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Helicobacter pylori: Epidemiology, Pathogenesis, Molecular Identification, Virulence Factors, and Antimicrobial Resistance – Current Perspectives and Therapeutic Challenges

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ABSTRACT
Helicobacter pylori is a Gram-negative, spiral, microaerophilic bacterium that resides in the stomach of humans, affecting almost fifty percent of the world's population. This microorganism is known to be an etiologic cause of diseases such as chronic gastritis, peptic ulcers, gastric adenocarcinoma, and MALT lymphoma. Its ability to survive in the hostile stomach is made possible through various adaptive mechanisms, including its capacity to produce urease, its motility through flagella, and virulence factors like cagA, vacA, oipA, and dupA. The mode of transmission is believed to be mainly through oral-oral or fecal-oral means, and high incidences of the disease are found in developing nations owing to sociocultural and environmental reasons. The diagnosis of the condition can be achieved using non-invasive procedures, including the urea breath test, stool antigen test, and serologic tests. Invasive procedures such as endoscopic biopsies with histologic assessment, culture, and genetic analysis can be used. PCR-based procedures have improved the ability to detect virulent factors and drug resistance markers in the organism. A combination of antibiotics is generally used as a treatment method, but due to rising drug resistance towards widely prescribed antibiotics like clarithromycin and metronidazole, there has been a decline in successful eradication of *H. pylori* infection, resulting in the emergence of new approaches towards treating this disease. In this review, the focus is on the epidemiology, pathogenicity, virulence factors, methods of diagnosis, and approaches to treatment and management of *H. pylori* infection.

1. INTRODUCTION:

Helicobacter pylori (H. pylori) is also known as the most frequent human pathogen, infecting more than half of the world's population. *H. pylori* is the most important cause of chronic or atrophic gastritis, peptic ulcer, gastric lymphoma, and gastric carcinoma (1). It is a microaerophilic, Gram-negative, spiral coccoid flagellated bacterium with a length of 2-4 µm and a width of 0.5-1 µm. *Helicobacter pylori* colonizes the stomach and intestines of humans and some animal species. *H.pylori* was first isolated in 1983 by Barry Marshall and Robin Warren. The bacteria multiply rapidly in the stomach due to the production of urease, the ability to penetrate mucus using motility, and the ability to adhere to the gastric epithelium (2). Urease makes the bacterial virulence of *H. pylori* high since it converts urea into NH3 and H20, which makes the

Journal of Molecular Science
Volume 36 Issue 1, Year of Publication 2026, Page 309-325
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stomach acid alkaline. It is transmitted through oral-oral, fecal-oral, and gastro-oral routes. It is classified as a class 1 carcinogen by the World Health Organization (WHO) because of its association with peptic ulcer disease and gastric cancer. The prevalence of *H. pylori* infection is 30-50% in developed and 85-95% in developing nations (3). The pathogenicity of the bacterium is caused by a number of virulence factors. The cytotoxic-associated gene A (cagA) protein is injected into the gastric epithelial cell by a unique secretion system called the type 4 secretion system. At the same time, the vacuolating cytotoxin A (vacA) protein is secreted outside the bacterial cell and is engulfed by the host cell (4). The infection causes chronic inflammation due to the release of cytokines (IL-1β, IL-6, TNF-α) and immune cells, but *H. pylori* evades the immune system by antigenic variation, molecular mimicry, and immune suppression. There is also modulation of mucin synthesis, which reduces the protective mucus barrier. With time, this chronic infection and inflammation result in tissue damage, peptic ulcers, and genetic instability that pose a substantial risk for the development of gastric adenocarcinoma and MALT lymphoma, besides being associated with extra-gastric diseases such as cardiovascular and autoimmune diseases (5). In other nations, it was reported that the majority of the bacterial strains express CagA and VacA, and that the proteins encoded by these virulence proteins have varied clinical consequences (6). This review compiles existing information on its epidemiology, pathogenesis, clinical significance, antibiotic resistance, and novel diagnostic and treatment approaches, with a focus on the recent molecular insights into the bacterium.

Epidemiology:

Global Prevalence & Geographic Distribution:

However, its global prevalence rate has fallen since the beginning of the 1990s, having declined from 52.6% before 1990 to 43.9% from 2015 to 2022 (7). Nevertheless, developing nations like Cameroon, Chile, Bangladesh, and Bhutan keep having a high prevalence, standing over 50%-70%, mostly because of sanitation issues, among other aspects (8). According to research, there has been a consistent decline in the prevalence of *H. pylori* infections over time, especially among children, largely due to improvements in hygiene standards, more antibiotic usage, and increased public health interventions (9). Moreover, *H. pylori* infections have been linked to other illnesses, including diabetes, autoimmune thyroiditis, glaucoma, osteoporosis, as well as neurological and dermatological problems (10). This means that there could be some connection between the infection by this bacterium, inflammation, and immune response. In general, it would be right to suggest that *H. pylori* remains a major public health concern worldwide, even though it is not as common as before. It also manifests a varied distribution pattern in different countries, races, and at-risk populations.

Age, Socioeconomic, and Environmental Factors Influencing *Helicobacter pylori* Infection:

Helicobacter pylori infections show greater prevalence among some age groups, mainly due to an infection that usually happens during childhood and persists into adulthood in the absence of treatment. Colonization occurs during the first five years of life among children born in developing countries. Adulthood acquisition is, however, quite rare (11). Socioeconomic factors are among the most determining factors in the transmission of *Helicobacter pylori* infection. Several studies have shown the clear relationship between poor socioeconomic status, such as poverty, education level, crowding, lack of healthcare provision, and infection from *Helicobacter pylori* (12). More often than not, poor socioeconomic status results in delays and inefficiencies in treatment procedures, leading to more serious cases, including those of antibiotic-resistant infection. Environmental determinants significantly influence the spread of the organism at the global level. Poor sanitation, improper sewage disposal, utilization of contaminated water, and insufficient hygiene in food handling have all been associated with an increased prevalence of the bacterium (13). Ingestion of poorly washed or improperly washed foods may enhance infection levels, just like consumption of contaminated water. There is a considerable reduction in infection levels in highly industrialized nations, which has been attributed to better water quality, improved sanitation, housing, and hygiene levels among the population (14).

Transmission and Risk Factors:

Route of Transmission:

Transmission methods are not known accurately, but experts have highlighted two modes of transmission, namely, oral-to-oral and oral-to-fecal transmissions. Transmission mostly occurs when one has proximity to others, particularly in environments where the bacteria are prevalent. It is also possible for one to contract it when they are exposed to saliva during sexual intercourse involving the bacterium, or even when they share utensils with a person already infected with the bacteria(15). This risk is higher in settings with poor sanitation and hygiene practices. Although less common, transmission in healthcare environments has also been reported. Overall, both interpersonal contact and environmental exposure contribute to the spread of *H. pylori.*

Journal of Molecular Science
Journal of Molecular Science
Volume 36 Issue 1, Year of Publication 2026, Page 309-325
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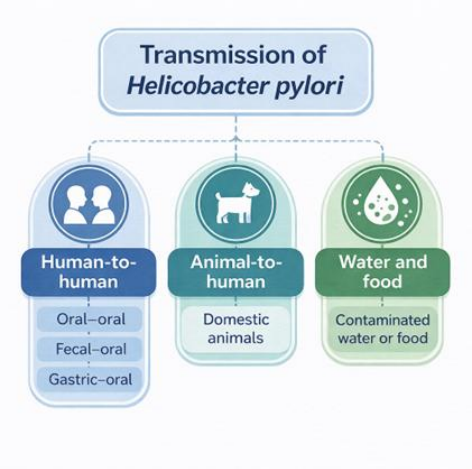

Fecal-Oral Route:

Helicobacter pylori finds itself in the gastric juices and has a chance to move around the digestive tract to be later released from the body with feces. This opens up the potential for the transmission mechanism, either through direct contact or due to ingestion of contaminated food or water. It seems like it is difficult for *H. pylori* to withstand such an environment, as it might have high levels of bile acids, among other factors. The DNA of *H. pylori* was found in the stool. Sometimes, the viable cells could even be isolated from patients suffering from diarrhoea. The epidemiology of this issue depends on where the research was done. So, in Brazil, *H. pylori* infections were associated with the possibility of fecal transmission, such as the co-infections with Giardia, as well as lower sanitation levels. No evidence has been found regarding hepatitis A virus in Turkey and Taiwan (16).

Oral- Oral Route:

The presence of oral-oral transmission is possible as *Helicobacter pylori* bacteria are detected in saliva, dental plaque, tonsils, and even in the gastric juice. Such facts prove that infection occurs because of contact with the mouth as the primary source of infection. Ordinary actions such as kissing, pre-chewing of food for babies, common usage of eating utensils and toothpicks, vomiting, and regurgitation can facilitate the transmission of the pathogen. In addition, medical manipulations such as endoscopy can lead to nosocomial infection. The proof that the mouth plays an important role in the process of infection is the high rate of detecting *Helicobacter pylori* bacteria in the mouth (saliva, dental plaque, and dental pulp). Strains of pathogens that are detected in the mouth may be similar to strains in the stomach, indicating that bacteria can become the source of re-infection. The survival of bacteria despite the unfavourable environment in the mouth is provided by the formation of biofilms, interaction with microflora, and hibernation (17).

Gastro- Oral route:

Transmission via the gastric- oral route is one of the most commonly recognized forms of *H. pylori* transfer, especially in children. If someone throws up, the gastric juices filled with the living pathogens will get into the environment, leading to a high probability of spreading. Scientific studies confirm that *H. pylori* pathogens survive in the extra-body environment, and the vomitus can include large amounts of bacteria, thus providing a reasonable explanation for the spread through this route, especially in conditions of poor hygiene (18). Clinical evidence confirms that considerable numbers of pathogens were identified during the analysis of infected persons' vomitus, sometimes even in the ambient air when the process of throwing up took place. This provides sufficient evidence of the ability of *H. pylori* to be transmitted directly by this route, especially in crowded places like homes and institutions. The additional proof comes from the observation that people in institutions who have the habit of regurgitating food have higher rates of *H. pylori* infections (19).

Host, Environmental, And Lifestyle Risk Factors:

The response to *H. pylori* infection and its effects on people's health may vary significantly, and a person's genotype is a crucial factor in this regard. Mutations in certain genes that control immune function, such as those that encode the cytokines IL-2 and IL-6 and the TLR1 receptor, may shift the direction of the immune response to the infection. This leads to different outcomes, while one patient stays healthy without symptoms, another may even develop stomach cancer (20).

Lifestyle choices and environmental factors have also been found to play an important role in determining susceptibility to infection. Among these, hygiene habits and the availability of clean water are particularly influential. Higher infection levels have been seen among those practicing poor hand hygiene and using contaminated sources of water, such as well water. Factors like eating habits and general lifestyle do not seem to have much impact (21). Moreover, there are several medical and environmental factors that can upset the equilibrium in the microbiome of the stomach. Such disruption is referred to as gastric dysbiosis and can be brought about by diet, age, tobacco usage, and alcohol consumption. Medical conditions can even have a more pronounced impact on altering the equilibrium. Long-term use of antibiotics, PPIs, and NSAIDs is known to adversely affect the microbiota of the stomach (22).

Survival in the Gastric Environment:

Acid Resistance Mechanism:

Journal of Molecular Science
Volume 36 Issue 1, Year of Publication 2026, Page 309-325
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The *H. pylori* is able to maintain its optimal physiologic activity in the very hostile acidic environment inside the stomach due to the fact that the surface urease does not function well at low pH. Organisms achieve this by maintaining an ideal buffer system within their structure. One way *H. pylori* maintains homeostasis regarding pH regulation involves the use of a protein channel called UreI, which is activated in low pH environments. Once activated, the UreI protein facilitates the transportation of urea to the interior part of the cell. Inside the cell, the urea will then undergo hydrolysis using urease to produce ammonia and carbon dioxide. Ammonia helps neutralize the acidity inside the periplasm to bring it back to a more manageable level, which is around 6.2, while carbon dioxide is used as a buffer inside the cell.(23,24).

Role of Urease and Ph Regulation:

The urease enzyme is large and consists of subunits, and the enzyme complex is composed of UreA and UreB. The enzyme is essential for the bacteria's survival in the stomach due to its ability to convert urea to ammonia and carbon dioxide, thus creating an alkaline microenvironment near the bacteria. However, apart from being a protective factor, urease also takes part in pathogenicity. For instance, urease can interfere with epithelial tight junctions, alter the mucus layer, and activate immune cells, thereby contributing to inflammation. Apart from the catalysis process, urease has been associated with other mechanisms, including the prevention of apoptosis in gastric epithelial cells and angiogenesis stimulation by changing regulatory factors (25). To increase its survival probability in an acidic environment, *H. pylori* quickly regulates its genes according to environmental changes. For example, low pH stimulates the urease gene cluster, comprising ureA, ureB, and accessory genes, to ensure efficient conversion of urea to ammonia through the UreI channel. At the same time, the bacterium accelerates its metabolism. It activates the mechanisms for the uptake of glutamine and glutamate dehydrogenase, which maintains the synthesis of ammonia. In addition, it increases the expression of genes encoding motility, fine-tunes the flagellum, and moves towards regions of the stomach where conditions are more favourable. Importantly, not all reactions are uniformly activated during acid shock; some genes are inhibited. Genes involved in pathogenicity, such as cagA and vacA, as well as outer membrane proteins, are suppressed, suggesting that the bacteria stop interacting with the host to ensure survival. Regulatory processes do not stand still; two-component regulatory systems, including HP1021, are activated, confirming their importance in managing acid shock. There are genes whose repression does not affect survival in vitro but hinders colonization in the host. Overall, *H. pylori* copes with changes in pH using a holistic approach involving metabolic adaptation, increased mobility, and regulation of virulence factors (26).

Motility and Chemotaxis:

Flagellar Structure & Function:

In most bacteria, the structure of flagella is rather basic: basal body, hook, and filament. However, in the case of H. pylori, the flagellum has four important components: basal body, hook, filament, and sheath. The basal body contains rings and motors responsible for rotation and secretion of flagellin protein. The hook consists primarily of FlgE protomers and serves as a hinge point that allows the bacteria to move with great force despite the high viscosity of the environment. The flagellum filament itself is constructed from two types of proteins: FlaA and FlaB flagellins, which work together with additional proteins such as FliD, HpaA, and FaaA, producing propulsion forces and providing stability to resist depolymerization under acidic conditions (27). This attachment occurs through a terminal bulbous part, and the flexible, fluid sheath covers the flagellum. The flagella of *H. pylori* not only facilitate the motility of this organism through the mucosa towards its attachment site on the epithelium but also serve as a virulence factor. This is due to their ability to aid the organism's invasion and evasion from the immune system. The other aspect of the flagella is that they provide antigenic and phase variation, enabling this organism to survive within the host through immune evasion (28).

Chemotactic Responses and Mucus Penetration:

The bacterium detects the presence of urea gradients using chemoreceptors, which initiate signalling pathways that inhibit tumbling and promote directed movement. Thus, they are able to move effectively towards more favourable habitats. The role of urease is twofold; first, it breaks down urea to ammonia, which neutralizes the acidic contents of the stomach; second, it changes the surrounding environment to enable easy movement through mucus (29). Bacteria detect levels of urea gradients using their chemoreceptors and associated signalling cascades. This leads to behavioural changes were, instead of random tumbling, they now swim in a directed manner towards environments rich in nutrients(30). Following ingestion, urease breaks down urea into ammonia, which neutralizes the gastric acid and, at the same time, modifies the bacterial environment to allow for easier navigation through the viscous mucus in the stomach (31). Following ingestion, urease breaks down urea into ammonia, which neutralizes the gastric acid and, at the same time, modifies the bacterial environment to allow for easier navigation through the viscous mucus in the

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stomach.

Role of Motility in Colonisation:

Motility is one of the most important features associated with the ability of the bacteria from the genus Helicobacter to cause infection. As mentioned earlier, the flagellum is responsible for the mobility of the bacteria within the thick mucus layers covering the inner walls of the stomach. Thus, the bacterium uses motility to reach the epithelium and infect a human being. It was shown that motility plays a critical role in establishing infection because flagellated strains without motility do not infect any animals due to their inability to move (32). The structure of the bacterium itself allows moving in a corkscrew fashion through viscous layers thanks to the presence of flagellae and a spiral shape. In addition, a chemotaxis system of the bacteria allows finding a way through a thick layer of mucus because of the ability to sense environmental changes. For example, changes in pH were found to be used by the bacterium as an indicator of better conditions for colonization of the stomach. Therefore, *H. pylori* uses pH values to move to different regions of the stomach, including the antrum with low acidity, followed by the colonization of the corpus (33). Motility is an indispensable component of the success of the bacterium in causing an infection; thus, experimental studies showed that a lack of flagella leads to decreased ability to colonize the stomach, while normal bacteria can cause infection even at low concentrations. In case of co-infection, motile strains survive longer than non-motile strains (34).

Major Virulence Factors of h. Pylori:

Urease:

One of the most important virulence factors of *H. pylori* is the enzyme urease, which is secreted by the bacteria in massive quantities. The primary mechanism of action involves degradation of urea to ammonia and carbonic acid via a nickel-dependent mechanism, resulting in pH increase. As a result, a favourable microenvironment that protects the pathogen from the highly acidic milieu is formed. There are two types of urease depending on their localization, namely external and internal. External urease, which is often extruded as a result of bacterial cell lysis, exhibits enzymatic activity in an alkaline pH environment and does not contribute significantly to acid resistance. On the contrary, the internal form of urease plays an extremely crucial role in the pathogen's life cycle. This enzyme acts intracellularly and performs such functions as protection against gastric acid, support of metabolism, and facilitation of colonization (35). Besides acid-neutralizing ability, urease is responsible for a range of host-cell interactions performed by *H. pylori*. The enzyme consists of UreA and UreB subunits. These proteins can be transported into gastric epithelial cells via cholesterol-mediated endocytosis, which leads to changes in the expression of apoptosis-regulating proteins. In particular, the level of the anti-apoptotic Bcl-XL is increased, while that of the pro-apoptotic BAD protein is reduced, causing cell survival (37). Apart from that, *H. pylori* urease is capable of affecting angiogenesis in the stomach. This factor leads to increased production of pro-angiogenic cytokines and growth factors along with a reduction of inhibitors of angiogenesis (38). All in all, the results discussed above suggest that *H. pylori* is not inherently resistant to high pH and relies heavily on urease to protect itself from the acid, providing optimal conditions for further proliferation and colonization (39).

Flagellum:

The flagellum of *H. pylori* is a sheathed structure that is critical to the mobility and pathogenicity of the bacterium (40). By means of this special structure, the organism can move through the thick and sticky mucus layer of the stomach necessary for efficient colonization. There are usually multiple flagella present on one pole of the bacterium's body. These enable the bacterium to move inside the gastric mucus, allowing the organism to come into close contact with the surface of the epithelium (41). The bacterium also uses a number of regulatory proteins involved in the synthesis and functioning of the flagella. It should be noted that *H. pylori* synthesize a unique group of flagellar switches, including FliG, FliM, FliN, and FliY. While the presence of FliG and FliM is required for flagella formation and mobility (the absence of these proteins results in non-motile bacteria lacking flagella), FliN and FliY proteins perform similar functions. Each of these proteins is sufficient for partial functionality of the structure; however, both are required for its proper formation and complete mobility (42).

Cytotoxic Associated Gene A:

Another critical virulence factor of *H. pylori* is known as CagA (cytotoxin-associated gene A), which is part of the cag pathogenicity island (PAI). After invading the gastric epithelial cells, CagA protein is transferred to them via a type 4 secretion system. As a result, CagA is subsequently phosphorylated on specific sites in the protein (EPIYA motifs) and interacts with essential cellular signaling pathways (43). One of the significant impacts of the CagA protein after tyrosine modification is the interaction with cellular proteins, including SHP2 phosphatase. Such interactions result in inappropriate cell signaling that causes changes in cell growth and movement, thus forming characteristic cellular elongations called the

Journal of Molecular Science
Volume 36 Issue 1, Year of Publication 2026, Page 309-325
DoI-10.004687/1000-9035.2026.040

"hummingbird phenotype" (44). Ultimately, these alterations lead to further tissue injury. The presence of the cagA-positive strains increases the risk of developing severe gastric disorders, including gastric adenocarcinoma, as a consequence of CagA protein's activity. Thus, CagA protein can promote the formation of inflammation and tumor suppression, as well as cause epithelial-mesenchymal transition (45). The distribution of the cag pathogenicity island across the globe varies; for example, about 70% of *H. pylori* strains have cagA in comparison with 95% of East Asian isolates but only 60% of Western samples (46). Hence, overall, the cagA protein has a substantial contribution to more severe diseases associated with *H. pylori* infections, especially peptic ulcer disease, gastric cancers, and MALT lymphomas (47).

Vacuolating Cytotoxin A Gene:
The vacA gene encodes a protein called VacA, which is roughly 140 kDa in size and crucial for colonization and disease pathogenesis. While the gene is found in almost all *H. pylori* strains, the protein is synthesized in an inactive form and later cleaved to an active protein weighing 88 kDa. The latter inserts itself in host cell membranes, creates anion-selective channels, and induces the creation of large cytoplasmic vacuoles (48). Nonetheless, even though the gene is ubiquitous, the sequence variability is relatively high, especially in the signal (s) and middle (m) domains. Differences in their expression result in varying levels of toxicity. For instance, s1/m1 genotypes show much greater cytotoxicity than s2/m2 variants and correlate with more pronounced gastric diseases (49). Functionally, VacA engages the gastric epithelium with its p55 domain, while the p33 domain is necessary for channel formation. These channels disrupt ion homeostasis by allowing chloride ions to influx, causing osmotic disturbances and creating vacuoles resembling endosomes and lysosomes (50). Furthermore, VacA influences many other biological processes. Namely, it targets the mitochondrial network, promotes fragmentation, and activates apoptosis pathways. VacA also inhibits autophagy, disrupting the intercellular tight junctions and diminishing the barrier function of the stomach lining.

Additionally, VacA modulates the host immunity response. Specifically, it prevents T-cell activation and proliferation, thereby reducing the organism's capability to eliminate the infection and increasing the bacterial persistence. In conclusion, VacA facilitates the establishment of infection by damaging cellular structures and impairing immunity, contributing to chronic inflammation and increased chances of gastric diseases, such as peptic ulcers and cancer (50,51).

Outer Inflammatory Protein A:
Outer inflammatory protein A (OipA) is an essential factor present in the outer membrane of *Helicobacter pylori* responsible for adherence and the inflammatory response. This factor assists the bacteria in adhering to the epithelial lining of the stomach and stimulates production of inflammatory cytokines, such as interleukin-8 (IL-8), causing mucosal inflammation. The expression of the oipA gene is regulated through the slipped-strand mispairing process in CT repeats that regulate its function between on (expressed) and off (not expressed). In cases where OipA is expressed, it has shown a positive correlation with duodenal ulcers, and the presence of OipA is significantly higher among patients with ulcers rather than non-ulcer gastritis. The expressed form correlates with high bacterial colonization and an increased number of infiltrating inflammatory cells, particularly neutrophils, and elevated IL-8 concentration in the stomach lining. (53).

According to structural analysis, OipA can be described as a β-barrel protein that has external parts that facilitate binding of OipA to the surface receptors of host cells, which include some components of the HGF–MET pathway. Using such interaction, apart from helping bacteria adhere, OipA might even affect host signalling and proliferation. Such properties of OipA, which contribute to both colonization and manipulation of host responses, are likely to increase inflammation and may cause a higher chance of developing gastric carcinoma (54).

Duodenal Ulcer Promoting Gene A:
The dupA gene (duodenal ulcer–promoting gene A) acts as a virulence factor that is located within the plasticity region of the *H. pylori* chromosome. The gene consists of two components, jhp0917 and jhp0918, homologous to VirB ATPases, involved in bacterial secretion systems. The dupA gene was found to be associated with an increased susceptibility to duodenal ulcers, while at the same time reducing the risk of developing atrophic gastritis and gastric cancer. These facts show that the gene might serve as a biomarker of a disease (55).

Two types of dupA genes have been described: a functional dupA1 gene and a non-functional dupA2 gene. The functional dupA1 gene is found in patients with duodenal ulcers more often than in patients with stomach ulcers or those without ulcers, indicating an association of the gene with duodenal ulcers. Additionally, the functional dupA1 gene is correlated with another genetic factor responsible for the antibiotic resistance, clarithromycin resistance mutation A2147G, but no associations

Journal of Molecular Science
Volume 36 Issue 1, Year of Publication 2026, Page 309-325
DoI-10.004687/1000-9035.2026.040

were found with other resistance mutations like A2146G or levofloxacin (56).

According to epidemiological evidence, the significance of dupA is regional, as shown by the strong association between dupA and duodenal ulcer found in certain areas of East Asia, as well as some countries such as India, South Korea, China, and Iraq. Nonetheless, there have been conflicting results from other nations, including Brazil, Iran, and Turkey, among others, and Western countries. In general, dupA's intactness and functionality are more significant in the clinic, especially in relation to duodenal ulcer, than the pathogenesis of gastric cancer (57).

Gene Functionb Mechanism Clinical Association:
cagA Cytotoxin-associated gene- A Injected into gastric epithelial cells, disrupts the cell signalling pathway.Gastric cancer vacA Vacuolating cytotoxin A Enhance colonization and cause gastric cell damage. Epithelial damage, ulcer oipA Outer inflammatory protein A Enhance IL 8 secretion Inflammation dupA Duodenal ulcer-promoting gene Stimulate inflammatory pathways Duodenal ulcer

Table 1: Key Virulence Gene of *Helicobacter pylori* (Sterbenc et al.)

Gene	Function	Mechanism	Clinical association
cagA	Cytotoxin-associated gene- A	Injected into gastric epithelial cells, disrupts the cell signalling pathway.	Gastric cancer
vacA	Vacuolating cytotoxin A	Enhance colonization and cause gastric cell damage.	Epithelial damage, ulcer
oipA	Outer inflammatory protein A	Enhance IL 8 secretion	Inflammation
dupA	Duodenal ulcer-promoting gene	Stimulate inflammatory pathways	Duodenal ulcer

Lipopolysaccharide & Immune Evasion:
Helicobacter pylori Lipopolysaccharide (LPS) has been identified as a key molecule enabling *H. pylori* to escape the host immune response. In contrast to enterobacterial LPS, which is well recognized by the host immune system, LPS of *H. pylori* is much poorer in activating the innate immune system, thus exhibiting very poor pyrogenic and mitogenic activities (58). Poor ability of LPS in stimulating the host immune system is mainly attributed to the structure of lipid A, which is composed of shorter fatty acids with fewer acyl chains. In comparison with typical enterobacterial LPS, it possesses lower endotoxic activity, thereby inducing weak NF-κB activation via TLR4 and low expression levels of pro-inflammatory cytokines, including IL-1β, TNF-α, and IL-8 (59). In addition to its anti-inflammatory effects, *H. pylori* LPS also hinders antigen presentation. It inhibits the trafficking of MHC class II molecules to the cell membrane, leading to their accumulation inside the cell. This reduces the ability to activate CD4+ T cells and impairs the adaptive immune system. An additional characteristic of the LPS is the variable presence of Lewis antigens, LeX, and LeY. They have the potential to bind with the DC-SIGN receptor on dendritic cells and induce the secretion of anti-inflammatory cytokines like IL-10, thereby favouring an immune response dominated by Th2-type reactions (60).

Pathogenic Mechanism:
Host pathogen Interaction:
Helicobacter pylori infection occurs through attachment of the pathogen to the gastric mucosa using multiple adhesins such as BabA, SabA, AlpA/B, HopZ, and surface-associated urease. This process allows the bacterium to bind tightly to the host cells. Moreover, the action of urease inactivates the gastric acid environment, thus making it easier for bacteria to survive. Bacterial virulence involves the injection of effector proteins like CagA into host cells using the type IV secretion system. In host cells, CagA modifies signaling pathways and junctions between epithelial cells, causing tissue damage and inflammation. Another protein, VacA, leads to the development of vacuoles, mitochondrial dysfunction, and apoptosis, as well as affects antigen processing and T-cell responses (61).

Moreover, there are some immune evasion mechanisms that are used by the bacterium. Modifications in the lipopolysaccharide and flagellin of the bacterium prevent the interaction of these proteins with immune receptors. The ability of *H. pylori* to inhibit the maturation of dendritic cells and expansion of regulatory T cells helps to escape immune attack (49). As for host factors, genetic variation is important for disease progression and severity. Genetic variation may affect susceptibility and severity of inflammation caused by *H. pylori* due to polymorphisms in cytokine genes and innate immune receptors. Inflammation is associated with high concentrations of pro-inflammatory cytokines (IL-1β, TNF-α, IL-8), leading to oxidative stress and DNA damage in the long-term period. This process leads to malfunctioning of repair systems, which results in the development of complications, such as gastric cancer. In conclusion, depending on the virulence of *H. pylori* and the host genetic background, the disease develops as chronic gastritis or as peptic ulcers, lymphoma, or carcinoma (62).

Journal of Molecular Science
Volume 36 Issue 1, Year of Publication 2026, Page 309-325
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Immune Modulation & Chronic Infection:
Helicobacter pylori bacteria have a unique ability to manipulate the immune response of their host, helping them remain within their host for prolonged periods and influencing the type of inflammation created. One important mechanism by which *H. pylori* manipulate immune responses is its ability to influence dendritic cells. Rather than activate these cells completely, it leads to the development of immature or semimature dendritic cells that help induce the proliferation of regulatory T cells through the production of IL-18, IL-10, and TGF-β cytokines (63). Regulatory T cells help dampen T-cell immunity against both allergens and self-antigens as well as limit Th1 and Th17 activity, thus reducing inflammation caused by the bacterium. Although these responses play an important role in preventing tissue damage caused by the initial inflammation, they also enable the bacteria to remain within the body and cause chronic infection, which leads to more serious illnesses such as chronic gastritis, peptic ulcers, gastric carcinoma, and MALT lymphomas. With research shifting away from eliminating the bacteria to manipulating the immune responses, more focus is being placed on inducing protective responses, including Th2 and mucosal antibodies (64).

Clinical Manifestation & Disease Outcome:
Chronic Gastritis:
The condition of chronic gastritis is characterized by the presence of an enduring inflammation in the stomach wall. Chronic gastritis normally starts with an acute form of inflammation, which gradually progresses into more permanent effects like atrophy of the epithelium, reduction in mucin secretion, development of pit abscesses, and formation of lymphoid follicles in the gastric mucosa (65).

The occurrence of this disease is extremely widespread; it affects about half of the world's population, and its frequency is increased in areas that are affected by social and environmental determinants. The significance of this disease is associated with the possibility of developing more severe diseases, such as stomach atrophy, peptic ulceration, adenocarcinoma, and even lymphoma. Due to its close link to stomach cancer, *H. pylori* was defined as a Class I carcinogen (66).

The eradication of the infection will help improve some of the initial lesions, especially gastric atrophy, and possibly prevent the development of cancer. On the other hand, the effects of the infection in some of the advanced lesions, like intestinal metaplasia, are unpredictable. This is due to the fact that once the lesion becomes too advanced and some molecular and structural alterations occur, there might be no chance of reversing the effects. As such, early diagnosis and treatment of the infection are the most efficient methods of prevention (67).

Peptic Ulcer Disease:
Peptic ulcer disease involves the development of an ulcer or an open sore in the stomach and proximal regions of the small intestine. This disease results from an imbalance in the interaction between harmful factors and protection mechanisms in the mucosal tissue. The two common causes of peptic ulcer disease are infection caused by *Helicobacter pylori* and chronic use of NSAIDs. Individuals affected by peptic ulcers often have symptoms including epigastric pain, nausea, and feeling full. Complications include gastrointestinal bleeding and perforation that may prove fatal in some instances (68). Identification of the causative agent for peptic ulcer disease resulted in considerable advances in management strategies. Initially, treatment methods were aimed at reducing acid secretion, but the treatment has evolved to focus on the eradication of the infection. The bacterium invades the stomach tissues, producing enzymes and toxins that harm the epithelial tissues, causing inflammation and ulcers (69).

Gastric Adenocarcinoma:
Gastric adenocarcinoma is one of the most common types of stomach cancer, which originates in the glandular cells of the stomach. The incidence of the disease varies from place to place, with high levels observed in East Asia, South America, and Eastern Europe, as compared to low levels in North America and Africa. In general, the development of this cancer is a slow process resulting from gradual damage to the stomach mucosal membrane. This condition is primarily caused by the presence of the bacterium Helicobacter pylori, which induces a series of events beginning with gastritis and ending with carcinoma (70). Other environmental and behavioural risk factors also contribute to disease development. High-salt diets and the use of salted or smoked foods increase risk, as does the low consumption of fresh fruits and vegetables. The smoking habit also serves as a known risk factor for developing this condition. Also, a genetic predisposition can have a direct impact on the development of the disease, exemplified in hereditary diffuse gastric cancer caused by a mutation in the E-cadherin gene. Along with all these risk factors, *H. pylori* infection is still considered one of the main contributors to carcinogenesis in stomach cancers (71). Genetically, gastric adenocarcinoma is a very heterogeneous form of cancer with multiple subgroups. These are cancers that may be associated with chromosomal instability, microsatellite instability, Epstein–Barr virus (EBV) association, and genome stability.

Journal of Molecular Science
Volume 36 Issue 1, Year of Publication 2026, Page 309-325
DoI-10.004687/1000-9035.2026.040

Mutations in TP53, ARID1A deletion and mutations, and RHOA mutations are often identified in the tumors alongside amplifications of oncogenes, including HER2, EGFR, and MET. Apart from these mutations, epigenetic changes, the functioning of non-coding RNA molecules, as well as the involvement of tumor-associated components, such as angiogenesis and immune cells, also have great significance in disease pathophysiology (72).

Malt Lymphoma (Mucosa-Associated Lymphoid Tissue Lymphoma):
MALT lymphoma is an extra nodal marginal zone B cell lymphoma typically found in the stomach and strongly linked with chronic *Helicobacter pylori* infection. In a healthy individual, there would be no organized lymphoid tissue in the stomach. However, due to long-standing infection, there would be the development of lymphoid follicles that would appear like MALT. In some individuals, the chronic inflammation, coupled with virulence factors like CagA and VacA, among others, and some genetic features of the host, may lead to the generation of a malignant B cell clone (73). The continuous antigenic stimulus from the microbe contributes significantly to this development. It causes continued activation and proliferation of B cells with the assistance of T cells, and in some instances, the condition may become aggressive and advance to diffuse large B cell lymphoma (74). Clinically, most cases are associated with nonspecific symptoms in the gastrointestinal tract that may pose a challenge in diagnosing the problem. Diagnosis of the disease is carried out based on the results of histopathology and immunohistology, which reveal the expression of CD20 and Bcl-2. Management of the disease will depend on the affected body organs and the stage of the condition. For instance, many cases of gastric MALT lymphoma will be associated with the eradication of H. pylori, causing regression of the growth of tumors (75). On the other hand, in cases where the disease affects the small intestine, additional strategies might have to be taken, like chemotherapeutic treatment or surgery.

Diagnostic Methods:
Invasive Method:
1, Histology:
Gastric biopsy samples viewed microscopically remain one of the most dependable ways to diagnose *H. pylori* infection. Using a routine hematoxylin and eosin (H&E) stain, it may be possible to visualize the bacteria directly, but this method relies on certain parameters like bacterial density and location in the sample. To increase accuracy, specific staining methods are employed to ensure that both sensitivity and reproducibility are increased (76). These diagnostic tools are effective, but IHC stands out because of its great sensitivity and specificity. This method can detect low levels of bacteria, such as coccoid bacteria, and can give further data regarding strain typing. Another important factor is that biopsy specimens must be collected in a particular way; sampling from the corpus along with the antrum will enhance the rate of detection. Nevertheless, there are certain disadvantages associated with histology as well. Firstly, sensitivity can be decreased by some factors, such as gastric atrophy and intestinal metaplasia, because bacterial density decreases under these conditions. Second, the uneven distribution of the *H. pylori* infection leads to false results as well (77).

2, Rapid Urease Test:
The Rapid Urease Test (RUT) is a popular invasive procedure that is utilized for testing *H. pylori* infections, due to the organism's ability to produce a large amount of urease. In particular, the procedure includes inserting a small piece of a gastric mucosal tissue in a solution, which contains urea and a pH sensitive indicator during an endoscopy. The presence of the bacterium will result in the splitting of urea into ammonia and carbon dioxide, which leads to a pH increase and subsequent colour change, mostly from yellow to red/pink.

Among the benefits of using the RUT test is the availability and ease of use, as well as the low cost and short duration of the test. In general, the effectiveness of the procedure is rather high, with the sensitivity level ranging between 80-100%, while specificity is usually very high, at 97-100%. However, its accuracy may be affected by various factors, including the location of the biopsy and bacterial colonization density. It has been observed that false-negative results occur due to recent use of proton pump inhibitors, antibiotics, and bismuth preparations. This happens because these drugs inhibit bacterial growth. Additionally, certain factors like intestinal metaplasia and reduced bacterial load may lead to negative results. However, false-positive results are rare and may be observed if there are urease-positive bacteria other than H. pylori, especially in tests conducted after long incubation periods (78,79). Although this test is not perfect, it is still valuable for the diagnosis of *H. pylori* infection.

3, Culture:
Helicobacter pylori culture requires special handling of the gastric biopsy specimen and strict incubation conditions. The biopsy specimen is usually minced and suspended in saline before inoculation on selective media like Columbia agar supplemented with 5% sheep blood or chocolate agar. These cultures are grown aerobically in an atmosphere containing 5% CO2 for about 10 days at 35 °C. Parallel to the above, a culture tube for urease testing can be grown and examined after 30 minutes,

Journal of Molecular Science
Volume 36 Issue 1, Year of Publication 2026, Page 309-325
DoI-10.004687/1000-9035.2026.040

4 hours, and 24 hours, with a maximum period of 48 hours for the absence of growth taken as negative results (76). Colonies growing are usually small and gray to white with a moist appearance and are identified based on their typical curved Gram-negative morphology with oxidase, catalase, and urease tests (80). Different media may be employed, such as Brucella, Columbia, brain-heart infusion or trypticase soy agar, usually containing additional elements, such as blood to stimulate the organism's growth. In certain instances, β-cyclodextrin or egg yolk emulsion can be applied as an alternative to blood products. When working with liquid media, special media, such as Brucella medium with fetal bovine serum, are usually used, with additives like charcoal, starch, or β-cyclodextrin being added to eliminate toxic metabolites (81). Despite the great amount of information received by using cultures, this test is not regularly performed, since it is complicated, requires a lot of time, and is quite insensitive compared to other tests.

4, Molecular Methods:

The molecular methods of diagnosis are currently considered a powerful tool in the detection and research of H. pylori, which can be attributed to their sensitivity and specificity. The molecular diagnostic approach allows not only detecting the pathogen but also its virulence factors and any mutations leading to antibiotic resistance. Another significant advantage of molecular techniques is that they do not need invasive sampling; they can be used on both gastric biopsy samples and on stool and saliva samples. Among the molecular techniques for detection, PCR is one of the most popular methods and is often used as a good alternative to cultivation. The conventional PCR and RT-PCR can be used to directly detect *H. pylori* DNA from patient materials, including gastric tissue, gastric juice, saliva, and stool samples. These techniques are characterized by high speed and the ability to estimate the bacterial load in patients. Moreover, they can use either the conserved sequences (16S rRNA/16S rDNA) or virulence factor genes (cagA/vacA) (82). However, more sophisticated methods like digital PCR and next-generation sequencing (NGS) provide an even greater degree of accuracy. Such methods allow the bacterial genome to be studied in depth, thereby giving valuable information on the nature of genetic diversity, the mechanism behind antibiotic resistance, and transmission. Even though molecular techniques present many strengths, there are still drawbacks associated with them. Molecular testing is quite costly, requires special tools, and can easily get contaminated when not done right.

Non-Invasive Methods:

Urea Breath Test:

One of the most popular tests to diagnose *H. pylori* infection is called the urea breath test (UBT). This test involves ingesting labelled urea, which is broken down by urease into ammonia and CO2. Urease is produced by H. pylori, and therefore only infected individuals will breathe out labelled CO2 (83). UBT is often used not only for initial diagnosis but also as a follow-up test to prove eradication of the infection, as it does not measure antibodies that were already developed against the bacteria, but only active infections. The test is highly sensitive and specific; the values of sensitivity and specificity are over 90–95%. However, the accuracy of the test might be compromised by recent intake of proton pump inhibitors, antibiotics, and bismuth compounds, which inhibit urease production and thus lead to false negative results. Therefore, before conducting UBT, all those medications should be stopped (84). However, certain limitations should be mentioned. The chances of getting false positive results are relatively low, yet they may happen because of the existence of other bacteria that produce urease. Moreover, this test does not reveal any information regarding the resistance of the bacteria to antibiotics. Another disadvantage of the radioactive version of this test (^{14}C-UBT) is its radioactivity, which makes it undesirable for pregnant women to undergo it. However, despite the mentioned limitations and absence of strict protocols, this test remains preferable (85).

Stool Antigen Test:

The Stool Antigen Test can be considered as one of the most convenient and easy ways of detecting *H. pylori* infections in an individual. They are not only affordable but are also commonly used in clinical settings. There are two kinds of SATs that exist: enzyme immunoassays (EIA) and immunochromatographic assays (ICA). EIA testing methods that utilize monoclonal antibodies exhibit great levels of reliability and precision; hence, they are suggested as the best choice by many international guidelines both for diagnosing *H. pylori* and as confirmatory tests after eradication (86).

Serology:

Serological testing is another simple technique used for the detection of *H. pylori* infection and can be considered as the first-line test in most settings because of its simplicity and non-invasive nature. Serological tests detect IgG antibodies produced in response to the presence of *H. pylori* in the body. This test detects both current infection and previous exposure. The benefit of using this kind of test is that it does not require discontinuation of any drugs and involves a non-invasive procedure for collecting blood samples (87). However, this type of testing is inexpensive and easily accessible to most

Journal of Molecular Science
Volume 36 Issue 1, Year of Publication 2026, Page 309-325
DoI-10.004687/1000-9035.2026.040

populations; it has certain limitations. The greatest disadvantage of using this technique is low specificity as compared to other tests. Serological tests cannot differentiate active from latent infections. As such, it is not commonly recommended in most diagnostic settings where there is an alternative method (88).

Antibiotic Resistance in Helicobacter Pylori:
Resistance Pattern:
Antibiotic resistance among *Helicobacter pylori* is an emerging issue that poses a significant problem, considering its direct contribution to the efficacy of the eradication process. Resistance trends differ from one geographical location to another, and factors such as past antibiotic consumption and local prescription practices affect the trend. However, some general observations are noted among different populations.

Clarithromycin:
Clarithromycin, which belongs to the macrolides, is one of the essential agents in *H. pylori* therapy. Unfortunately, the use of clarithromycin has been less effective owing to antibiotic resistance among other factors. Resistance to clarithromycin can be detected using conventional phenotypic techniques, including agar dilution, disc diffusion, and E-test. Moreover, more accurate tests based on PCR are becoming widely adopted since they enable quick identification of gene alterations associated with resistance in biopsy samples (89).

Mode of Action:
Clarithromycin acts on *Helicobacter pylori* through its effect on the protein synthesis system. The drug attaches itself to 23S rRNA of the 50S subunit of the ribosome, especially those sites that play a critical role in peptide chain assembly. In the process, it interferes with the normal activity of the synthesis process since it triggers early disassembly of the growing peptide chain, thus stopping its elongation. Consequently, the organism does not synthesize necessary proteins for its existence (90). Resistance to clarithromycin is commonly acquired by point mutations in the peptidyl transferase site of the 23S ribosomal RNA gene. Such mutations limit the capacity of clarithromycin to bind to its target site. Although there is also the possibility for efflux pumps to confer additional resistance, such a phenomenon usually occurs alongside the mentioned genetic mutations. As for the acquisition of resistance against the drug, there is evidence that it is the result of genetic mutations, dissemination of resistant strains, and wide use of macrolide antibiotics (91).

Metronidazole:
Metronidazole (Mtz) is an antimicrobial agent belonging to the group of nitroimidazoles, which is often administered in combination therapy for Helicobacter pylori, a bacterium responsible for peptic ulcers and stomach cancer. The mechanism of action of metronidazole relies on its capability to penetrate anaerobic and microaerophilic microorganisms, where metronidazole is then turned into metabolites that cause the destruction of various components, such as DNA, within the cell. Although metronidazole is effective, resistance to this drug has developed as an issue during the treatment of infections caused by *H. pylori.* The matter has been exacerbated in the areas where the use of metronidazole was widespread for other infections (92).

Mode of Action:
Metronidazole is a nitroimidazole antibiotic prodrug that needs activation inside the bacteria. The activation of Metronidazole in *Helicobacter pylori* takes place under microaerophilic conditions; the activation happens as a result of its reduction by certain bacterial enzymes, specifically, rdxA and frxA. During this process, the formation of very reactive products happens. These reagents lead to the damage of many elements necessary for bacterial life: particularly, the DNA molecule gets broken, loses its structure, and nucleic acids cannot be synthesized anymore. Thus, the bacteria cannot live as they cannot perform their functions properly and die. The action of these reagents may be directed not only against DNA but also against other elements in the bacteria, including proteins and cell membranes, which additionally contribute to the antimicrobial properties of Metronidazole. The activation of the drug occurs in the cellular environment, and the process depends on the redox environment of the bacterium (92).

Levofloxacin:
Levofloxacin belongs to the class of fluoroquinolone antibiotics and is widely prescribed for eradicating *H. pylori* infections. The mechanism of action is based on inhibiting specific enzymes involved in DNA replication and thus preventing the growth of bacteria. Unfortunately, the efficacy of the drug is threatened due to the increasing occurrence of resistance. The source of this phenomenon lies in genetic mutations resulting in impaired function of enzymes necessary for replication, making them less accessible to the drug. Therefore, the occurrence of resistant strains limits the application of the drug in eradication therapy (93).

Mode of Action:
Levofloxacin is an antibiotic belonging to the class of fluoroquinolones, which disrupts DNA replication in bacteria. This is achieved through inhibition of two crucial enzymes – DNA gyrase and

Journal of Molecular Science
Volume 36 Issue 1, Year of Publication 2026, Page 309-325
DoI-10.004687/1000-9035.2026.040

topoisomerase IV – which ensure that there is maintenance of DNA integrity. Mutations in the gyrA gene cause resistance to levofloxacin in *Helicobacter pylori* since the QRDR of the gene affects the binding of levofloxacin to the DNA gyrase enzyme, thus lowering its efficiency in DNA repair. Other less frequent causes include mutations in the gyrB gene and efflux pumps. Resistance to fluoroquinolones is increasingly common among H. pylori; hence, the ineffectiveness of levofloxacin regimens. This has necessitated the development of treatment protocols using antibiotic susceptibility tests (60, 94).

Mechanism Of Resistance:

1, rdxA GENE: Metronidazole resistance in *Helicobacter pylori* is associated with mutations in the rdxA gene. Metronidazole is a pro-drug and needs to be activated within the bacterial cell in order for it to exert its effects. The process of activation involves conversion to reactive derivatives by an enzyme known as oxygen-insensitive NADPH nitro reductase. Such an enzyme is coded for by the rdxA gene. When functioning properly, the enzyme acts on metronidazole and converts it to metabolites that lead to the destruction of bacterial nucleic acid and protein, hence killing the bacteria. Mutations in the rdxA gene cause resistance to metronidazole. The mutations could involve single-base changes, deletions, additions, or shifts, which lead to inactivation of the enzyme. Inactivation of the enzyme means the drug remains inactive and cannot exert its effects on the bacteria. This mechanism is clearly evident from experiments that have revealed that most resistant strains have mutated genes, but restoration of the normal rdxA gene confers sensitivity. Other genes, such as frxA, might play a role in some cases, but the loss of enzymatic activity due to mutations in rdxA is mostly involved in resistance to metronidazole (95).

2, frxA A GENE: The gene frxA also contributes to the development of metronidazole resistance in H. pylori; its significance is subordinate to that of the rdxA gene. Similarly to the rdxA gene, the frxA gene codes for a nitroreductase enzyme that is responsible for transforming metronidazole into a lethal form. In many cases, metronidazole resistance is achieved when the rdxA gene is inactivated, and it is sufficient for type I resistance. However, in some cases (type II resistance), resistance appears only when both genes, rdxA and frxA, are deactivated. By itself, the loss of function of the frxA gene rarely causes metronidazole resistance. Rather, it delays the action of metronidazole and increases its resistance when the rdxA gene is inactive. Therefore, the frxA gene is not an independent factor of metronidazole resistance, but it contributes to and strengthens the development of resistance due to mutations in the rdxA gene (96).

3, 23S rRNA GENE: Clarithromycin resistance in *Helicobacter pylori* is usually due to the point mutations found on the 23S rRNA gene, especially at the peptidyl transferase domain of the 23S rRNA domain V. These include A2142G and A2143G, which modify the ribosomal binding site and decrease the efficacy of the drug's binding and inhibition of protein synthesis (97). Other point mutations that occur in *H. pylori* include A2115G, G2141A, A2144T, and T2182C. However, some of these mutations are known to have lower resistance rates, while others are inconsistently correlated with resistance. Since there are two copies of the 23S rRNA gene in H. pylori, even a mutation in only one copy leads to partial resistance. Resistance development is also affected by the use of antibiotics, leading to the selection of resistant strains, even though these may exist only in trace amounts initially. Other strategies, including increased pump function or other modifications within the ribosome, can also complement mutations within the 23S rRNA gene in enhancing resistance. Clarithromycin resistance in *H. pylori* mainly results from modifications in the site of action of the drug, which inhibit its binding and lead to therapy failure (98).

4, gyrA GENE: Resistance to fluoroquinolones by H. pylori, especially levofloxacin, is primarily due to mutations in the gene gyrA, encoding one of the subunits of DNA gyrase. The mutations take place in a defined portion called the quinolone resistance-determining region (QRDR). Most of the critical mutations are located at codons 87 and 91, such as Asn87Lys, Asp91Gly, Asp91Asn, and Asp91Tyr. Due to these mutations, there is a change in the amino acid sequence of the drug-binding region, resulting in a reduction of the binding affinity of the drug. Mutations occurring in codon 87 are frequently associated with increased resistance. While the majority of resistant mutants have mutations in gyrA, there are exceptions, implying that other factors, such as the presence of an efflux system, may also contribute to resistance. Changes in the gyrA gene, specifically codons 87 and 91, account for resistance to fluoroquinolones among *H. pylori* isolates, with certain mutations determining the level of resistance (99).

5, gyrB GENE: Levofloxacin resistance in *H. pylori* bacteria is thought to be related to mutations that occur within the gyrB gene coding for the B subunit of DNA gyrase, which is targeted by the fluoroquinolones. Mutations within the quinolone binding site decrease the efficiency of levofloxacin to inhibit DNA synthesis. This is believed to be the

Journal of Molecular Science
Volume 36 Issue 1, Year of Publication 2026, Page 309-325
DoI-10.004687/1000-9035.2026.040

cause of the lower rates of eradication obtained by regimens that involve levofloxacin in regions that exhibit a high frequency of resistant bacteria. In fact, studies show a correlation between the lower efficiencies of regimens such as BPAL-7 and BPAL-10 and the regional prevalence of fluoroquinolone resistance (100).

6, Pbp1A GENE: Mutations associated with pbp1a in *H. pylori* are often related to modifications in the transpeptidase domain of PBP1A, a key component of β-lactams, including amoxicillin. The binding efficiency and consequent bactericidal activity of these drugs can be affected when certain amino acid substitutions are present. Unlike other resistance factors, this resistance mechanism is not caused by one mutation but rather occurs due to the cumulative effect of several changes. Collectively, these modifications alter the structure of the enzyme's active site, enhancing its resistance to antibiotics while retaining its functionality. Mutations involving pbp1a frequently coexist with other resistance genes, suggesting their role in an adaptive strategy that is more complex than previously thought. Generally, this trend demonstrates the development of drug resistance through a series of structural modifications, resulting in a decrease in antibiotic efficacy while ensuring the survival of the bacteria (101).

Treatment and management:

1. Standard triple therapy:

Triple therapy has traditionally been applied as the first line of treatment for *H. pylori* infections. Triple therapy consists of proton pump inhibitors like lansoprazole 30 mg, clarithromycin 500 mg, and amoxicillin 1 g, taken twice a day over a period of ten days (102). In the past, triple therapy was extremely successful with a high success rate of over 90%. Nowadays, its effectiveness has dropped drastically, with fewer than 60% of patients being cured of their infection, primarily because of increased antibiotic resistance to clarithromycin (103). Every drug included in the therapy plays a distinct role. Proton pump inhibitors decrease stomach acid, which creates a favourable environment for the other drugs to act. Clarithromycin blocks the synthesis of proteins in bacteria, whereas amoxicillin acts on the cell wall of bacteria. The combination of these drugs worked efficiently in removing the infection. Due to increased resistance, today's treatment protocols do not consider standard triple therapy as a first-line treatment approach unless the bacteria causing the infection are susceptible to clarithromycin. Rather, other treatment modalities, like bismuth-containing quadruple therapy, are considered. However, when clarithromycin is shown to be effective against the bacteria causing the infection, standard triple therapy remains a viable treatment modality (104).

2.Quadruple Therapy:

Quadruple therapy has proven to be an effective first-line therapy in the elimination of *H. pylori* infection amid the growing problem of antibiotic resistance and increasing inefficiency of triple therapy treatment. Based on the Toronto consensus, there are two common approaches that have been widely applied. These are bismuth quadruple therapy (PBMT), which involves a combination of proton pump inhibitors, bismuth, metronidazole, and tetracycline; and the non-bismuth quadruple therapy known as PAMC, consisting of a proton pump inhibitor, amoxicillin, metronidazole, and clarithromycin. Generally, these therapies require 14 days of treatment due to the efficacy of the extended duration period. Bismuth-containing treatment is especially valuable in the treatment of patients with a high degree of clarithromycin resistance because the efficacy of such a treatment is less vulnerable to this condition. In turn, concomitant treatment can provide successful results in cases of partial resistance to bacteria if all medications are taken simultaneously instead of consecutively. Overall, quadruple treatment has proved to be more efficient in comparison with the classic combination of medications and is currently recommended for eradicating *Helicobacter pylori* infection (105).

3.Bismuth-Based Quadruple Therapy:

Quadruple therapy with bismuth involves the use of PPI, bismuth preparations, tetracycline, and metronidazole, which have been extensively used for the eradication of *H. pylori* infection. Quadruple therapy with bismuth is advantageous when resistance to clarithromycin is prevalent, since this therapeutic approach does not use macrolide antibiotics. In addition, the advantage of using this method lies in its efficacy in spite of metronidazole resistance. Increasing the dose and extending the duration of treatment can help address the issue of decreased sensitivity. The drug bismuth also plays an active role in the combination therapy through the improvement of antibacterial action and, hence, the effectiveness of the treatment. Although antibiotic resistance cases continue to rise around the globe, bismuth quadruple therapy remains effective and is therefore reliable. Bismuth quadruple therapy has been seen as the treatment of choice, even as a second or last resort after other therapies have failed.

4.Non-Bismuth Quadruple Therapy:

Concomitant or non-bismuth quadruple therapy comprises a proton pump inhibitor in combination with clarithromycin, amoxicillin, and metronidazole. This therapy emerged as a more effective substitute for traditional triple therapy, with the hope of achieving higher success rates by

Journal of Molecular Science
Volume 36 Issue 1, Year of Publication 2026, Page 309-325
DoI-10.004687/1000-9035.2026.040

administering various antibiotics at once. Nevertheless, its efficacy depends greatly on the prevalence of antibiotic resistance within the region, specifically, resistance to clarithromycin. The success rate is often lower than satisfactory in places where clarithromycin resistance exceeds 15-20%. Moreover, the therapy is even less efficient where there exists dual resistance to clarithromycin and metronidazole, rendering the therapy highly ineffective in such cases. Although research findings are not consistent, with varying eradication rates depending on the population, the therapy is increasingly discouraged as a routine empirical therapy option due to its inefficacy in some populations (91).

Challenges in Eradication:

Eliminating *Helicobacter pylori* is difficult because of the emergence of drug resistance despite the advent of new treatment methods. One reason why eradication of this infection is difficult is due to the increase in the number of antibiotic-resistant strains, especially to clarithromycin and metronidazole, which has lowered the efficacy of existing treatment methods, leading to a high failure rate in the treatment of the bacteria. Some of the factors that lead to the development of these antibiotic-resistant strains are mutations within the drug target sites, a decrease in the activation of specific antibiotics, and increased efflux pump activities. Genetic variations in the virulence factors, like cagA and vacA, may affect the severity of the illness and its treatment efficacy. Moreover, the bacteria's capability to develop biofilm formation and heteroresistance, which means that some subpopulations of *H. pylori* have varying sensitivity levels to antibiotics, contributes further to its survival during treatment. The patient-specific characteristics also become significant in terms of eradication. The complexity of multidrug treatments, which may lead to nonadherence because of side effects, poses a serious risk for the success of eradication therapy. Despite the potential of individualized therapy according to antibiotic resistance tests, the widespread implementation of this approach is complicated due to the necessity for invasive sampling and difficulties in cultivating the bacteria (106).

CONCLUSION:

Helicobacter pylori remain a major public health concern due to its known involvement in the development of chronic gastritis, peptic ulcers, gastric adenocarcinomas, and MALT lymphomas. H. pylori-associated chronic gastritis can nowadays be regarded as a disease entity with an infective nature, which means that every infected individual needs to be cured regardless of the presence of symptoms. The last decade saw major progress in improving the diagnostic accuracy of the disease through the introduction of new diagnostic tools like the urea breath test, stool antigen test, and a reliable serology test. Alongside the advances in diagnostics, individualized therapy is becoming more common, considering the growing number of antibiotic-resistant strains. It is especially important since there is resistance towards drugs such as clarithromycin, metronidazole, and fluoroquinolones, rendering the previous treatment protocols less efficient and necessitating the use of optimized quadruple therapy. Eradication of *H. pylori* results in the resolution of gastritis and reduces the likelihood of experiencing adverse consequences such as gastric cancer. Nevertheless, in case severe conditions like intestinal metaplasia occur, they are much more difficult to reverse. Looking ahead, future treatment of *H. pylori* infection will rely on public health strategies, incorporation of cancer prevention strategies, and better knowledge of the relationship between the host and the gastric microbiota. It is crucial to monitor resistance, improve diagnostic techniques, and develop new approaches to continue making advancements in treatment (107).

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