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Pathogenicity and Antimicrobial Resistance of Helicobacter Pylori Review: Article

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Abstract

Helicobacter pylori is a leading cause of peptic ulcer disease and gastric cancer comprising a major global health concern ana public health threat because of its persistent colonization, multiple pathogenic mechanisms, and the rapid rise in antimicrobial resistance. The bacterium is supplied with several virulence factors, such as urease, adhesins, CagA and VacA that allow it to survive in the acidic gastric environment and attach to gastric epithelial cells, modulate host immune responses and induce chronic gastric inflammation. In susceptible hosts, persistent infection can play a role in the development of gastritis, peptic ulcer disease, gastric mucosal atrophy and gastric adenocarcinoma. Furthermore, increasing resistance rates to widely used antimicrobial agents, including clarithromycin, metronidazole and fluoroquinolones are compromising the efficacy of standard eradication regimens resulting in treatment failure. Chromosomal mutations (e.g. of antibiotic targets or drug activation) ultimately lead to H. pylori antimicrobial resistance, but this has been engrained by prior exposure to a number of antimicrobials and/or suboptimal antibiotic regimens leading to selection for more resistant strains. Recent advancements in molecular diagnostics, antimicrobial susceptibility testing, resistance monitoring, and alternative eradication strategies has offered additional perspectives on this transforming therapeutic landscape of H. pylori treatment. This review summarizes the pathogenicity and major virulence mechanisms of H. pylori, highlights the molecular and epidemiological features of antimicrobial resistance, and outlines current challenges to effective eradication and control of H. pylori-associated diseases along with novel concepts for appropriate solutions.

Keywords: *Antimicrobial Resistance, Virulence Factors, H pylori*

Introduction

Helicobacter pylori is a Gram-negative, spiral-shaped microaerophilic bacterium that has the ability to colonize the human gastric mucosa. *H. pylori* has become one of the most studied bacterial pathogens in chronic infection due to its unique ability to survive in a very challenging environment as well as the broad spectrum of gastrointestinal diseases it has been associated with since it was recognized as an important human pathogen (Clyne & ÓCróinín, 2025). Although its infection is asymptomatic in most infected people, prolonged colonization can lead to chronic gastritis and promote the later development of peptic ulcer disease, gastric mucosa-associated lymphoid tissue lymphoma and gastric adenocarcinoma. The bacterium is designated as a Group 1 carcinogen, highlighting its significance in gastric malignancy pathogenesis and prevention (Duan et al., 2023; Mohammadzadeh et al., 2023).

Pathogenicity of H. pylori is multifactorial and mediated by the interaction of bacterial virulence factors, host predisposition, immune responses, and the local host microenvironment. In order for colonization to be successful, organisms must be able to survive gastric acidity, traverse the mucus layer, colonize and adhere strongly to gastric epithelial cells, where the organism is sustained long-term (Elbehiry & Marzouk, 2026). Urease hydrolyzes urea to ammonia, which is required for the bacteria to survive, because this reaction contributes to local buffering of gastric acid (Baj et al., 2020). Bacterial motility factors like flagella and flagellin also play an important role (e.g. Togiviruses—a non-enveloped, single-strand RNA virus) and adhesins like blood group antigen-binding adhesin (BabA) and sialic acid-binding adhesins (SabA); their corresponding roles are to attach to gastric epithelial surfaces. These characteristics enable H. pylori to persist in a compartment of the stomach that is otherwise subjected to repeated challenge by host defense mechanisms (Al-Fakhrany & Elekhnawy, 2023; Mohammadzadeh et al., 2023).

Accessory virulence factors also play a role in the severity and potential clinical outcomes of H. pylori infection. Cytotoxin-associated gene A (CagA) and vacuolating cytotoxin A (VacA) are the most well characterized genes. CagA is translocated into gastric epithelial cells through type IV secretion system to activate intracellular signaling disturbance, change cell polarity, alter epithelial response and promote inflammation (Sukthaworn et al., 2024) VacA is associated with cell damage through its actions on membrane surface stabilization, intracellular transportation, immune-cell activity and epithelium equilibrium. As well as the virulence factors, other bacterial components like outer inflammatory protein A (OipA), adhesins, lipopolysaccharide, and outer membrane proteins affect colonic colonization, inflammation, immune modulation, and tissue damage. This implies that different bacteria strains have a different virulence profile which likely plays a role in the different clinical presentation seen between infected patients (Mohammadzadeh et al., 2023; Clyne & Ó Cróinín, 2024).

An additional property that enables H. pylori to endure is its intricate interaction with the host immune response. Although infection triggers innate and adaptive immune responses, the bacterium can modulate host immune signaling to escape eradication (Fan et al., 2024). But chronic inflammation is not limited to reversible alterations in the gastric mucosa alone, and mechanisms providing sustained microbial infection and survival evolve through interference with cellular signaling networks and redirection of host evasion responses. As a result, the fate of an infection is influenced not only by the organ and virulence features of the bacteria but rather from the synergism of microbial genotype, host genetic and immune responses, and the environment (Mohammadzadeh et al., 2023; Clyne & Ó Cróinín, 2024).

Consequently, Antimicrobial resistance has rendered the clinical management of H. pylori more challenging. Eradication therapy has been based on the combination of acid suppression with one or more antimicrobial agents and the declining susceptibility to commonly prescribed antibiotics has resulted in reduced efficacy in many parts of the world. Resistance to clarithromycin, metronidazole, and levofloxacin is particularly important as these have been the cornerstone of eradication regimens for some time (Hasanuzzaman et al., 2024). Resistance can be caused by genetic changes to the antibiotic targets or transport (or drug activation), and can be selected by long term exposure of cell populations to antimicrobials. The widespread emergence and dissemination of multidrug-resistant strains has therefore been identified as one of the most important barriers to successful eradication (Kim et al., 2024; Yamaoka et al., 2024).

Antimicrobial resistance is a global health problem; however, recent evidence has documented large geographical and population variability associated with the patterns of antimicrobial-use and prior treatment exposure. Results from a 2024 systematic review and meta-analysis emphasized high global variability in primary *H. pylori* antibiotic resistance over the last decade, again supporting the need for regional resistance monitoring (Yu et al., 2024). Even pediatric populations are affected, with global meta-analysis have shown alarming levels of resistance among common antibiotics and usefulness of some commonly used antibiotics already being relevant in early infection phases. These results reinforce growing interest in susceptibility-guided therapy, enhance effective antimicrobial stewardship, novel combination therapies and alternative treatment strategies (Salahi-Niri et al., 2024).

Due to the large and persistent global burden of *H. pylori* infection, its considerable variety in virulence mechanisms, association with life-threatening gastric diseases, and rapidly changing antimicrobial-resistance profile, an updated scientific view on its pathogenicity and resistance features is warranted (Menbari et al., 2025). Accordingly, the aim of this review is to

describe the pathogenicity and principal virulence determinants of *H. pylori* as well as highlining its mode of persistency and transition to disease development; moreover, we shall comprehensively discuss current trends, mechanisms and clinical relevance of Antimicrobial resistance (AMR).

Pathogenesis of H. pylori

Helicobacter pylori is remarkably well adapted to the acidic conditions of the human stomach and can persistently colonize this niche for decades. There is no single virulence factor responsible for its pathogenicity; rather, disease can occur as a result of complex integration between specific mechanisms to colonize the gastric mucosa and host responses (Ansari & Yamaoka, 2017). While a significant proportion of infected individuals are asymptomatic, chronic infection can lead to chronic gastritis and in those at risk resulting in peptic ulcer disease, gastric atrophy, intestinal metaplasia and gastric cancer (Clyne & Ó Cróinín, 2024; Salvatori et al., 2023).

Gastric colonization and survival

The first stage of *H. pylori* pathogenesis includes overcoming the gastric environment followed by colonization within the mucus, which covers the surface of the gastric epithelium. Gastric acidity is a physiological barrier to bacterial colonization. But *H. pylori* primarily disarms this barrier with its exceptionally active urease enzyme (Rhee et al., 2014). Urease catalyzes the hydrolysis of urea [(NH2)2CO)] to ammonium hydroxide (ammonia and carbon dioxide), increasing the pH surrounding the bacterium, allowing it to survive in a strong acidic environment. This adaptation is assisted by the flagella of the organism, providing motility and movement across the viscous gastric mucus towards the epithelial surface (Clyne & Ó Cróinín, 2024).

Upon the arrival to the epithelial surface of gastric epithelium, *H. pylori* apply a number of outer-membrane adhesins that make it in intimate contact with gastric epithelial cells. The attachment to host-cell and bacterial persistence is enhanced by blood group antigen-binding adhesin (BabA), which binds to Lewisb antigens on the epithelial cells of the gastric mucosa, sialic acid-binding adhesin (SabA), and other adherence-associated proteins (Huang et al., 2016). Recent research has focused on the ability of H. pylori to colonize gastric glands rather than remaining confined to the superficial mucus layer. Colonization of these anatomically protected niches may facilitate bacterial persistence and evade host clearance, thereby contributing to sustained epithelial injury and chronic inflammation within the gastric mucosa. (Beccaceci & Sigal, 2023; Mu et al., 2023).

Bacterial virulence factors

The virulence properties of particular strains are important determinants of the severity of disease associated with *H. pylori*. The cag pathogenicity island (cagPAI) which encodes a type IV secretion system is one of the most extensively studied predictors (table 1). Using this secretion apparatus, H. pylori can directly interact with gastric epithelial cells and translocate the CagA effector protein into host cells (Tegtmeyer et al., 2011). After translocation, CagA is phosphorylated and interacts with various intracellular signaling pathways. These interactions, in turn, will affect aspects like epithelial-regulated polarity, cytoskeletal organization, cell-cell adhesion, and proliferative signaling pathways that lead to the loss of epithelial function and remodeling of tissue development (Clyne & Ó Cróinín, 2024; Salvatori et al., 2023).

CagA also induces abnormal signal cascades that regulate cell proliferation and survival resulting in inflammatory and likely carcinogenic changes. More recently, the presence of the bacterial HtrA protease—known to cleave epithelial junctional proteins such as E-cadherin and occludin—further highlighted its importance. Disruption of these junctions compromises epithelial integrity and allows bacteria access to epithelial cells thereby enhancing CagA delivery (Taglialegna, 2023).

Another important virulence factor of H. pylori is Vacuolating cytotoxin A (VacA). This secreted toxin interferes with various cellular processes such as immune-cell activity, apoptosis, mitochondrial function, intracellular trafficking, and membrane permeability. VacA may inhibit T- and B-cell responses, and hence assist in the persistence of H. pylori in the gastric mucosa (Palframan et al., 2012). CagA and VacA, critically, do not work separately: the combinatorial effects of these factors can cause damage to epithelial cells, perturb normal signaling cascades, and subvert the immune response and disease progression (Clyne & Ó Cróinín 2024).

Host inflammatory response

The colonization of H. pylori elicits innate and adaptive immune responses. Bacterial components recognized by gastric epithelial cells and immune cells induce excretion of inflammatory mediators, such as neutrophils, macrophages, and lymphocytes by triggering chemokines and cytokines in gastric mucosa (Kheiruralla et al., 2025; Zhang et al., 2025). Importantly this response associated to the infected cells is only a reflection of a trying to control infection, but in most cases, only prevents the total elimination of the bacterium. On the other hand, under normal condition, H. pylori reinfection interacts with the immune system leading to chronic inflammation that is a key component of the disease pathogenesis (Reyes, 2023; Clyne & Ó Cróinín, 2024). Such a chronic inflammatory environment may gradually cause injury to gastric epithelium and lead to disorganization and dysfunction of mucosal membrane. This is because reactive oxygen and nitrogen species produced during inflammation can be cytotoxic and mutagenic, while inflammatory signaling can modify epithelial proliferation, apoptosis and tissue healing. In

this way, tissue injury is caused by not only bacterial virulence factors but also prolonged inflammatory response of host (Costa et al., 2025).

Progression toward gastric disease and cancer

Persistent *H. pylori* infection can lead to progressive pathological changes within the gastric mucosa. In genetically predisposed persons, chronic active gastritis may progress to gastric gland loss and atrophy before intestinal metaplastic and dysplastic changes occur. The progression of infection is determined by bacterial factors such as virulence, host genetic susceptibility factors, environmental exposures, dietary factors and composition of the gastric microbiota (Salvatori et al., 2023; Reyes, 2023).

Chronic inflammation is especially relevant to gastric carcinogenesis. Persistent injury followed by epithelial repair enhances the likelihood of DNA damage and accumulation of atypical cells. This molecular cascade could cumulatively lead to neoplastic conversion through CagA-mediated signaling, oxidative stress, disruption of cell junctions and changes in apoptosis and epithelial–mesenchymal signaling (Rasch & Algül, 2014). *H. pylori* may affect gastric stem-cell and glandular responses as well, which triggers further mechanisms via which chronic infection can promote carcinogenesis (Beccaceci & Sigal, 2023; Salvatori et al., 2023).

Thus, the pathogenesis of H. pylori infection should be considered to be a complicated process consisting of acid adaptation and gastric colonization followed by epithelial adherence, delivery of bacterial virulence factors, immune activation and persistent inflammation that eventually leads to progressive mucosal injury (Sgouras et al., 2015). Only in a few of those infected individuals, however, can these mechanisms culminate in peptic ulceration or gastric carcinoma. The natural course of H. pylori infection relies not only on bacterial colonization, and their interaction but on the interaction among bacterial virulence, host immune responses, environmental factors, and genetic susceptibility (Clyne & Ó Cróinín, 2024; Kesharwani et al., 2023).

Table1. Biological function, role in pathogenesis and virulence factor relation of main *H pylori* virulence factors (Bhattacharjee et al., 2024)

Virulence factor	Biological function	Role in pathogenesis	Clinical implications
Urease (UreA/UreB)	Hydrolyzes urea into ammonia and carbon dioxide, buffering the acidic gastric environment.	Enables survival in gastric acidity and facilitates initial colonization; ammonia may contribute to epithelial injury and inflammation.	Essential for gastric colonization
CagA	Effector protein delivered into gastric epithelial cells through the Cag type IV secretion system.	Alters intracellular signaling, cytoskeletal organization, epithelial polarity, cell adhesion, proliferation, and inflammatory responses.	Strongly associated with more severe gastritis and i peptic ulceration and gastric adenocarcinoma
Cag pathogenicity island (cagPAI)/T4SS	Specialized secretion apparatus that mediates interaction with and delivery of bacterial effectors into host cells.	Promotes CagA translocation and activates inflammatory and oncogenic signaling pathways in gastric epithelial cells.	Associated with more severe gastric disease.
VacA	Secreted multifunctional cytotoxin that forms membrane channels and affects intracellular organelles and signaling.	Promotes cellular vacuolation, alters membrane permeability and intracellular trafficking, affects mitochondrial function, induces apoptosis, and modulates immune-cell activity.	Associated with increased gastric epithelial injury, peptic ulcer disease, and gastric cancer risk.
BabA	Outer-membrane adhesin that binds Lewis b and related fucosylated blood-group antigens on gastric epithelial cells.	Facilitates firm attachment to gastric epithelial cells and promotes persistent colonization and delivery of bacterial virulence factors.	BabA-positive strains have been associated with enhanced colonization
SabA	Adhesin that recognizes sialylated glycans expressed on gastric epithelial cells, particularly during inflammation.	Promotes adhesion to inflamed gastric mucosa and supports persistent colonization as the glycosylation pattern of the gastric epithelium changes during infection.	Associated with chronic inflammation and carcinogenesis.

OipA	Outer-inflammatory protein and outer-membrane adhesin involved in bacterial–host interaction.	Enhances epithelial adhesion and contributes to inflammatory signaling and immune responses.	Associated with increased inflammation
HopQ	Outer-membrane adhesin that interacts with CEACAM receptors on gastric epithelial and immune cells.	Facilitates intimate bacterial–host interaction and contributes to efficient CagA delivery through the T4SS.	Tthe severity of H. pylori-associated gastric inflammation.
HtrA	Secreted serine protease that cleaves epithelial junctional proteins, including E-cadherin and occludin.	Disrupts epithelial barrier integrity, facilitates access to epithelial surfaces, and enhances CagA translocation.	May facilitate processes involved in chronic inflammation and carcinogenesis.
Flagella	Provide motility through the viscous gastric mucus layer.	Allow migration from the gastric lumen toward the epithelial surface and support effective colonization.	Essential for efficient gastric colonization and long-term persistence.
NapA	Neutrophil-activating protein involved in interaction with immune cells.	Promotes neutrophil recruitment and oxidative inflammatory responses, contributing to gastric mucosal inflammation.	May contribute to chronic gastritis and tissue injury.
Virulence factor	Biological function	Role in pathogenesis	Clinical implications
Urease (UreA/UreB)	Hydrolyzes urea into ammonia and carbon dioxide, buffering the acidic gastric environment.	Enables survival in gastric acidity and facilitates initial colonization; ammonia may contribute to epithelial injury and inflammation.	Essential for gastric colonization

Antimicrobial Resistance to H pylori

Antimicrobial resistance (AMR) is one of the most critical concerns in *H. pylori* infection that impairs the effective treatment and eradication therapy. Because H. pylori colonizes the gastric mucosa in a persistent manner, effective eradication generally requires multidrug protocols that include acid suppression along with two or more antimicrobial agents. Consequently, loss of susceptibility to commonly-used antibiotics may greatly compromise the efficacy of treatment (Sohn et al., 2025). Global data from recent studies reported that resistance is continentally heterogeneous yet increasing over time. This trend highlights the critical need for local surveillance and the optimized use of eradication regimens protocols (Yu et al., 2024).

Clarithromycin, metronidazole, amoxicillin, tetracycline and fluoroquinolones such as levofloxacin are the main antibiotics used to combat *H. pylori*. Of these agents, clarithromycin, metronidazole and levofloxacin resistance is especially clinically relevant since the results of resistance testing can be reflected in traditional eradication protocols (Boyanova et al., 2023). A current global systematic review and meta-analysis of 47,002 isolates from 36 countries showed considerable geographical heterogeneity of resistance and a significant increase over time between 2013 to 2023. Examining regional differences, investigators concluded these were substantial and thus argue for location-specific resistance surveillance opposed to the assumption of uniform treatment regimen effectiveness across different regions of the world (Yu et al 2024).

Mechanisms of antimicrobial resistance

In *H. pylori* infection, resistance is primarily mediated by chromosomal mutations that either modify the drug target or alter antimicrobial activity restriction and uptake. Clarithromycin resistance is mainly correlated with point mutations in the 23S rRNA gene. So that, these mutations change the macrolide-binding site on the bacterial ribosome, and therefore decrease the inhibition of bacterial protein synthesis by clarithromycin (Marques et al., 2020). Since clarithromycin resistance can severely impact the efficacy of protocols containing this antibiotic, local resistance patterns should be taken into consideration when using it (Hasanuzzaman et al., 2024).

Inhibition of metronidazole is mediated by multiple resistance mechanisms that is well related to mutations in genes associated with drug activation in bacterial cells. Changes in oxygen-insensitive nitro-reductases can decrease the conversion of metronidazole to its bioactive antimicrobial metabolites. Further mechanisms related to oxidation stress responses and DNA repair alterations may also be involved in the resistant phenotype (Thomas & Gwenin, 2021). Therefore, metronidazole resistance has become a global challenge and particularly alarming because it has become widespread in most of the regions. Using a systematic review of resistance in India, exceptionally high metronidazole-resistance has been reported which highlights a large regional variability (Dutta et al., 2024). They are also structurally associated with fluoroquinolone resistance, especially levofloxacin resistance, mediated by mutations in the quinolone-resistance-determining regions of genes encoding DNA gyrase gyrA being most important, but not

only one. These mutations result in lower binding of the antibiotic to the bacterial DNA replication machinery, leading to decreased antimicrobial activity (Minarini & Darini, 2012). The greater use of fluoroquinolones in clinical practice facilitates selection of resistant *H. pylori* strains, whereas previous exposure to this class of antibiotic is a key factor in selecting ensuing eradication therapy (Hasanuzzaman et al., 2024). Amoxicillin resistance is less common than for levofloxacin, metronidazole, and clarithromycin in many populations but increasing resistance rates has been documented in some regions. Mechanisms suggested include changes in penicillin-binding proteins and modifications to events affecting cell-wall synthesis (Xu et al., 2022). Tetracycline resistance is also mostly less common but can occur by mutations affecting the ribosomal target in bacteria. Most importantly, however, resistance patterns are neither static nor fixed and can shift in response to antimicrobial prescribing practices and population-level antibiotic exposure (Yu et al., 2024).

Multidrug resistance and treatment failure

The development of *H. pylori* strains resistant to multiple antibiotics has become an extraordinary concern due to the potential for simultaneous resistance, which may limit treatment choices even more substantially. Systematic research has focused on the well-known link between failure of eradication and emergence of resistance, which underscores optimal treatment choice as well as verification of successful eradication after therapy and detailed in a recent work (Al-Jumaily & Al-jubori, 2024). Patient factors affecting the resistance are related to a prior exposure to macrolides, nitroimidazole or fluoroquinolones. Thus, treatment history should be considered when selecting subsequent therapeutic regimens. Increasingly, international recommendations support susceptibility-guided treatment, where appropriate, with avoidance of antibiotics to which resistance is known or suspected. The Maastricht VI/Florence consensus report acknowledges resistance as one of the pillars driving eradication therapy and supports adjusting treatment strategies based on resistance profiles or previous antimicrobial exposure (Malfertheiner et al., 2022).

Geographic variation in resistance

Geographical heterogeneity is a key feature of *H. pylori* AMR. Resistance rates vary widely between countries, and between geographical regions within a country. This variation is mainly due to the differences in antimicrobial consumption, prescribing practices, economic status, prior eradication efforts, diagnostic method and access to healthcare (Medakina et al., 2023). For instance, a systematic review of Indian studies showed vast regional differences in the resistance of metronidazole, clarithromycin, amoxicillin and levofloxacin which suggest that local epidemiological data is an essential component when deciding on treatment (Dutta et al., 2024). Another key challenge between children and adolescents is resistance. Antimicrobial resistance is not isolated to adult populations and can impact decision making early in the indicated white blood cells infection burden, information emerging from a 2024 systematic review of Latin American pediatric populations demonstrated that resistance of H. pylori isolates identified in studies conducted from 2008 to 2023 continues to be notable (Cabrera et al., 2024)

Implications for eradication strategies

As the burden of antimicrobial resistance continues to rock the globe, studies have attempted to deploy and evaluate empirical treatments. Bismuth-based quadruple therapy is still a relevant regimen, particularly in areas of high clarithromycin resistance. Data from a meta-analysis confirm that bismuth inclusion improves eradication efficacy of several therapeutic regimens over placebo (Choe et al., 2024). Moreover, recent interest is given for newer acid-suppressive approaches such as potassium-competitive acid blockers, as it may improve antimicrobial activity and ultimately treatment success due to more effective perturbation of the gastric microenvironment (Ouyang et al., 2024). The evolution of antimicrobial resistance has turned *H. pylori* eradication from a mostly uniform therapeutic approach into one that more and more relies on local resistance rates, prior antibiotic exposure, and past treatment history. Thus, maintenance of eradication efficacy requires continued surveillance coupled with antimicrobial stewardship and susceptibility testing, as well as development of alternative treatment approaches. Because the identification of infected individuals, along with the different management strategies, will effectively limit *H. pylori* infection only when reasonable therapies are prescribed for individual patients, it is especially important to consider both the molecular mechanisms and epidemiological distribution of resistance (Hasanuzzaman et al., 2024; Yu et al., 2024).

Conclusion

The colonization and persistence of the human stomach by Helicobacter pylori is a remarkable ability characteristic of this leading gastric pathogen. Synergistic actions of these virulence factors are responsible for damaging epithelium and causing chronic inflammation, thereby mediating pathogenicity. It can cause gastritis, peptic ulcer disease, gastric atrophy and finally carcinogenesis in susceptible hosts through a persistent infection. Significant obstacles for successful eradication of *H. pylori* are the increasing resistance against clarithromycin, metronidazole, levofloxacin, and other antibiotic classes. This highlights the importance of regional antimicrobial-resistance surveillance, appropriateness of antibiotic selection and susceptibility-guided therapy as well as an improved antimicrobial stewardship. Pathogen virulence, resistance mechanisms, and novel therapeutic avenues with prolonged study on pathogens virulence should still be included within the pursuit

of the goals to enhance the eradication of H. pylori and mitigate the related public health load.

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