-being. (Source: SDG, WHO).

RESUMEN

Introducción: *Helicobacter pylori* es una bacteria estrechamente relacionada con la gastritis crónica y el cáncer gástrico. En Colombia, su alta prevalencia, junto con las marcadas diferencias geográficas en la incidencia del cáncer gástrico, han motivado estudios centrados en la resistencia antimicrobiana de esta bacteria. **Objetivo:** Caracterizar el resistoma de *Helicobacter pylori* en Colombia a través del análisis de estudios fenotípicos y genotípicos, con el fin de evaluar los patrones de resistencia. **Materiales y métodos:** Se realizó una revisión de tema en bases de datos científicas, seleccionando 21 estudios originales. Se evaluaron mutaciones en genes asociados a resistencia y se llevó a cabo un análisis estadístico descriptivo utilizando el *software* R. **Resultados:** Se identificó una alta resistencia a metronidazol, resistencia variable a claritromicina y tetraciclina, resistencia moderada a amoxicilina y levofloxacina y baja resistencia a furazolidona y rifampicina. **Conclusión:** La alta resistencia al metronidazol lo descarta como opción fiable de primera línea. La resistencia variable a claritromicina y tetraciclina demanda pruebas de susceptibilidad regionales. La amoxicilina y levofloxacina mantienen eficacia moderada, mientras que furazolidona y rifampicina destacan como alternativas prometedoras. Es fundamental implementar pruebas fenotípicas o genotípicas antes del tratamiento y actualizar guías empíricas basadas en vigilancia local.

Palabras clave: Resistencia a antibióticos; *Helicobacter pylori*; cáncer gástrico; Colombia. (Fuente: DeCS, Bireme).

Objetivos de desarrollo sostenible: Salud y bienestar. (Fuente: ODS, OMS).

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RESUMO

Introdução: *Helicobacter pylori* é uma bactéria intimamente associada à gastrite crônica e ao câncer gástrico. Na Colômbia, sua alta prevalência, juntamente com marcantes diferenças geográficas na incidência de câncer gástrico, motivou estudos focados na resistência antimicrobiana dessa bactéria. **Objetivo:** Caracterizar o resistoma do *Helicobacter pylori* na Colômbia por meio da análise de estudos fenotípicos e genotípicos, a fim de avaliar os padrões de resistência. **Materiais e métodos:** Foi realizada uma revisão da literatura em bases de dados científicas, selecionando-se 21 estudos originais. Foram avaliadas mutações em genes associados à resistência e realizada uma análise estatística descritiva utilizando o *software* R. **Resultados:** Foram identificadas alta resistência ao metronidazol, resistência variável à claritromicina e tetraciclina, resistência moderada à amoxicilina e levofloxacina e baixa resistência à furazolidona e rifampicina. **Conclusão:** A alta resistência ao metronidazol o descarta como uma opção confiável de primeira linha. A resistência variável à claritromicina e à tetraciclina exige testes de suscetibilidade regionais. A amoxicilina e a levofloxacina mantêm eficácia moderada, enquanto a furazolidona e a rifampicina se destacam como alternativas promissoras. É essencial implementar testes fenotípicos ou genotípicos antes do tratamento e atualizar as diretrizes empíricas com base na vigilância local.

Palavras-chave: Resistência a antibióticos; *Helicobacter pylori*; câncer gástrico; Colômbia. (Source: DeCS, Bireme).

Metas de desenvolvimento sustentável: Saúde e bem-estar. (Fonte: MDS, OMS).

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INTRODUCTION

Helicobacter pylori (*H. pylori*) is a Gram-negative bacterium that colonizes the gastric mucosa of approximately half of the global population[1,2]. Its infection is strongly associated with gastric lesions such as chronic gastritis, atrophic gastritis, metaplasia, dysplasia, and ultimately gastric cancer[3,4]. In 1994, the International Agency for Research on Cancer (IARC) classified *H. pylori* as a Group I carcinogen[5].

H. pylori is one of the microorganisms that has infected *Homo sapiens* since its origin in the African savannas approximately 130,000 years ago and has accompanied human migrations outside East Africa for around 60,000 years[6-9]. Due to different allopatric processes, distinct populations and subpopulations of *H. pylori* emerged, each with unique genetic characteristics associated with environmental conditions and those of its host[9]. The bacterium possesses two oncogenes, *cagA* and *vacA*, which encode proteins that trigger a pro-inflammatory immune response, ultimately leading to genetic and physiological alterations in gastric cells and inducing carcinoma in gastric tissue[10,11].

Each year, approximately 1.1 million people are diagnosed with gastric cancer worldwide, of whom around 768,793 die[12]. Gastric cancer is the third most common cancer and the second leading cause of cancer-related death[12-14]. In 42 countries, gastric cancer ranks among the top three causes of cancer mortality, and in 13 countries it is the leading cause[15]. The annual burden of gastric cancer is projected to increase to approximately 1.8 million new cases and 1.3 million deaths by 2040[15].

In Colombia, gastric cancer is the leading cause of cancer-related mortality[16]. However, the country's high geographic diversity has led to notable disparities in incidence and mortality across regions. For instance, in the Andean region, incidence is significantly high at around 150 cases per 100,000 inhabitants[8,9]. In contrast, in the Pacific coast region, incidence is considerably lower, with approximately 6 cases per 100,000 inhabitants; this marked difference has given rise to the "Colombian Enigma," which seeks to understand the reasons behind these geographic variations in disease incidence[8,9].

The only known valid strategy to prevent the development of gastric cancer is the eradication of *H. pylori* through the use of antimicrobial agents[9,17]. The most widely used eradication therapy worldwide is that recommended by the *Maastricht VI/Florence* Consensus, which includes bismuth-based quadruple therapy consisting of a proton pump inhibitor (PPI), tetracycline, and metronidazole for 10 to 14 days[18,19]. However, the efficacy of these treatments is compromised by the growing problem of antibiotic resistance, highlighting the importance of epidemiological surveillance of *H. pylori*[18,19].

In Colombia, *H. pylori* eradication has been challenging due to increasing resistance and multidrug resistance to antimicrobials used in conventional therapies, such as metronidazole (99.3%), amoxicillin (25.9%), and levofloxacin (12.4%)[20]. In this context, the term resistome refers to the complete set of antimicrobial resistance genes present in a microorganism or microbial community, enabling the analysis of genetic mechanisms involved in resistance and their evolution in response to selective antibiotic pressure[20-22].

Although the existing literature has extensively documented the biology, evolution, and epidemiology of *H. pylori*, there is a need to strengthen the understanding of the genetic mechanisms that confer resistance to commonly used antibiotics, as well as the clinical relevance of the bacterial resistome. In Colombia, heterogeneity in resistance patterns particularly to antibiotics recommended by the Maastricht Consensus has compromised eradication therapy efficacy, making a systematic characterization of associated mutations and their geographic distribution essential. Therefore, the objective of this review is to analyze the available evidence on antimicrobial resistance of *H. pylori* in Colombia, describing the genetic mutations involved in the main resistance-associated genes and their relationship with reported phenotypic patterns, in order to provide a foundation for optimizing therapeutic strategies and genomic surveillance in the country.

MATERIALS AND METHODS

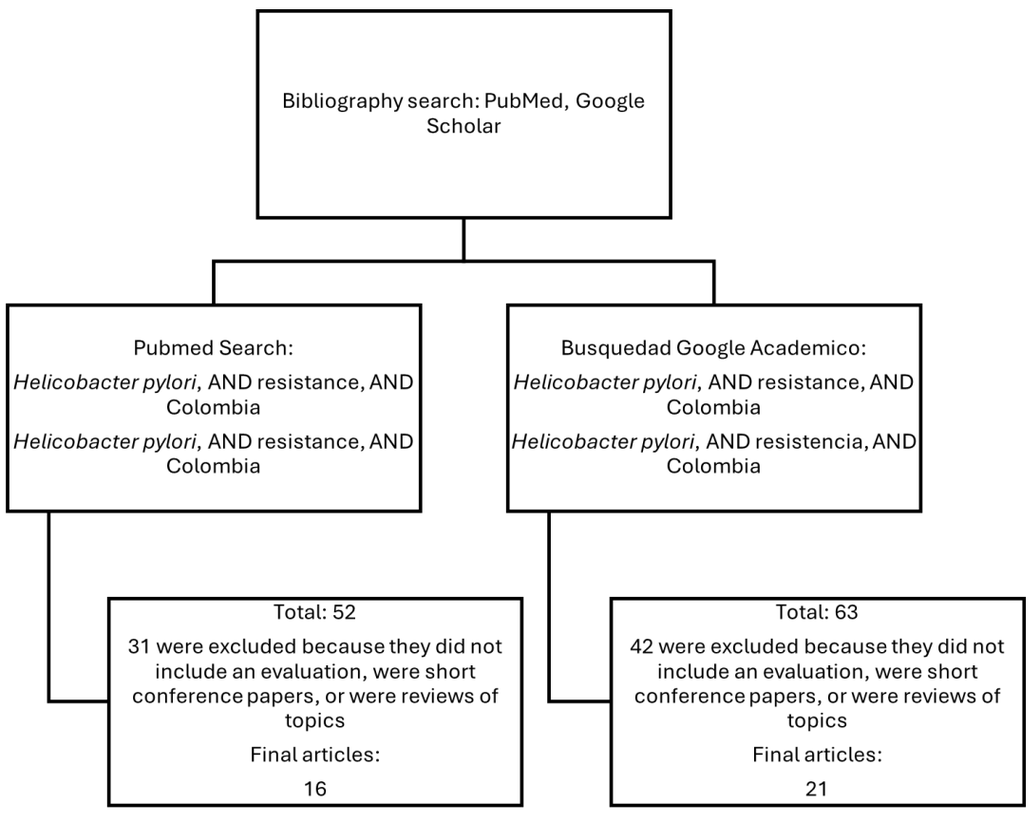
Literature search

Review focused on the antimicrobial resistance of *H. pylori* in Colombia. Its purpose was to analyze and synthesize the available scientific evidence on the genetic mutations associated with the *H. pylori* resistome and the phenotypic resistance patterns reported in the country between 2000 and 2025.

Information search and selection

An exhaustive bibliographic search was conducted in the PubMed and Google Scholar databases, using the MeSH and DeCS descriptors "*Helicobacter pylori*", "Colombia", and "resistance", combined with Boolean operators (AND, OR). The search included articles published in English and Spanish between January 2000 and June 2025 (Figure 1).

Figure 1.
General diagram of the article review strategy for the literature search on *Helicobacter pylori* antibiotic resistance in Colombia.



Prioritized original studies reporting information on antimicrobial resistance rates, genetic mutations, or genomic analyses of Colombian *H. pylori* isolates (Table 1). Publications were included if they met at least one of the following criteria:

1. Reporting data on antimicrobial resistance or associated genes in Colombian *H. pylori* strains, published in English or Spanish, with no age restriction.
2. Analyzing genomic or molecular aspects related to the bacterial resistome.

Studies unrelated to the Colombian context, duplicates, and case reports were excluded.

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Table 1.
Phenotypic and genotypic studies with recorded antibiotic resistance, location, and study methods in Colombia

Antibiotic	Resistance %	Location	Method	Reference
Clarithromycin	2.20	Pereira and Armenia	E-test	23
	8.20	Pereira	E-test	24
	13.60	Bogotá	Phenotypic	25
	15	Bogotá	Phenotypic	26
	17.20	Bogotá	Phenotypic	27
	38.1	Bogotá	Phenotypic	28
	63.10	Bogotá	Phenotypic	29
	4	Popayán	Sanger sequencing	30
	18.8	Medellín	Genotyping	31
	19.8	Tumaco	Agar dilution	32
	3.62	Colombia	WGS	9
	3.61	Colombia	WGS	33
	0	Nariño	MIC and WGS	34
Tetracycline	85.70	Bogotá	Disk diffusion in culture	29
	1.7	Nariño	MIC and WGS	34
	3.6	Colombia	WGS	33
	7.23	Bogotá and Nariño	WGS	20
Amoxicillin	3.8	Bogotá	E-test	27
	9.5	Bogotá	Disk diffusion in culture	29
	19.8	Tumaco	MIC	32
	7.21	Colombia	WGS	33
	25.9	Bogotá and Nariño	WGS	20
	5.4	Túquerres	MIC and Genotyping	34
Metronidazole	81.01	Bogotá	E-test	27
	77.3	Pereira and Armenia	E-test	23
	72	Bogotá	E-test	39
	97.6	Bogotá	Disk diffusion in culture	29
	78	Popayán	Sanger sequencing	40
	78.60	Pereira	E-test	24
	100	Tumaco	MIC and WGS	34
	99.3	Bogotá and Nariño	WGS	20
	86	Túquerres	MIC and WGS	34
	75.75	Colombia	WGS	33
Levofloxacin	20.3	Nariño	MIC and WGS	34
	10.35	Colombia	WGS	33
	12.04	Colombia	WGS	20
	27.3	Bogotá	Agar dilution and sequencing	35
Furazolidone	0.84	Colombia	WGS	42
	1.7	Medellín	Phenotypic and sequencing	43
Rifampicin	0	Colombia	WGS	42

Illustration of resistance mechanisms and mutations

A diagram of *H. pylori* resistance mechanisms to the main antibiotics recommended in the *Maastricht VI/Florence* Consensus was generated using the BioRender tool (https://www.biorender.com) for the genes involved in antibiotic resistance: metronidazole (*rdxA* and *frxA*), clarithromycin (*23S*), tetracycline (*16S*), amoxicillin (*pbp1A, pbp3*), levofloxacin (*gyrA*), and furazolidone (*porD*).

Statistical analysis

A statistical analysis was conducted on antimicrobial resistance data for various antibiotics commonly used in the treatment of *H. pylori* in Colombia. Percentage resistance data for each antibiotic (amoxicillin, metronidazole, tetracycline, levofloxacin, clarithromycin, furazolidone, and rifampicin) were compiled from the existing scientific literature and organized into a data frame for analysis. The variable Resistance was treated as numerical and expressed as a percentage.

All analyses were performed using R software (version 4.4.1). First, a descriptive analysis was carried out by grouping resistance values by antibiotic, calculating the number of observations (*n*), mean, median, minimum value, maximum value, and standard deviation (*SD*). Normality was then assessed using the Shapiro-Wilk test, which indicated that most distributions did not follow a normal distribution ($p < 0.05$ in several groups).

Given the violation of the normality assumption, the non-parametric Kruskal-Wallis test was applied to compare median resistance across antibiotics, revealing statistically significant differences ($x^2 = 22.0$; $p = 0.000198$). Finally, boxplot-type graphical representations were generated to visualize antimicrobial resistance distributions for each antibiotic.

RESULTS

Helicobacter pylori treatment regimens in Colombia

In Colombia, *H. pylori* treatment is based on triple and quadruple therapies, which combine a proton pump inhibitor (PPI) with antibiotics targeting different physiological processes of the bacterium. These treatments act by inhibiting DNA transcription, protein synthesis, and the integrity of the bacterial cell membrane. The most commonly used antibiotics include clarithromycin, amoxicillin, metronidazole, tetracycline, levofloxacin, furazolidone, and rifampicin, depending on the therapeutic regimen and local antibiotic resistance patterns[18] (Table 2).

Table 2.
Helicobacter pylori eradication treatment recommended by the Maastricht Consensus

Treatment Regimen	Antibiotics	Duration
First-line therapy	PPI + clarithromycin + amoxicillin + metronidazole	14 days
First-line therapy (second option)	PPI + bismuth + tetracycline (doxycycline) + metronidazole	14 days
Second-line therapy	PPI + bismuth + amoxicillin + levofloxacin	14 days
Rescue therapy with furazolidone	PPI + bismuth + furazolidone + tetracycline	14 days
Rescue therapy with rifampicin	PPI + bismuth + amoxicillin + rifampicin	14 days

Clarithromycin

Clarithromycin is a macrolide antibiotic derived from erythromycin A, used for the eradication of *H. pylori* in the treatment of peptic ulcer disease. Its mechanism of action is based on the inhibition of bacterial protein synthesis through its binding to the 50S ribosomal subunit, blocking tRNA translocation during peptide chain elongation. This interruption in translation prevents the growth and proliferation of *H. pylori*, leading to its elimination. However, resistance to clarithromycin in *H. pylori* has increased due to mutations in the *23S* rRNA gene, which reduce the affinity of the antibiotic for its binding site, compromising treatment effectiveness[9].

In Colombia, a study conducted in 2009 using E-test assays and PCR-RFLP genotyping in the cities of Pereira and Armenia reported a low clarithromycin resistance rate of 2.2%[23]. In a more recent study, a resistance rate of 8.20% was found in Pereira[24]. In contrast, significantly higher resistance rates have been reported in Bogotá, with values of 13.6%, 15%, 17.2%, 38.1%, and up to 63.1%, according to different studies based on phenotypic tests[25-29]. In the city of Popayán (Cauca), an analysis using Sanger sequencing identified a 4% resistance rate in the *23S* gene[30]. Similarly, a study conducted in Medellín, also using *23S* gene sequencing, showed a resistance rate of 18.8%, with the A2143G mutation being the most frequent among the isolates, followed by A2142G[31]. Finally, in a population from the Pacific coast of Nariño, an agar dilution study reported a clarithromycin resistance rate of 19.8%[32].

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Studies employing whole-genome sequencing (WGS) methods for *H. pylori* have identified point mutations in the *23S* rRNA gene associated with clarithromycin resistance. In the analysis of 166 Colombian genomes, a resistance rate of 3.62% was reported[9]. In another study, resistance-related mutations were detected in 3.61% (8/221) of the genomes analyzed; among these, six (2.7%) carried the A2143G mutation and two (0.9%) the A2142G mutation[33]. Conversely, a study conducted in the department of Nariño, specifically in the municipalities of Túquerres and Tumaco, did not identify clarithromycin-resistant isolates[34] (Figure 2).

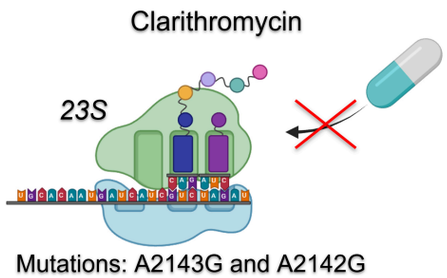

Figure 2.
Mutations in the *23S* gene associated with clarithromycin resistance in *Helicobacter pylori* in Colombia

Tetracycline

Tetracycline is a broad-spectrum antibiotic used in the eradication of *H. pylori*, particularly in bismuth-based quadruple therapies. Its mechanism of action is bacteriostatic, meaning that it inhibits bacterial growth. It acts by binding to the *30S* ribosomal subunit, blocking the attachment of aminoacyl-tRNA to the A site of the ribosome and thereby preventing the synthesis of bacterial proteins essential for survival[35]. Resistance to tetracycline in *H. pylori* is primarily associated with mutations in the *16S* rRNA operon, particularly in the antibiotic-binding region, which decreases drug affinity and compromises treatment efficacy.

A study conducted in Bogotá reported an unusually high resistance rate of 85.7%, determined using disk diffusion assays[29]. However, more recent investigations using molecular methods have revealed significantly lower frequencies. In the department of Nariño, resistance was found to be 1.7% and was associated with the A926G mutation in the *16S* rRNA gene[34]. At the national level, a resistance frequency of 3.6% was also confirmed, likewise linked to the A926G mutation [33]. In another recent study, a resistance rate of 7.23% was detected in strains from Bogotá and Nariño, identifying the A926G, A926T, and A928C mutations in the *16S* rRNA, which have been implicated in reduced tetracycline affinity for the bacterial ribosome[20] (Figure 3).

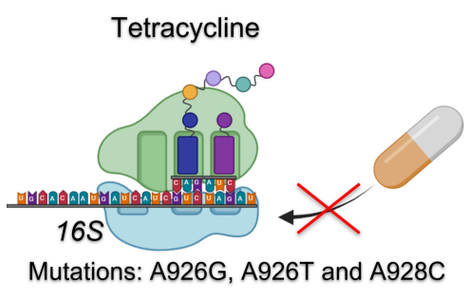

Figure 3.
Mutations in the *16S* gene associated with tetracycline resistance in *Helicobacter pylori* in Colombia

Amoxicillin

Amoxicillin is a broad-spectrum semisynthetic aminopenicillin with bactericidal activity against *H. pylori*. Its mechanism of action is based on the inhibition of bacterial cell wall synthesis through irreversible binding to penicillin-binding proteins (PBPs), specifically PBP1A, PBP2, and PBP3, which are located in the inner membrane of *H. pylori*[18]. Inactivation of these PBPs interferes with the cross-linking of peptidoglycan chains, a process essential for the stability and rigidity of the bacterial cell wall. As a consequence, the structural integrity of the bacterium is compromised, weakening the cell wall and leading to bacterial lysis[36].

In Colombia, *H. pylori* resistance to amoxicillin has shown considerable variability across regions and detection methods. In Bogotá, a resistance rate of 3.8% was reported using E-test assays in a study involving Colombian patients[27]. Another study in the same city, using disk diffusion tests in culture, found a higher resistance rate of 9.5%[29]. In the Tumaco region of Nariño, considered a low-risk area for gastric cancer, a resistance rate of 19.8% was observed using minimum inhibitory concentration (MIC) phenotypic tests[32]. Nationally, a recent whole-genome sequencing (WGS) study identified mutations in the *pbp3* gene specifically A50S and F490Y with an estimated resistance rate of 7.21%[33]. Likewise, another genomic analysis identified mutations in the *pbp1A* gene, including T556S, T593, R649K, R656P, and R656H, with a resistance frequency of 25.9% in isolates from Bogotá and Nariño[20]. More recently, a study conducted in Túquerres reported a resistance rate of 5.4%, associated with F125L and I79V mutations in the transglycosylase domain of the *pbp1A* gene, confirmed through MIC testing and genotyping[37] (Figure 4).

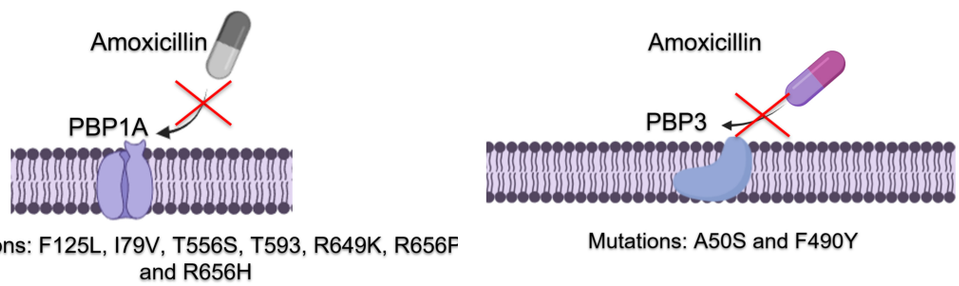

Figure 4.
Mutations in the PBP1A and PBP3 proteins associated with amoxicillin resistance in *Helicobacter pylori* in Colombia.

Metronidazole

Metronidazole is a prodrug with selective bactericidal activity against *H. pylori* and other anaerobic bacteria. Its action is mediated by the intracellular reduction of the nitro group by bacterial enzymes, generating reactive intermediates capable of covalently binding to bacterial DNA[38]. This process disrupts the helical structure of DNA, induces strand breaks, and blocks nucleic acid synthesis, ultimately resulting in the death of *H. pylori* cells. Resistance to metronidazole is associated with the inactivation of genes encoding reductase enzymes, reducing the conversion of the drug into its active metabolites and diminishing its effectiveness in eradicating the microorganism[40].

H. pylori resistance to metronidazole in Colombia has consistently been high across various regions of the country. In Bogotá, resistance rates of 81.01%, 72%, and up to 97.6% have been reported using E-test and disk diffusion assays[27,29,39]. In Pereira and Armenia, similar studies documented resistance rates of 77.3% and 78.6%, respectively[23,24], whereas in Popayán a rate of 78% was observed, associated with mutations in the *rdxA* gene, which is involved in drug activation[40].

In regions with different gastric cancer risk levels, such as Tumaco, studies based on MIC and WGS reported a resistance rate of 100%, with truncations identified in the *rdxA* and *frxA* genes[34]. In Túquerres, a resistance rate of 86% was recorded, with similar mutations[34]. In Bogotá and Nariño, D59N and D59S mutations in the *rdxA* gene were identified, associated with a resistance rate of 99.3%[20]. Nationally, a resistance rate of 75.75% was reported, also linked to mutations and truncations in *rdxA* (D59N, D59S, H97T, A118T, R131K, R90K) and *frxA* (stop codon), according to genomic sequencing analyses[33] (Figure 5).

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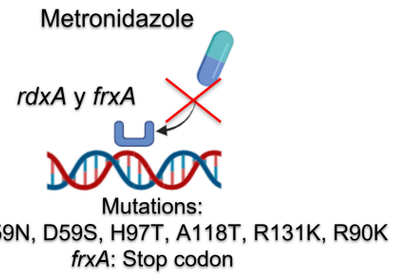

Figure 5.
Mutations in the *rdxA* and *frxA* genes associated with metronidazole resistance in *Helicobacter pylori* in Colombia

Levofloxacin

Levofloxacin is a broad-spectrum fluoroquinolone used in the treatment of *H. pylori*, particularly as part of rescue therapies when standard regimens have failed. Its mechanism of action is based on the inhibition of DNA *gyra*se and topoisomerase IV, two essential enzymes for bacterial DNA replication, transcription, and repair. By blocking the activity of these enzymes, levofloxacin interferes with the supercoiling and stability of *H. pylori* DNA, leading to the interruption of DNA synthesis and ultimately to bacterial cell death[41].

In Colombia, *H. pylori* resistance to levofloxacin has been reported at moderate levels, with clear evidence of specific mutations in the *gyrA* gene, which encodes the A subunit of DNA *gyra*se. In the department of Nariño, a resistance rate of 20.3% was observed using MIC testing and WGS analysis, associated with N87I/K and D91G/Y mutations in *gyrA*[34]. At the national level, resistance frequencies of 10.35% and 27.3% were identified, with mutations such as D91G, D91Y, D91N, as well as N87K and N87I in *gyrA*, and R484K in *gyrB*[33,35]. Complementary data reported a resistance rate of 12.04%, confirming the presence of mutations N87K, N87I, D91G, D91N, and D91Y in the *gyrA* gene[20]. These substitutions at codons 87 and 91 widely described in the literature alter the affinity of levofloxacin for its molecular target, reducing its clinical efficacy (Figure 6).

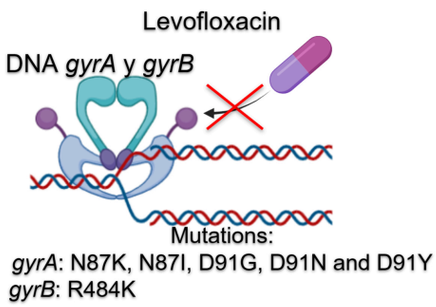

Figure 6.
Mutations in the *GyrA* and *GyrB* proteins associated with levofloxacin resistance in *Helicobacter pylori* in Colombia

Furazolidone

Furazolidone is a nitrofuran antibiotic with bactericidal activity against *H. pylori*. Its mechanism of action is based on the intracellular reduction of the nitro group by bacterial flavoproteins, generating reactive oxygen species and toxic metabolites that damage bacterial DNA. This interaction induces DNA fragmentation, interferes with replication and transcription, and ultimately leads to bacterial cell death[41].

Furazolidone has shown a low resistance rate among *H. pylori* isolates, positioning it as a promising therapeutic alternative, particularly in settings with high levels of multidrug resistance. At the national level, a whole-genome sequencing (WGS) study reported a resistance frequency of 0.84%, associated with a point mutation (C357T) in the *porD* gene involved in drug activation[42]. In Medellín, another study combining phenotypic and genotypic methods documented a resistance rate of 1.7%[43].

Rifampicin

Rifampicin acts by binding to the β-subunit of DNA-dependent RNA polymerase in *H. pylori*, encoded by the *rpoB* gene. This interaction forms a stable complex that blocks RNA chain elongation during transcription, effectively inhibiting RNA synthesis and thus bacterial proliferation. However, point

mutations at codons V149F, Q527R, D530, and H540 in the *rpoB* gene can reduce rifampicin's affinity for its target, conferring antibiotic resistance[43]. In Colombia, rifampicin resistance in *H. pylori* isolates is virtually nonexistent. A whole-genome sequencing (WGS) study reported no resistant isolates among the strains analyzed nationwide (0%)[43].

Statistical analysis of antibiotic resistance in Colombia

The statistical analysis of antimicrobial resistance in *H. pylori* revealed marked heterogeneity among the seven antibiotics evaluated. Metronidazole showed the highest and most consistent resistance levels, with a mean of 84.3% and a median of 81.0%, confirming significantly compromised clinical efficacy in most isolates. At an intermediate level, tetracycline and levofloxacin exhibited mean resistance rates of 24.6% and 17.5%, respectively, with medians of 5.4% and 16.2%. These values reflect strong positive skewness, associated with highly resistant subpopulations within predominantly susceptible groups.

Clarithromycin showed a similar pattern, with a mean of 14.9% and a median of 8.2%, indicating the coexistence of susceptible isolates and others with high-level resistance. Amoxicillin presented a mean resistance of 10.5% and a median of 7.2%, suggesting a moderate level of preserved therapeutic efficacy in most clinical settings. In contrast, furazolidone and rifampicin recorded the lowest resistance values, with means of 1.27% and 0%, respectively, highlighting their superior sensitivity profiles among the antibiotics assessed (Figure 7).

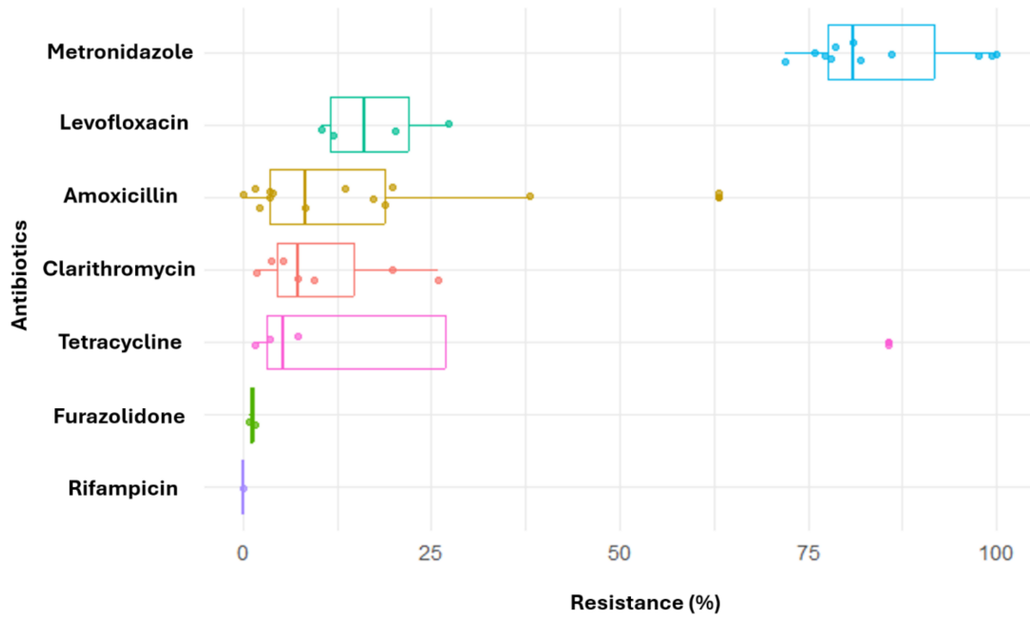

Figure 7.
Distribution of antimicrobial resistance by antibiotic among *Helicobacter pylori* isolates in Colombia

Analysis of resistance patterns reported by multiple phenotypic and genotypic studies for the seven most frequently used antibiotics in Colombia for *H. pylori* eradication therapy.

The nonparametric *Kruskal-Wallis* analysis revealed statistically significant differences in resistance levels among the different antibiotics evaluated ($H = 22.0$; df $= 4$; $p = 0.000198$). This result indicates that the distribution of resistance values is not homogeneous across the groups, confirming the existence of substantial variations in antimicrobial efficacy against *H. pylori* in Colombia. In particular, metronidazole showed the highest resistance values, in contrast with the low levels observed for furazolidone and rifampicin. This suggests the presence of differentiated antimicrobial resistance patterns, likely related to differences in genetic mechanisms, clinical use, or regional antibiotic pressure, and supports the need to adjust therapeutic guidelines based on local bacterial susceptibility profiles.

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DISCUSSION

H. pylori is one of the oldest microorganisms to have colonized humans. Its presence dates back approximately 130,000 years, having migrated from East Africa alongside *H. sapiens*[6,7]. It is estimated that half of the global population is infected with *H. pylori*. In developing countries such as Colombia, this figure rises to 90 %, making eradication extremely challenging[8,9].

Given its long period of coevolution with humans, *H. pylori* has developed multiple mechanisms to persist in the gastric environment. Although its main niche is the gastric mucosa, it can also colonize beneath the mucosa and even within gastric epithelial cells[41]. Furthermore, the bacterium forms biofilms and coccoid structures that enable it to withstand antibiotic treatment[41]. Mutations in resistance-related genes further contribute to its ability to survive in the gastric environment.

The results of this study confirm marked heterogeneity in antimicrobial resistance patterns of *H. pylori* in Colombia. Metronidazole exhibited the highest resistance rate (mean: 84.3%; median: 81.0%). However, despite its high in vitro resistance, international evidence suggests that metronidazole may retain therapeutic utility within bismuth-based quadruple regimens. Recent studies report that bismuth-based quadruple therapy combined with PPIs achieves eradication rates close to 85% even against resistant strains, due to the synergistic effect of bismuth [42]. Nevertheless, the Maastricht Consensus recommends excluding antibiotics with resistance rates above 15%, highlighting the need for more empirical therapeutic studies in Colombia to evaluate the effectiveness of this antibiotic in treatment regimens[18].

Regarding clarithromycin, its mean resistance of 14.9% and median of 8.2%, along with the marked dispersion among studies, reflects geographical heterogeneity in Colombia, a phenomenon also observed in Asia[43]. This variability suggests the coexistence of bacterial subpopulations with high resistance levels in specific regions. In Asia and Europe, clarithromycin resistance rates above 15% have reduced the efficacy of *H. pylori* therapies to below 80%[18,43]. Global evidence emphasizes that genotypic detection of mutations in the *23S* rRNA gene (A2142G, A2143G) is essential for guiding personalized treatments[18], which should be implemented within the Colombian context.

Tetracycline showed a similar pattern, with a mean resistance of 24.5% and median of 5.4%. Although mutations in the *16S* rRNA gene associated with resistance are infrequent, its use in combination with bismuth and other antibiotics has proven particularly effective in rescue therapies, achieving eradication rates > 90%[44]. Resistance to tetracycline remains low in many countries, and bismuth-based quadruple regimens containing tetracycline, combined with metronidazole, furazolidone, amoxicillin, or levofloxacin, can achieve higher eradication rates[44]. However, current studies on tetracycline have been conducted mainly in Asia and Europe and are largely retrospective. Efficacy and safety must therefore be further evaluated through large-scale prospective multicenter studies, considering regional antibiotic resistance rates and generating more data within Colombia.

Amoxicillin and levofloxacin exhibited moderate resistance (10.5% and 17.5%, respectively). In the case of amoxicillin, resistance mechanisms are associated with alterations in penicillin-binding proteins (PBP1A)[34], while levofloxacin resistance is linked to mutations in the *gyrA* and *gyrB* genes[33]. Nevertheless, international literature supports their efficacy within second- or third-line combination regimens. Clinical trials and meta-analyses have shown that levofloxacin-based therapies achieve eradication rates above 85% when administered for 14 days and combined with bismuth and tetracycline[45]. However, some regions report resistance rates exceeding 15%, underscoring the need for continuous surveillance and pre-treatment susceptibility testing to optimize therapeutic decisions and avoid eradication failures.

By contrast, furazolidone and rifampicin exhibited the lowest resistance rates (1.27% and 0%, respectively). Recent national studies confirm the high susceptibility of *H. pylori* to furazolidone[46-48], although its clinical use is limited by regulatory restrictions and potential adverse effects, which in Colombia hinder its availability for *H. pylori* treatment. Conversely, the use of rifampicin is not recommended as first-line therapy due to its essential role in tuberculosis management and the risk of inducing cross-resistance with *Mycobacterium tuberculosis*[49].

Currently, *H. pylori* treatments are based on empirical studies regarding the efficacy of therapeutic

regimens, with those exceeding a 90% eradication rate considered effective[50]. However, increasing bacterial resistance challenges the effectiveness of traditional regimens such as standard triple therapy. In this context, the integration of advanced molecular technologies, such as second- and third-generation sequencing and real-time PCR diagnostics, could facilitate the implementation of personalized medicine as recommended by the Maastricht Consensus[17]. This strategy would enable more targeted and effective treatments, particularly in populations with high incidence and mortality from gastric cancer in Colombia, contributing to reduced therapeutic failure.

Additionally, it is relevant to evaluate the potential of complementary therapies alongside conventional antibiotic regimens, such as the use of probiotics. A study conducted in the department of Nariño reported that *Lactobacillus casei subsp. rhamnosus* exerts an inhibitory effect in vitro against *H. pylori* [51]. Similarly, the consumption of kefir and probiotics such as *Saccharomyces boulardii*, *Lactobacillus reuteri*, and *Lactobacillus johnsonii* has demonstrated the ability to reduce gastric colonization by *H. pylori* and mitigate adverse effects of antibiotic treatment. However, their isolated use does not guarantee full eradication of the pathogen; therefore, their implementation should be considered as an adjuvant strategy within standard antimicrobial therapy[51].

Regarding phytotherapies, a recent study conducted in the department of Nariño reported that sulforaphane, a molecule found in broccoli sprouts (*Brassica oleracea var. italica*), exhibits in vitro inhibitory activity against *H. pylori*, particularly against strains isolated from the Andean region, where gastric cancer mortality is highest[52,53]. Likewise, Indigenous communities of the Amazon region in Brazil, Peru, Ecuador, and Colombia, especially in the departments of Amazonas, Putumayo, Cauca, and Nariño, have used *Croton lechleri* ("dragon's blood") for centuries as part of their traditional medicine for its wound-healing properties in treating gastric lesions and as a natural remedy against *H. pylori* [54-58]. These findings highlight the value of local ethnomedical practices as potential sources of bioactive compounds for developing novel complementary therapeutic strategies.

Among the main strengths of this study is the integration of data from multiple published studies conducted in different regions of the country, which provides a representative overview of the national landscape of antimicrobial resistance. Additionally, classifying antibiotics by resistance level offers a useful tool for therapeutic decision-making. However, limitations include methodological heterogeneity across studies and variable sample sizes. Moreover, genotypic information regarding specific mutations remains limited in several regions.

CONCLUSIONS

High and consistent resistance to metronidazole makes it an unreliable first-line option. Clarithromycin and tetracycline exhibit variable and heterogeneous resistance, requiring a deeper understanding of regional resistance patterns, ideally through individualized susceptibility testing. Amoxicillin and levofloxacin show moderate resistance levels, while furazolidone and rifampicin emerge as highly promising alternatives due to their currently low resistance.

These results underscore the need to strengthen epidemiological surveillance and implement phenotypic or genotypic susceptibility testing prior to treatment, in order to optimize therapeutic decisions and reduce eradication failures. Furthermore, the complementary use of probiotics and phytotherapies with inhibitory activity against *H. pylori* represents a promising alternative that requires clinical validation. Overall, the findings reinforce the importance of integrating advanced molecular tools and personalized approaches for the rational management of antimicrobial resistance, contributing to improved eradication rates and reduced gastric cancer burden in the Colombian population.

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