ECRONICON OPEN ACCESS

EC GASTROENTEROLOGY AND DIGESTIVE SYSTEM

Review Article

Friend or Foe? *Helicobacter pylori* Infection: Epidemiology, Signs, and Symptoms, and Treatment

Nicholas A Kerna[1,2]*, Kyle Kadivi[3], Olufemi Odugbemi[4], John V Flores[5,6], Hilary M Holets[5,6], Shain Waugh[7], Ijeoma Nnake[2] and Fernand Jean-Baptiste[8]

[1]*SMC–Medical Research, Thailand*

[2]*First InterHealth Group, Thailand*

[3]*Global Health Group LLC, USA*

[4]*Olabisi Onabanjo University, Nigeria*

[5]*Beverly Hills Wellness Surgical Institute, USA*

[6]*Orange Partners Surgicenter, USA*

[7]*Fettle Path, USA*

[8]*Department of Biological Sciences, Florida Atlantic University, USA*

***Corresponding Author:** Nicholas A Kerna, (mailing address) POB47 Phatphong, Suriwongse Road, Bangkok, Thailand 10500. Contact: medpublab+drkerna@gmail.com

Received: November 30, 2020; **Published:** December 31, 2020

DOI: 10.31080/ecgds.2021.08.00685

Abstract

H. pylori can induce gastritis, peptic ulcer diseases, and cancer, including mucosa-associated lymphoid tissue lymphoma. It is also associated with numerous comorbidities. Nevertheless, several purported positive impacts of the bacterium have been noted, such as maintaining the stomach's healthy environment. Non-pathogenic *H. pylori* strains may aid in normalizing excess stomach acids and regulating appetite. Patients with *H. pylori* infection can experience acute gastritis symptoms with acute-onset abdominal pain, nausea, and vomiting. Non-specific abdominal pain, a sense of bloating, belching, and appetite loss are signs of infection. However, about 90% of individuals infected with *H. pylori* may never experience any symptoms during their lifetime, although 10–20% are at risk for peptic ulcer disease. The precise routes of *H. pylori* transmission remain unclear, although contaminated food, water, or soil are strongly suspected as well as person-to-person transmission through feco-oral and oral-oral routes. Treatment with antibacterial and antisecretory agents is the standard of care for *H. pylori* management. Also, phytomedicines and probiotics have been reported effective not only as a treatment but also in lessening the side effects of antimicrobial therapy, such as diarrhea. There are various drug combinations for eradicating *H. pylori* as described in this paper. Although the recurrence rate of *H. pylori* infection after eradication is relatively low, it remains a cause for concern and antibiotic resistance. Poor socio-economic conditions and sanitary habits are risk factors associated with the recurrence of *H. pylori* infection after successful eradication.

Keywords: *Dyspepsia; Heartburn; Hematemesis; Melena; Peptic Ulcer; Phytomedicines; Probiotic; Triple-Drug Therapy*

Abbreviations

AD: Alzheimer's Disease; AID: Autoimmune Disease; AIN: Autoimmune Neutropenia; ATS: Atherosclerosis; CAD: Coronary Artery Disease; DM: Diabetes Mellitus; GBS: Guillain-Barré Syndrome; GERD: Gastroesophageal Reflux Disease; GOO: Gastric Outlet Obstruction; H2RA:

H2-Receptor Antagonist; HFL Hepatic Fibrosis; HSP: Henoch-Schönlein purpura; IBD: inflammatory bowel disease; IDA: iron-deficiency anemia; ITP: Idiopathic Thrombocytic Purpura; ITT: Intention-To-Treat; MALT: Mucosal-Associated Lymphoid Tissue; OAG: Open-Angle Glaucoma; PD: Parkinson's Disease; PPI: Proton Pump Inhibitor; PUD: Peptic Ulcer Disease; TCM: Traditional Chinese Medicine; UBT:13C-Urea Breath Test; VBD: Vitamin B12 Deficiency; WS: Warthin-Starry

Introduction

Helicobacter pylori (*H. pylori*), previously known as *Campylobacter pylori*, is a gram-negative, helical microaerophilic bacterium commonly found in the stomach [1–5]. The bacterium's helical shape facilitates its way through the mucosal layer of the stomach, causing infection [2,4]. *H. pylori* was first identified by Australian physicians, Barry Marshall and Robin Warren, in 1982 [6,7]. *H. pylori* can cause several conditions, such as gastritis, peptic ulcer diseases of the stomach and the proximal small intestine, and cancer, including mucosal-associated lymphoid tissue (MALT) lymphoma, in about 20% of patients positive for *H. pylori* [4,6].

Research has pointed towards an association between *H. pylori* infection and comorbidities: idiopathic thrombocytic purpura (ITP), iron deficiency anemia (IDA), atherosclerosis (ATS), Alzheimer's disease (AD), Parkinson's disease (PD), Guillain-Barré syndrome (GBS), psoriasis, rosacea, Henoch-Schönlein purpura (HSP), coronary artery disease (CAD), vitamin B12 deficiency (VBD), diabetes mellitus (DM), open-angle glaucoma (OAG), blepharitis, hepatic fibrosis (HF), and autoimmune diseases (AIDs), such as autoimmune neutropenia (AIN) and various types of allergies [8].

Discussion

H. pylori variants as beneficial (non-pathogenic) bacteria

H. pylori's negative impacts have been well established; however, there are several purported positive impacts. *H. pylori* may protect the host from other pathogenic infections, asthma, obesity, celiac disease, inflammatory bowel disease (IBD), atopic dermatitis, rhinitis, esophageal cancer, and gastroesophageal reflux disease (GERD) [9]. However, comprehensive studies confirming these purported benefits of *H. pylori* are lacking. Also, specific studies have contradicted any protective effects of *H. pylori* [8–11].

Certain studies have indicated *H. pylori's* possible role in maintaining the stomach's healthy environment, similar to the functioning of the intestinal microflora colonizing the intestine and aiding digestion. The microflora supports digestion, assisting in the degradation of indigestible carbohydrates, synthesis of vitamins (vitamin K, thiamine, folate, and biotin), and protection against infection from harmful pathogens [8–11].

Other studies have suggested the possible contribution of non-pathogenic *H. pylori* strains in normalizing excess stomach acid and regulating appetite, although these effects lack adequate experimental evidence [12].

Epidemiology

According to one estimate, *H. pylori* infection has a high incidence rate, affecting about half of the global population. Moreover, its prevalence varies between developing and developed countries. Compared to developed countries, there are more cases of *H. pylori* infections in developing countries, with a prevalence rate of about 25% [13].

The age at which *H. pylori* infection has been acquired might influence the pathological outcome in patients. The earlier the age of *H. pylori* infection, the higher the risk of severe inflammatory response, leading to atrophic gastritis, gastric ulcer (peptic ulcer disease), and

gastric cancer. Advanced age onset is more likely to result in duodenal ulcers [4].

In developing countries, children are more likely to acquire *H. pylori* infection than their counterparts from developed and industrialized countries. This difference could be attributed to poor sanitary practices and infrequent use of antibiotics for other indications in developing countries [4].

The prevalence of *H. pylori* infection increases with age. About 50% of infected individuals are ≥60 years; whereas, 10% belong to the age group of 18–30 years [14]. However, despite *H. pylori's* widespread infectivity, the overall infection rate has been decreasing [4,13,15].

Signs and symptoms

About 90% of individuals infected with *H. pylori* may never experience any symptoms during their lifetime, although 10–20% are at risk for peptic ulcer disease. In lesser cases, acute *H. pylori* infection results in acute gastritis symptoms with acute-onset abdominal pain, nausea, and vomiting [16].

In chronic gastritis, non-specific abdominal pain, a sense of bloating, belching, and appetite loss are the primary symptoms. Pain onset typically occurs between meals when the stomach is empty, especially in the early morning [17]. In some cases, the stomach or duodenal ulcers bleed, resulting in black (tarry) stools (melena) and anemia (when the bleeding is long-term). Heavily bleeding ulcers lead to hematemesis and hematochezia [18].

Peptic ulcer disease (PUD) caused by *H. pylori* infection is of two types: duodenal ulcer and gastric ulcer. Duodenal ulcer affects the duodenum's first part and or the pyloric antrum, connecting the stomach to the duodenum. Gastric ulcer affects the body of the stomach [2,4,19–21].

H. pylori infection may lead to polyps in the stomach (gastric polyps) or colorectal region (colorectal polyps). These polyps are often asymptomatic. Nevertheless, gastric polyps induce dyspepsia, heartburn, bleeding, and gastric outlet obstruction (GOO) syndrome; whereas, colorectal polyps result in bleeding, constipation, diarrhea, weight loss, and abdominal pain [2,4,10].

Transmission routes

The precise routes of *H. pylori* transmission remain unclear. Epidemiological studies implicate contaminated food, water, or soil as possible sources of *H. pylori* infection, in addition to the person-to-person transmission through feco-oral and oral-oral routes [2,4]. Improvements in sanitary practices, hygiene, and living standards reduce *H. pylori* infection prevalence [22].

Management

Treatment with antibacterial and antisecretory agents is the standard of care for *H. pylori* management. Also, phytomedicines and probiotics have been reported effective. According to Peterson (1997), "The efficacy of antibiotics against *Helicobacter pylori* is enhanced by the co-administration of antisecretory drugs [23]. An antisecretory agent increases the gastric pH, facilitating the action of an antibacterial agent [24].

Antibacterial agents

Amoxicillin, clarithromycin, levofloxacin, metronidazole, tetracycline, and rifabutin are the most commonly used antibiotics and proton pump inhibitors (PPIs); omeprazole and pantoprazole are the preferred antisecretory agents for managing *H. pylori* infection [25].

Most antibacterial agents, like clarithromycin, levofloxacin, and metronidazole, act in a concentration-dependent manner [20]; whereas, other antibacterial agents, like amoxicillin, act in a time-dependent manner [26,27].

Bismuth salts, being poorly soluble in water, are poorly absorbed in the gastrointestinal tract; thus, acting locally against *H. pylori* [28]. With levofloxacin and clarithromycin, an additional post-antibiotic effect against *H. pylori* has been documented [26–28].

Antisecretory agents

H2-receptor antagonists (H2RAs), such as ranitidine and famotidine, are classified as antisecretory agents, but PPIs are considerably more effective than H2RAs in elevating gastric pH. PPIs act by inhibiting the H,K-ATPase proton pump (located on the canalicular membrane, responsible for secreting hydrochloric acid). Moreover, PPIs have a direct antimicrobial effect against *H. pylori.* According to a study by Kawakami., *et al.* (2000), the anti-*H. pylori* effects, measured in terms of the minimum inhibitory concentration (MIC_{90}), of different PPIs and the antimicrobial agents amoxicillin, clarithromycin, and metronidazole were comparable [29].

Alternative drug therapy for *H. pylori* eradication

The use of antibiotics alters gut microflora, leading to various complications, such as diarrhea. Also, resistance against antibiotics in previously susceptible bacteria limits antimicrobial efficacy and use. Thus, alternative drug therapies, such as phytomedicines and probiotics, are being more widely utilized for *H. pylori* infection. According to Traditional Chinese Medicine (TCM), phytomedicines are beneficial in different diseases, including the eradication of *H. pylori*. Probiotics are living microorganisms with distinct health benefits, typically presented in oral formulations. Yang., *et al.* (2014) reported that although *Saccharomyces boulardii* and *Lactobacillus* strains, along with triple-drug therapy, for *H. pylori* infection significantly reduced diarrheal episodes, their efficacy when used alone is debatable [26].

Regimens for *H. pylori* eradication

There are different drug combinations for eradicating *H. pylori*, including triple-drug therapy, quadruple-drug therapy (with bismuth), sequential therapy, and concomitant therapy (quadruple-drug therapy without bismuth). According to the Maastricht IV Consensus Report, anti-*H. pylori* regimens should achieve an eradication rate of at least 80% [24].

There are several guidelines for managing *H. pylori* infection, mainly depending on the geographic location. However, first-line and rescue drugs are similar in most areas [30].

First-line drugs

The standard triple-drug therapy for *H. pylori* infection includes a PPI and two antibiotics (clarithromycin and amoxicillin or metronidazole) [31,32]. Triple-drug therapy's recommended duration is 7 days in Europe and Asia and 14 days in the United States. However, recent data have revealed that the standard triple-drug therapy's efficacy has been decreasing, with the rate of eradication falling to less than 80% of the desired level [33].

In a study based on pharmacogenomics (*CYP2C19* genotype) and susceptibility to clarithromycin, Furuta., *et al.* (2007) found a 96% intention-to-treat (ITT) eradication rate. However, the cost-effectiveness of the therapy needs to be established before its widespread application [34].

According to the updated recommendations of Maastricht IV and Florence Consensus Reports, to overcome the concern of clarithromycin resistance, quadruple-drug therapy with bismuth can be substituted for standard triple-drug therapy in areas with reported re-

sistance >15–20% against clarithromycin [31]. In countries such as Japan, Australia, and Malaysia, where bismuth is unavailable because of the associated adverse effects, quadruple-drug therapy without bismuth (concomitant treatment) has been approved as a first-line therapy alternative to standard triple-drug therapy in areas with high clarithromycin resistance [35].

Sequential therapy (10 days) has shown an eradication rate of approximately 98% [26,36]. In this regimen, dual therapy with a PPI and amoxicillin is administered for 5 days, followed by triple-drug therapy (PPI, clarithromycin, and metronidazole or tinidazole) for an additional 5 days. Compared to standard triple-drug therapy of 7 days, sequential therapy has demonstrated higher eradication rates [26,36].

Sequential therapy is recommended as an alternative to standard triple-drug therapy in many countries. However, a clinical trial conducted in seven Latin America sites revealed that standard triple-drug therapy for 14 days is preferable to 10-day sequential therapy in managing *H. pylori* infection in the Latin American population, with eradication rates of 82.2% and 76.5%, respectively [37]. Thus, the choice of first-line drug therapy for eradication of *H. pylori* might depend, in part, on the geographic location.

Rescue therapy

Quadruple-drug therapy with bismuth and levofloxacin-containing triple-drug therapy is considered rescue therapy in the case of first-line therapy [26].

Recurrence after successful eradication

Xue., *et al*. (2019) conducted a study exploring *H. pylori* infection recurrence rate following successful eradication and the factors responsible for such [29]. Overall, the 1050 patients involved in the study were followed with the ^{13}C-urea breath test (UBT) or Warthin-Starry (WS) staining at 8–12 weeks and 1 and 3 years after successful completion of therapy. The researchers found that *H. pylori* infection's recurrence rates were 1.75% and 4.61% after 1 and 3 years of successful infection eradication, respectively [38]. The researchers further concluded that poor socio-economic conditions and sanitary habits are risk factors associated with the recurrence of *H. pylori* infection after successful eradication [38].

Conclusion

Eradication of *H. pylori* infection is of utmost importance as the infection can lead to peptic ulcer disease, gastritis, and malignancy. *H. pylori* infection should be treated appropriately to avoid associated diseases, sequelae, and recurrence. Combination therapy with antimicrobial agents and PPIs are recommended for managing the infection. Several regimens have been approved for treating the infection, but the standard 7-day triple-drug therapy and sequential 10-day therapy are typically considered first-line treatments. These regimens' efficacy is influenced by various factors, such as geographic location, intragastric pH, and resistance of *H. pylori* to antibacterial drugs. In addition to the approved pharmaceutical regimens, alternative therapies with purported benefits for managing *H. pylori* infection include probiotics and phytomedicines.

Conflict of Interest Statement

The authors declare that this paper was written in the absence of any commercial or financial relationship that could be construed as a potential conflict of interest.

References

1. Alfarouk KO., *et al*. "The possible role of helicobacter pylori in gastric cancer and its management". *Frontiers in Oncology* 9 (2019): 75.
2. Brown LM. "Helicobacter pylori: Epidemiology and routes of transmission". *Epidemiologic Reviews* 22.2 (2000): 238-297.
3. Backert S., *et al*. "Pathogenesis of Helicobacter pylori infection". *Helicobacter* 21.1 (2016): 19-25.
4. Camilo V., *et al*. "Pathogenesis of Helicobacter pylori infection". *Helicobacter* 22.1 (2017).
5. Kusters JG., *et al*. "Pathogenesis of Helicobacter pylori infection". *Clinical Microbiology Reviews* 19.3 (2006): 449-490.
6. Sanders MK and Peura DA. "Helicobacter pylori-Associated Diseases". *Current Gastroenterology* Reports 4.6 (2002): 448-454.
7. Marshall B and Warren R. "Unidentified Curved Bacilli on Gastric Epithelium In Active Chronic Gastritis". *The Lancet* 1 (1983): 1237-1275.
8. Gravina AG., *et al*. "Helicobacter pylori and extragastric diseases: A review". *World Journal of Gastroenterology* 24.29 (2018): 3204-3221.
9. Laird-Fick HS., *et al*. "Gastric adenocarcinoma: The role of helicobacter pylori in pathogenesis and prevention efforts". *Postgraduate Medical Journal* (2016).
10. Bravo D., *et al*. "Helicobacter pylori in human health and disease: Mechanisms for local gastric and systemic effects". *World Journal of Gastroenterology* 24.28 (2018): 3071-3089.
11. Blaser MJ. "Who are we? Indigenous microbes and the ecology of human diseases". *EMBO Reports* 7.10 (2006): 956-960.
12. Blaser M. "Antibiotic overuse: Stop the killing of beneficial bacteria". *Nature* 476.7361 (2011): 393-394.
13. Pounder RE NgD. "The prevalence of Helicobacter pylori infection in different countries". *In: Alimentary Pharmacology and Therapeutics* 9.2 (1995): 33-39.
14. Burucoa C and Axon A. "Epidemiology of Helicobacter pylori infection". *Helicobacter* 19.1 (2017): 1-5.
15. Malaty HM. "Epidemiology of Helicobacter pylori infection". *Best Practice and Research: Clinical Gastroenterology* 21.2 (2007): 205-214.
16. Narayanan M., *et al*. "Peptic Ulcer Disease and Helicobacter pylori infection". *Malignant Hyperthermia* 115.3 (2018): 219-224.
17. Talley NJ., *et al*. "ABC of the upper gastrointestinal tract: Indigestion: When is it functional?" *BMJ: British Medical Journal* 323.7324 (2001): 1294-1297.
18. Kim BS., *et al*. "Diagnosis of gastrointestinal bleeding: A practical guide for clinicians". *World Journal of Gastrointestinal Pathophysiology* 5.4 (2014): 467-478.
19. McColl KEL. "Helicobacter pylori infection". *New England Journal of Medicine* (2010).
20. Crowe SE. "Helicobacter pylori Infection". *New England Journal of Medicine* (2019).
21. Suerbaum S and Michetti P. "Helicobacter pylori infection". *New England Journal of Medicine* 347.15 (2002): 1176-1186.
22. Salih BA. "Helicobacter pylori infection in developing countries: the burden for how long?" *Saudi Journal of Gastroenterology* 15.3 (2009): 201-207.

23. Peterson WL. "The role of antisecretory drugs in the treatment of Helicobacter pylori infection". *Alimentary Pharmacology and Therapeutics* 11.1 (1997): 21-25.

24. Malfertheiner P., *et al*. "Management of helicobacter pylori infection-the Maastricht V/Florence consensus report". *Gut* (2017).

25. Safavi M., *et al*. "Treatment of Helicobacter pylori infection: Current and future insights". *The World Journal of Clinical Cases* 4.1 (2016): 5-19.

26. Yang JC., *et al*. "Treatment of Helicobacter pylori infection: Current status and future concepts". *World Journal of Gastroenterology* 20.18 (2014): 5283-5293.

27. De Brito BB., *et al*. "Pathogenesis and clinical management of Helicobacter pylori gastric infection". *World Journal of Gastroenterology* 25.37 (2019): 5578-5589.

28. Lambert JR and Midolo P. "The actions of bismuth in the treatment of Helicobacter pylori infection". *Alimentary Pharmacology and Therapeutics* 11.1 (1997): 27-33.

29. Kawakami Y., *et al*. "*In vitro* activities of rabeprazole, a novel proton pump inhibitor, and its thioether derivative alone and in combination with other antimicrobials against recent clinical isolates of Helicobacter pylori". *Antimicrobial Agents and Chemotherapy* 44.2 (2000): 458-461.

30. Saleem N and Howden CW. "Update on the Management of Helicobacter pylori Infection". *Current Treatment Options in Gastroenterology* (2020): 1-12.

31. Chey WD and Wong BCY. "American College of Gastroenterology guideline on the management of Helicobacter pylori infection". *American Journal of Gastroenterology* 102.8 (2007): 1808-1825.

32. Fock KM., *et al*. "Second Asia-Pacific Consensus Guidelines for Helicobacter pylori infection". *Journal of Gastroenterology and Hepatology* 24.10 (2009): 1587-1600.

33. Graham DY and Fischbach L. "Helicobacter pylori treatment in the era of increasing antibiotic resistance". *Gut* 59.8 (2010): 1143-1153.

34. Furuta T., *et al*. "Pharmacogenomics-based tailored versus standard therapeutic regimen for eradication of H. pylori". *Clinical Pharmacology and Therapeutics* 81.4 (2007): 521-528.

35. Hu Y., *et al*. "Recent progress in Helicobacter pylori treatment". *Chinese Medical Journal* 133.3 (2020): 335-343.

36. Zullo A., *et al*. "High eradication rates of Helicobacter pylori with a new sequential treatment". *Alimentary Pharmacology and Therapeutics* 17.5 (2003): 719-726.

37. Chen YI and Fallone CA. "A 14-day course of triple therapy is superior to a 10-day course for the eradication of Helicobacter pylori: A Canadian study conducted in a 'real world' setting". *Canadian Journal of Gastroenterology and Hepatology* 29.8 (2015): e7-e10.

38. Xue Y., *et al*. "Recurrence of Helicobacter pylori infection". *Chinese Medical Journal* 132.7 (2019): 765-771.

Volume 8 Issue 1 January 2021