Review Article

Overview of Helicobacter pylori Infection, Prevalence, Risk Factors, and Its Prevention

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Helicobacter pylori (H. pylori) (formerly known as Campylobacter pyloridis) has been studied for over a century due to its association with peptic ulcer disease and gastric cancer. Its prevalence has been declining due to improvements in hygienic conditions and effective curative and preventive approaches. However, it is still present in different communities and continues to spread, increasing its global presence in both developing as well as developed countries. Extensive research has been ongoing to eradicate this pathogen, and at present, scientists have discovered different management options. This article highlights the global prevalence of H. pylori infection and the factors responsible for its transmission, treatment regimens, and prevention.

1. Introduction

Helicobacter pylori belongs to the family Helicobacteraceae. It is a transmissible and pathogenic gram-negative spiral-shaped bacterium thought to be a contaminant of digested food as opposed to being a true colonizer of the gastric mucosa [1]. It was first successfully isolated and discovered by Barry Marshall and Robin Warren in 1980, for which they were awarded the Nobel Prize in 2005 [2]. They intentionally ingested the bacterium and subsequently developed persistent gastritis. Later, it was found that the bacteria are strongly associated with multiple upper gastrointestinal disorders, such as chronic gastritis, peptic ulcer disease, gastric mucosa-associated lymphoid tissue (MALT) lymphoma, and gastric cancer [3–5].

H. pylori is the most common human bacterial infection occurring in ~4.4 billion people, representing over 50% of the world population. The World Health Organization (WHO) now considers it a class 1 carcinogen leading to peptic ulcer disease and gastric cancer [6–8]. The H. pylori infection rate is 30–50% in developed and 85–95% in developing countries [9–12]. More specifically, the infection rate is 30% in Western countries and 20–30% in North America, in which it is 23% in the province of Ontario and 13% in Quebec. Infection rates are higher in Africans (25%), Asians (30%), and South Americans (34%) and significantly lower in Caucasians (8%) who reside in Canada [13–15]. The pathogen is more prevalent in North Americans, Aboriginals, and recent immigrants [16].

In 2006, the Canadian North Helicobacter pylori Working Group (CANHelp) was established to identify specifically the impact of H. pylori infection in the Canadian Arctic communities [15–17]. The rate of documented infection in these communities was 55% in the 2008 survey. In one study, 95% seropositivity was revealed in the native community in northwestern Manitoba and a 67% infection rate in children two years of age. The pathogen is also prevalent in Aboriginals of Russia, Alaska, and Greenland, and the infection ratio ranged from 47% to 88% [18–20]. Furthermore, the infection rate is relatively higher in immigrants from countries such as India or China than in those born in Canada from the same ethnic groups [14].

H. pylori infection prevalence increases with age within the first ten years of life [21–23]. The incidence of H. pylori infection in childhood varies greatly [24]. The childhood infection rate in some underdeveloped countries is reported...
to be 90% [25, 26], while in developed countries, it ranges from as low as 1.8% to as high as 65% [27, 28]. Details about the global prevalence are elaborated in Table 1.

1.1. Factors Contributing to H. pylori Infection. The exact mechanism of H. pylori infection is currently unknown; however, socioeconomic and environmental factors are known to play an important role [1, 31]. H. pylori infection occurs in early childhood and remains silent for years; only 30% of individuals develop observable signs and symptoms of gastritis. Transmission occurs through oral-oral, fecal-oral, and gastro-oral routes [32, 33]. As an example, mother-to-child transmission occurs if the mother’s saliva is contaminated or due to poor hand hygiene. The pathogen is transmitted by direct means, e.g., kissing or sharing utensils [34], or by indirect means, such as drinking water, air, animals, flies, and food [33]. The occurrence of H. pylori infection supports the transmission of fecal contaminants in the institutionalized young population during the epidemic of gastroenteritis [35]. Similarly, in refrigerated food, the pathogen may survive for a short period and is the source of infection [36]. Additionally, it is associated with dietary habits, particularly milk, meat, and vegetables [1, 37–39]. One Indian study revealed that the prevalence is more common in the lower socioeconomic group [40]. Drinking unfiltered water, tobacco, and meat consumption are risk factors for developing H. pylori infection. Moreover, drinking unboiled water in restaurants in urban areas increases the spread of the pathogen [41, 42]. The acquisition and transmission of the pathogen increase in dense living conditions, when using nonsteroidal anti-inflammatory drugs, in the blood group O, with obesity, and with a family history of gastric disease [43–46]. Eating fried food has a positive correlation with infection [47].

Antibiotic resistance is another contributing factor for H. pylori infection as antibiotic resistance is primarily responsible for failing to completely eradicate H. pylori. In certain cases, a patient will undergo 14 days of quadruple therapy and, subsequently, either develop the infection again or develop complications of H. pylori infection. The main cause of antibiotic resistance is the overuse of antibiotics; metronidazole shows the highest resistance rate and is widely used in most countries for various gastrointestinal illnesses [48–53].

A major contributor to the increased prevalence of bacterial infections, including H. pylori infection, is the global emergence of antibiotic-resistant bacteria, threatening the efficacy of antibiotics which have transformed medicine and saved countless lives [54–56]. The leading cause of antibiotic resistance is the overuse or misuse of antibiotics due to a misguided perception in many people that antibiotics can cure any kind of illness. This has caused people to view antibiotics as a cure-all and routinely request them from their physicians, even for viral illnesses. This, compounded with the improper use of antibiotics, leads to resistance. Additionally, incorrectly prescribed antibiotics also promote antibiotic resistance. Research reveals that in 30–50% of cases, the indication for treatment, antibiotic choice, and duration of antibiotic therapy is incorrect [57, 58]. In many countries, antibiotics are available over the counter without prescription; this ease of obtaining antibiotics also contributes to the problem [59, 60]. Lack of regulation and easy availability of a variety of cheap antibiotics in the market as well as online lead to the misuse and overuse of antibiotics [59].

Finally, the lack of new drug development by the pharmaceutical industry due to the decreased financial incentives and challenging regulatory requirements is contributing to the antibiotic resistance crisis [59, 61, 62]. New research policies and coordinated efforts to control antibiotic resistance are greatly needed [63]. This will help in the eradication of bacterial pathogens.

1.2. The Clinical Course of H. pylori Infection. H. pylori infection is not a disease in itself, but it presents with a spectrum of clinical disorders of the upper gastrointestinal tract and hepatobiliary tract [1]. Dyspepsia is the predominant symptom, and a patient may present with epigastric pain, early satiety, nausea, vomiting, and heartburn [64] (Figure 1). H. pylori infection positivity is two times more common in dyspeptic patients than in asymptomatic individuals [65], and the first warning sign for peptic ulcer disease and gastric cancer is dyspepsia [66]. The association between gastroesophageal reflux disease (GERD) and H. pylori infection is still in debate. However, esophageal inflammation is increased by H. pylori, and it increases the incidence of Barrett’s esophagitis (BE) and GERD [67, 68]. A casual causative factor for chronic gastritis is H. pylori infection, which leads to the persistent inflammation of the gastric mucosa that may progress to gastric atrophy and intestinal metaplasia [69].

The lifetime risk of developing ulcer disease is 10–20%, distal gastric cancer risk is 1–2% [70–72], and mucosa-associated lymphoid tissue (MALT) lymphoma risk is <0.1% [73] in H. pylori-positive patients (Figure 1). Both gastric and duodenal ulcers are strongly associated with this pathogen. In the initial decade after the H. pylori discovery, it was found that 95% of duodenal ulcers and 85% of gastric cancer occurred with H. pylori [72]. The development of peptic ulcer disease (PUD) is commonly caused by H. pylori and nonsteroidal anti-inflammatory (NSAID) use; nevertheless, every individual using NSAID and infected with H. pylori.
pylori does not develop PUD [74, 75]. Patients with duodenal ulcers usually complain of abdominal pain two to three hours after taking meals on an empty stomach or abdominal pain at night, whereas patients with gastric ulcers complain of nausea, vomiting, weight loss, and postprandial abdominal pain. The complication of PUD is bleeding, perforation, gastric outlet obstruction, and gastric malignancy (adenocarcinoma and MALT) [76]. Bleeding is the most common complication of PUD, and almost 40–60% of upper gastrointestinal bleeding is caused by PUD [77]. With regard to gastric cancer, which is the fifth most common cancer and the third leading cause of death globally, H. pylori is the major risk factor for its development. The precancerous lesion is usually started by the H. pylori infection with the transformation of the normal mucosa to non-atrophic gastritis that may lead to atrophic gastritis and intestinal metaplasia [78].

All these complications of H. pylori are attributed to the severity of gastric inflammation, which is determined by multiple hosts and bacterial factors. The cytotoxin-associated gene-A pathogenic island (cag PAI) is a well-characterized H. pylori virulence determinant. It is a 42 kb insertion element that consists of 32 genes that encode the bacterial type 4 secretion system. The cag A pathogenic island is 60–70% present in the western strain of H. pylori and almost 100% of the East Asian H. pylori strain. The cag PAI presence is associated with more severe gastritis, peptic ulceration, atrophic gastritis, and gastric cancer [79, 80]. Among host factors, the evidence emphasizes H. pylori-induced acid production. Increased production of acid limits H. pylori gastritis to the antrum, which increases the risk of duodenal ulceration, while reducing acid secretion promotes more proximal inflammation that favors the risk of atrophic gastritis, gastric ulcer disease, and gastric cancer [81].

1.3. Diagnosis and Management. Accurate diagnosis of H. pylori infection is essential for the effective treatment of various gastroduodenal diseases. Multiple tests have been developed over time for the detection of H. pylori infection. Each test has its benefits and limitations. In a clinical setting, the use of a single test is generally adequate for the diagnosis. Generally, the tests are divided into two categories, i.e., invasive and noninvasive tests (Table 2) [1, 82].

Invasive tests are based on the endoscopic biopsy taken from the gastroduodenal part for histology, culture, rapid urease test, and molecular methods. Noninvasive tests are based on peripheral samples, such as the blood, breath samples, and stool specimens, for the detection of antibodies, bacterial antigen, and urease activity. Fecal antigen tests and urea breath tests are the most widely used noninvasive tests in clinical settings for the detection of H. pylori infection and during follow-up after eradication antibiotic treatment, while blood samples are used for screening and epidemiological studies [83]. However, the complications of H. pylori infection are not diagnosed by noninvasive tests. H. pylori-infected individuals usually develop certain antibodies in their circulation, such as IgA, IgG, and IgM. These antibodies are determined by specific serological tests which are noninvasive, rapid, cheap, and helpful in diagnosing the H. pylori infection or when there are equivocal test results by other methods due to complications, e.g., bleeding ulcers, or when the patient is on antibiotics or antisecretory treatment [84]. The detection of serological responses to cytotoxin-associated gene A (cag A) gives useful information about serious gastroduodenal infections, such as gastric malignancy and MALT. cag A is common in Western and East Asian strains of H. pylori. However, this is not useful in other countries as the bacterial virulence strains are different in other countries [86]. Serum antibodies were detected via the enzyme-linked
Different antibiotic regimens have been used for the eradication of *H. pylori* infection. Generally, a single drug does not cure the infection. Usual treatment regimens consist of multiple antibiotics that are taken for two weeks (14 days). The standard triple therapy (STT) was established in the past for the eradication of this pathogen. STT consists of amoxicillin, clarithromycin, and proton pump inhibitor; however, the efficacy of the STT regimens has changed over time in many countries mainly because of antibiotic resistance, and other factors contributing to reduced eradication are patient compliance, genetic polymorphism, obesity, smoking, and reinfection. Most of the treatment regimens involve taking proton pump inhibitors, which reduce gastric acid production and allow the bacterial-damaged tissues to heal [88, 89].

Initial regimens to eradicate *H. pylori* in patients suffering from peptic ulcer disease relied on proton pump inhibitors (PPIs) to inhibit the final step in the acid secretion pathway (gastric H⁺ and K⁺-ATPase) [90] (Figure 2). However, PPIs and antibiotics were subsequently found to work synergistically with each other to eradicate *H. pylori*. Since then, antibiotics have been included in eradication regimens. Current treatments rely on acid suppression combined with at least two antibiotics. The role of acid suppression has been attributed to the antibacterial activity of PPIs, either directly through the inhibition of urease activity or through increased stability and activity of antibiotics [91–93].

One of the widely used first-line antibiotic regimens is the quadruple therapy for 14 days, which involves taking bismuth, tetracycline, PPI, and metronidazole [88, 89, 94]. The quadruple therapy is superior to the triple therapy (STT) [95]. Concomitant therapy consists of three antibiotics, i.e., metronidazole or nitroimidazole, amoxicillin, tetracycline, and PPI, for 14 days [88, 89, 94]. Concomitant therapy is better than STT [96]. Sequential therapy, which involves taking a PPI and amoxicillin for five days followed by clarithromycin, tinidazole, and PPI for another five days is less effective than the concomitant therapy; however, there is still debate about which one is superior [97, 98]. Some studies recommend a treatment of levofloxacin once daily along with PPI, cefuroxime, and bismuth for 7 to 14 days [99], while some suggest rifabutin-based therapy for rescue [100]. As PPI has a shorter duration of action, now, the longer-acting potassium competitive acid blocker (P-CAB), which has a rapid onset of action and is effective for a longer duration, is also used in some countries, such as Japan, and is considered a more potent first-line treatment in reducing gastric secretion [101]. In case primary therapy fails, the second line should be selected based on the previous therapy used and local antibiotic resistance data [88]. Different antibiotic regimens are shown in Figure 3 [88, 102].

### Table 2: Diagnosis of *H. pylori*.

<table>
<thead>
<tr>
<th>Methods</th>
<th>Sensitivity, specificity, pros</th>
<th>Cons</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Invasive tests</strong></td>
<td></td>
<td></td>
<td>[1, 85]</td>
</tr>
<tr>
<td>Endoscopy</td>
<td>&gt;95% definitive diagnosis</td>
<td>Time-consuming, needs special skill</td>
<td></td>
</tr>
<tr>
<td>Histology</td>
<td>&gt;95% gold standard</td>
<td>Observer dependency, high cost</td>
<td></td>
</tr>
<tr>
<td>Culture biopsy</td>
<td>&gt;95% alternative gold standard</td>
<td>Expensive, complicated</td>
<td></td>
</tr>
<tr>
<td>Rapid urease test</td>
<td>&gt;90% cost-effective and rapid test</td>
<td>Sensitivity specificity is low in gastric bleeding and intestinal metaplasia</td>
<td></td>
</tr>
<tr>
<td><strong>Noninvasive tests</strong></td>
<td></td>
<td></td>
<td>[1, 85]</td>
</tr>
<tr>
<td>Urea breath test</td>
<td>&gt;95% simple, safe detection of eradication of infection</td>
<td>False-negative findings in case of bleeding and antibiotic use; less accurate in intestinal metaplasia, atrophic gastritis, and gastric cancer</td>
<td></td>
</tr>
<tr>
<td>Fecal antigen test</td>
<td>&gt;90% simple, fast, inexpensive</td>
<td>False-negative results with the use of PPI, bismuth, antibiotics, and low bacterial load; the problem of keeping and carrying sample</td>
<td></td>
</tr>
<tr>
<td>Serology</td>
<td>80–90% cost-effective, applicable for patients treated with antibiotics and PPI, used for epidemiological studies</td>
<td>Insufficient reliability for routine screening, cannot distinguish between ongoing infection and previous contact, not applicable for confirming cure after therapy</td>
<td></td>
</tr>
</tbody>
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Figure 2: Three-dimensional atomic structure of the gastric proton pump. The gastric proton pump consists of two subunits (α and β); the α subunit is shown in black, and the β subunit is shown in cyan. The overall structure is shown to the left, and a zoomed-in representation omitting the β subunit is shown to the right (PDB ID SYLU).
1.4. Modern Approach. A novel approach utilizes the susceptibility-guided strategy that is published in the 2017 Maastricht VI guidelines to create a tailored therapy against *H. pylori* infection. The new approach depends on choosing the antibiotics according to local antibiotic resistance data. Maastricht guidelines propose different regimens of quadruple therapy, primarily concomitant therapy, and bismuth-based therapy [94]. Modifications in usual antibiotic regimens (metronidazole, amoxicillin, and clarithromycin) used in the treatment of *H. pylori* infection have also been proposed, such as sequential, hybrid, and reverse hybrid therapies [103, 104]. However, eradication efficacy is rarely above 90%, which has been the main goal of modified antimicrobial therapy, and this is due to complex multiple antibiotic use at one time and possible side effects of antibiotics limiting the compliance and effectiveness of therapy [105].

New proposals support the use of 14 days of triple therapy, usage of four drug regimens, higher doses of PPI, or the use of a novel PPI, i.e., vonoprazan (P-CAB) and probiotic supplementation with antibiotics [106]. Probiotics, such as *Lactobacillus* spp, *Bifidobacterium* spp, and *Saccharomyces boulardii*, are not directly involved in the eradication of *H. pylori* infection; rather, they reduce the side effects of antibiotics [103, 107, 108].

The 2022 Maastricht VI guidelines support susceptibility testing before prescribing antibiotics for *H. pylori* infection [104] by obtaining a culture from gastric mucosa following endoscopic biopsy and using agar dilution, disc diffusion, or an E test for the detection of antibiotic sensitivity [109]. The gold standard is the agar dilution method, but it is expensive, time-consuming, and labor-intensive [110]. The other method to test antibiotic sensitivity is by genotype molecular testing from the stool and stomach biopsy specimens using real-time polymerase chain reaction (PCR) and fluorescence in situ hybridization (FISH), while commercially available kits are used to detect point mutations related to specific antibiotic resistance [111]. Moreover, whole-genome sequencing techniques have been used to identify drug-resistant mutations [112]. These practices will need to be established in clinical settings as it is debatable whether each dyspeptic patient should be subjected to endoscopy. However, noninvasive techniques, i.e., PCR testing on stool samples or DNA extraction from stool samples, make it possible to avoid invasive testing, such as endoscopy, for the detection of antibiotic sensitivity [113, 114]. The prospects in *H. pylori* management [103, 115] are shown in Table 3.

Table 3: Prospects in the management of *H. pylori* infection.

| (i) Susceptibility-guided therapy/antibiotic sensitivity testing |
| (ii) PPI-high dose |
| (iii) Novel antibiotics |
| (iv) Clarithromycin avoidance, if used previously |
| (v) Antibiotic course for 14 days |
| (vi) Probiotics with antibiotics |
| (vii) Vonoprazan (P-CAB) instead of PPI |
| (viii) PCR/DNA extraction (from stool sample) for making a diagnosis |
| (ix) Nanotechnology use |

2. Conclusion

*H. pylori* infection prevalence has been reduced overall, but the pathogen is still present in different communities globally. Poor socioeconomic factors, hygiene, eating processed food, restaurant meals, meat, and unfiltered water have been the major contributing factors to *H. pylori* infection and its complications. Antibiotic resistance creates major problems in curing the infection and controlling the prevalence of *H.
H. pylori. However, antibiotic susceptibility testing is a novel way to provide a tailored therapy to achieve a complete cure. Lifestyle modifications are necessary to minimize the risk of H. pylori infection. These include proper hand washing, reducing the consumption of frozen/processed food, washing packed salads/vegetables properly before eating, and drinking boiled water. Overuse and misuse of antibiotics need to be discouraged, and completion of the antibiotic course along with probiotics should be promoted.

Hence, providing awareness through various ethnic media channels to various communities and demographic groups is the most important tool available to achieve these measures. Furthermore, routine screening for H. pylori infection in both immigrant and nonimmigrant populations will help in curing the infection. Ongoing research into new drugs and vaccines is greatly needed with a global collaborative effort to eradicate this pathogen, as H. pylori is a serious global health issue and a major cause of gastric cancer.

Data Availability

Previously reported (statistics) data were used to support this study. These prior studies (and datasets) are cited at relevant places within the text as references [1–98].

Conflicts of Interest

The authors declare that they have no conflicts of interest.

References

discrimination of single- and double-stranded conformational polymorphism
in juice for culture, nested-PCR detection, and combined


