REVIEW article

Exploring *Helicobacter pylori* infection, diagnosis, and prospect

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Abstract: *Helicobacter pylori* is a gram-negative, short helical, S-shaped microbe that is 0.5-1 micrometer broad and 2-4 micrometer long. It causes chronic gastric infections and is primarily located in the pyloric area of the stomach. It is believed that almost half of the world's population is infected with these bacteria. Although the precise mechanism of *Helicobacter pylori* infection and transmission remains unknown, it is believed that the fecal-oral and oral-oral pathways, facilitated by food or water consumption, are prevalent. The pathogenicity, microbial activity, genetic predisposition, and clinical therapies of *Helicobacter pylori*-induced gastric atrophy and gastric cancer have garnered more attention in the past three decades. Research has indicated that *Helicobacter pylori* infection may influence the prevalence of malnutrition in specific risk groups and that it may be linked to the inability to absorb vital minerals. An adequate and balanced diet, particularly one that is high in fruits and vegetables and low in processed salty foods, has been shown to have a protective effect against the consequences of *Helicobacter pylori* infection. On the other hand, dietary factors may play a significant role in H. pylori infection. The current review offers a comprehensive summary of every facet of *Helicobacter pylori* infection, including advanced treatment and diagnosis.

Introduction

About 50.0% of people worldwide suffer from a persistent infection caused by *Helicobacter pylori* (H. pylori) [1]. 1.0-3.0% of people with H. pylori infection develop gastric cancer (GC), which makes up 90.0% of all non-cardia GC (NCGC) and 20.0% of all cardia (CGC) cases. H. pylori are also responsible for 15.0% of the world's cancer burden [2, 3]. A threefold increase in CGC risk and a sixfold rise in NCGC risk may result from infection [4]. Furthermore, H. pylori infection is frequently the origin of all precancerous forms of GC, including gastric hyperplastic polyps generated from the stomach epithelium, metaplasia, foveolar hyperplasia, and chronic atrophic gastritis (CAG) [5]. Immunologically, it can avoid host immune clearance and continue to occupy the niches, which eventually causes pattern recognition receptors on neutrophils, stomach epithelial cells, and antigen-presenting cells to become active [7]. Furthermore, H. pylori cause leukocytes and gastric epithelial cells to activate NF-κB [7], which contributes to the long-term colonization of H. pylori, the chronic inflammatory microenvironment, clinical symptoms (**Figure 1**), and aberrant apoptosis. These factors further cause the accumulation of mutations and malignant transformation of gastric epithelial cells [8]. Another major component contributing to GC is oncoprotein cytotoxin-associated gene A (CagA), which inactivates tumor suppressors and stimulates oncogenic signaling pathways [9]. Before GC endoscopic or barium photofluorographic screening, H. pylori identification and eradication techniques are useful for GC prevention, particularly in regions with elevated GC risks [10, 11]. Idiopathic thrombocytopenic

purpura, vitamin B12 insufficiency, and unexplained iron-deficiency anemia are among the extra-gastric illnesses that have been strongly linked to H. pylori. Identifying and eliminating H. pylori in patients suffering from these illnesses is also advised [12]. Hepatobiliary disorders [15, 16], cardiovascular disorders [14], neurological disorders [13], and autoimmune disorders may also be impacted by H. pylori infection. This review's objective is to present current information on H. pylori infection diagnosis and therapy.

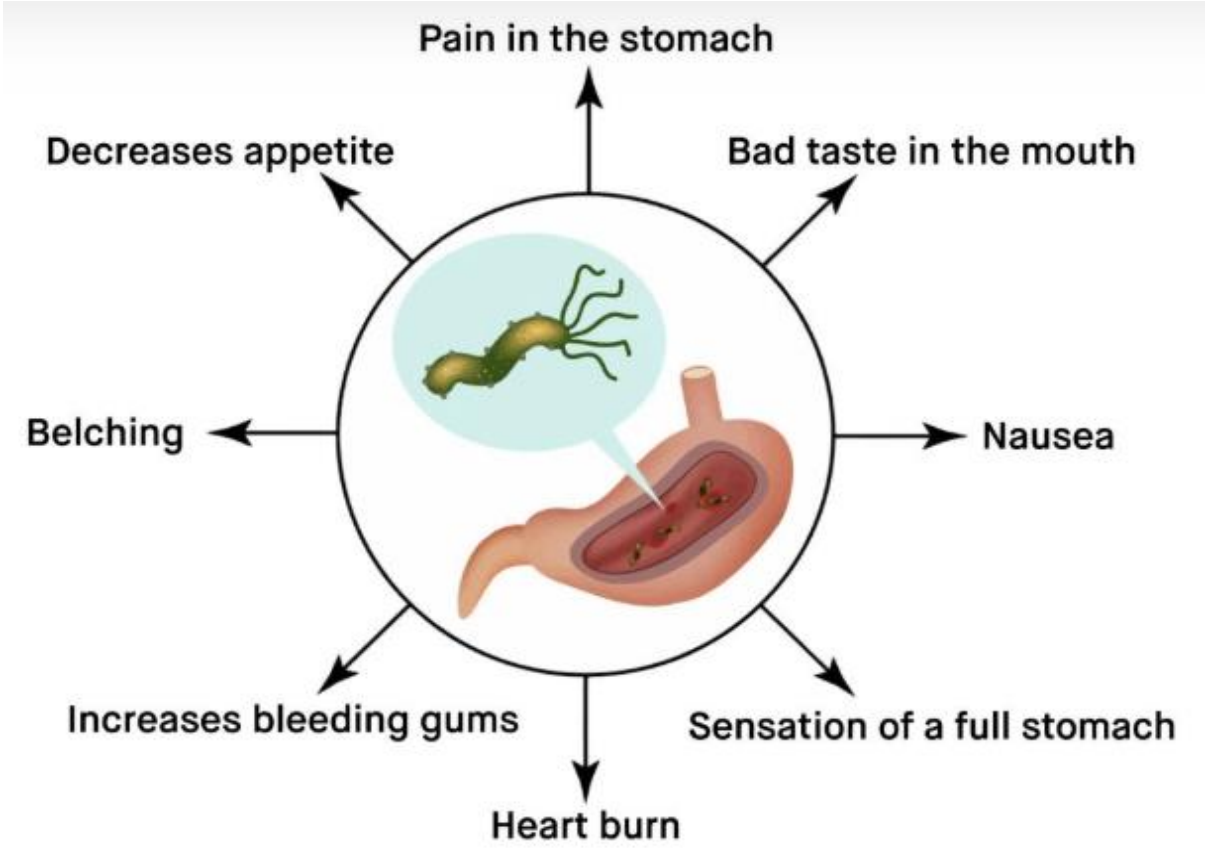

Figure 1: Symptoms of infection Helicobacter pylori [13]

H. pylori infection epidemiology: Despite claims that half of the world's population has an H. pylori infection, additional evidence-based study is required. This infection is more common in developing nations and among those with lower socioeconomic positions [17]. According to Vilaichone et al. [18], there are regional variations in H. pylori prevalence within a single nation as well as variations between nations. Determining its prevalence is extremely challenging because no health system in developing nations accumulates registry-based data on H. pylori prevalence [19]. Globally, there are an estimated 4.4 billion H. pylori-infected individuals, based on regional prevalence estimates [20]. Switzerland had the lowest H. pylori burden, while Nigeria, Portugal, Estonia, Kazakhstan, and Pakistan had the highest burden relative to the overall population [21]. According to Mezmale et al. [22], Russia, Jordan, Iran, China, Canada, and Latin American nations had high rates of H. pylori infection.

According to a 2011 study by Özen et al. [23], 161 out of 473 students in four separate Istanbul primary and secondary schools tested positive for H. pylori. The C-urea breath test was also used in 2013 to screen 4622 individuals in 55 cities for H. pylori infection, and 3852 individuals (2075 females and 1777 men) tested positive [24]. In a 2019 study by Soylu et al. [25], biopsy samples from 88 patients (53 females and 35 males) with dyspeptic complaints revealed that 46 patients (21 females and 25 males) had H. pylori-positive status. Male patients were found to be more H. pylori-positive than the overall number of participants. 18.2% of toddlers aged 06 to 59 months, 14.0% of boys and 16.0% of girls aged 10 to 19 years, and 40.0% of non-pregnant women aged 20 to 49 years had H. pylori infection, according to a study done in Nepal [26].

Transmission of H. pylori: It is believed that H. pylori can spread either directly from one person to another or indirectly from the environment to humans, while the precise route of transmission is unknown [27]. Particularly in industrialized nations, person-to-person transmission is believed to be the main mechanism of transmission. In impoverished nations, food and waterborne transmission are more common, and H. pylori spreads more quickly in unsanitary environments [28-30]. People who consume raw vegetables are more likely to be infected, according to a study by Goodman et al. assessing the incidence of H. pylori infection in the rural community. Additionally, consuming water from streams and rivers and swimming in them might raise the risk of infection due to pollution from unpurified or irrigation water [31]. It is believed that sexual, gastric-oral, fecal-oral, or oral-oral pathways are the means of person-to-person transmission [27]. According to the literature, H. pylori can be found in the saliva and dental plaque of infected people [32, 33], demonstrating that the illness spreads far more quickly than anticipated and that transmission between family members is particularly common [34].

Diagnosis process: There are numerous ways to identify an H. pylori infection [35]. The organism is mostly found in the stomach due to its trophic status for gastric epithelium, where it produces the distinctive and easily identifiable histologic pattern of acute-on-chronic inflammation [36]. Generally speaking, organisms are common and can be found with particular stains, the most precise of which is immunohistochemistry employing antibodies specific to H. pylori [37]. Numerous tests are available, ranging from molecular testing using next-generation sequencing to serologic testing for anti-H. pylori IgG antibodies [38]. While endoscopy is necessary for some tests to sample the stomach contents, others are noninvasive. Noninvasive testing is often recommended [39]. In addition to the clinical indication, the diagnostic approach should take patient preferences, local test costs, and availability into account. There are several commercially available tests for anti-H. pylori IgG, and the presence of the infection triggers a serum immune response. Serology was the most widely utilized diagnostic test until recently [40]. Currently, serology is typically not covered by Medicare and is not advised. Although some labs offer IgA and IgM anti-H. pylori testing, these tests are typically not authorized by the US Food and Drug Administration (FDA) and are not advised or reliable due to their poor sensitivity and specificity. Because commercial laboratories also provide and frequently favor utilizing in-house developed tests with unclear specificity and sensitivity, it is crucial to request only FDA-approved tests when working with large commercial laboratories in the United States. IgG, IgA, and IgM test panels typically comprise unapproved, unclearly diagnostic tests and offer little additional value above IgG testing. Serologic testing results should not be the sole basis for making treatment decisions because they can remain positive for a long time after the virus has been cleared (a serologic "scar"). Currently, a very high pretest probability of an H. pylori-related condition, such as an active duodenal ulcer, is one of the requirements for using IgG serology. Before beginning treatment, it is advised that the existence of an active infection be verified by a urea breath test (UBT), stool antigen test, or endoscopy, depending on the presentation, if serology is performed without a very high pretest chance. The clinical scenario determines which diagnostic method is used. For instance, endoscopy combined with H. pylori testing would be the most effective test for a patient exhibiting symptoms and indicators of a serious upper gastrointestinal condition, such as stomach cancer or a peptic ulcer. On the other hand, a noninvasive test like the stool antigen test or UBT would probably be more beneficial for an asymptomatic relative of a patient with peptic ulcer disease, provided that only stool antigen tests employing monoclonal antibodies are employed [41].

H. pylori and peptic ulcer: Peptic ulcer disease typically develops asymptomatically and is a major cause of morbidity and mortality globally. Epigastric pain accompanied by bloating, dyspepsia, nausea, early satiety, or abdominal fullness are signs of symptomatic peptic ulcer disease [42, 43]. The stomach and proximal duodenum are common sites for peptic ulcer detection [44]. The majority of peptic ulcer disease cases are believed to be related to either nonsteroidal anti-inflammatory drug (NSAID) use, H. pylori infection, or both [45]. Because there is less somatostatin in the antrum, those with non-atrophic antral-dominant gastritis have higher amounts of gastrin and highly accelerated acid production. Clinically, this group frequently has

duodenal ulcers [39]. Research has indicated that the removal of H. pylori can improve peptic ulcers [46, 47]. The gastric/duodenal mucosa is chronically colonized by H. pylori, which causes innate and specific immune responses as well as gastroduodenal disorders such as gastritis and peptic ulcers. Still, if the infection is not eradicated, the chronic active gastritis state may last a lifetime [48].

Current standard treatment protocols for Helicobacter pylori: The first-line treatment for patients in regions with high H. pylori clarithromycin resistance is bismuth quadruple therapy or nonbismuth concurrent quadruple therapy for 10-14 days, according to Clinical Guideline [49] (North America). Two different kinds of antibiotics, bismuth, and a proton pump inhibitor (PPI) make up bismuth quadruple treatment. Traditionally, the antibiotics that were included were tetracycline and metronidazole; more recently, amoxicillin, clarithromycin, and tinidazole have been included. A PPI and three different kinds of antibiotics, usually amoxicillin, clarithromycin, and metronidazole, make up concurrent quadruple treatment. In actual clinical practice in Europe, extensive observational studies have proven adequate eradication results (>90.0%) for both therapy modalities [50]. Clarithromycin-containing triple therapy is only advised by the previously mentioned guidelines in regions with low levels of clarithromycin resistance and in patients who have not previously taken macrolide antibiotics [51]. As an empirical treatment, 10- to 14-day bismuth quadruple therapy is also advised in Asia by the Chinese guidelines [52]. However, conventional triple therapy, which includes clarithromycin, is still advised as the first line of treatment in the Korean [53] and Japanese [54] guidelines. According to Korean guidelines, nonbismuth quadruple therapy (concurrent and sequential therapies) should be utilized as an empirical first-line treatment and triple therapy should have a longer treatment period of 14 days. Antimicrobial stewardship principles evaluate antimicrobial treatments according to their absolute cure rate, which is the capacity to consistently attain a predetermined cure rate, like ≥95.0% with susceptible infections. Additionally, suggested treatments are tailored to consistently produce the greatest cure rates. All facets of therapy, including medication choice, dose, duration, dosing intervals, and administration in connection with meals, are included in the optimization. Empirical therapy is by definition limited to treatment plans that have been shown to consistently produce high cure rates in the target group. It is recommended that clinical programs that incorporate the evaluation of targeted cure rates be implemented in order to monitor treatment outcomes, inform physicians and public health officials of the results, and alert them when cure rates start to decline [55]. (**Table 1**) lists the H. pylori eradication treatments currently in use worldwide along with their eradication rates. As the regularly used regimens vary by location and country due to variations in medical insurance coverage and drug availability, it is challenging to directly compare the effectiveness of each regimen in order to identify the "best" regimen.

Table 1: Current first-line H. pylori treatment protocols and rates of eradication

Drug regimen	PPI	Antibiotics	Duration (days)	Eradication rate per protocol	References
High-dose PPI-amoxicillin dual therapy	Esomeprazole (20 mg qid)	AMO (750 mg qid)	14	92.0%	[56]
PPI-based standard triple therapy	Lansoprazole (30 mg bid)	AMO (1000 mg bid); CLA (500 mg bid)	14	63.0%	[57]
Reverse hybrid therapy	Dexlansoprazole (60 mg qd)	AMO (1,000 mg bid); CLA (500 mg bid)	14	96.0%	[58]
Concomitant quadruple therapy	Esomeprazole (20 mg bid)	AMO (1,000 mg bid); CLA (500 mg bid); MET (500 mg bid)	14	94.0%	[59]
Bismuth quadruple therapy	Lansoprazole (30 mg bid)	MET (500 mg tid); TET (500 mg qid); Bismuth (300 mg qid)	10	93.0%	[60]

Key: AMO, amoxicillin; bid, twice daily; CLA, clarithromycin; MET, metronidazole; PPI, proton pump inhibitor; qd, once daily; qid, 4 times daily; TET, tetracycline; tid, 3 times daily.

Future directions: As gastroenterologists increasingly accept the idea that effective therapy delivery necessitates replacing the tried-and-true techniques used to treat infectious diseases with the trial-and-error approach that has defined H. pylori therapy since its inception, the management of H. pylori infection is undergoing a significant transformation [61]. The etiology of the common gastrointestinal disease is not known; there is a high placebo response to treatment, treatment success is limited, and true cures are uncommon [62]. When combined, these features necessitate that treatment trials include a comparator, frequently a placebo, and concentrate on comparing treatment success with a placebo or another antibiotic. The capacity to consistently attain high cure rates and the absence of a placebo response, on the other hand, make true cure rates the main outcome variable when considering H. pylori gastritis as an infectious condition. Future H. pylori therapy trials will concentrate on the real cure rate, and comparisons will be limited to selecting one of two extremely effective treatments. To do this, the previous strategy and most of the existing treatment recommendations that are based on comparisons of frequently ineffective medications must be abandoned. Given that the emphasis is now on finding locally highly effective therapies and creating feedback loops to assist clinicians in identifying, optimizing, utilizing, monitoring, and, when necessary, modifying the recommended regimens to ensure continuing locally highly effective therapy, those skilled in the prior art of treating H. pylori gastritis as another gastroenterological disease rather than an infectious disease may find the transition challenging.

Conclusion: Recent studies have unequivocally demonstrated the pathogenicity, microbial activity, and genetic propensity to aid in understanding the severity of H. pylori-caused gastric atrophy and gastric cancer. It is anticipated that this circumstance will have a beneficial impact on the therapeutic process. Combination therapies, such as those including probiotics and phytochemicals from natural sources, appear to be effective in eliminating H. pylori. It is crucial to ensure adequate nutrition by having qualified dietitians determine the best course of action and implement a diet that is appropriate for the individual. Furthermore, probiotics added to treatment plans have shown some encouraging results; still, more thorough research is required. Above all, a diet high in fruits and vegetables and low in processed meats and salt has good preventive potential, particularly against cancer and H. pylori eradication. Furthermore, possible substitute therapies could supplement the present antibiotic regimen. The development of a vaccine could be one way to accomplish a variety of eradication and preventive measures.

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