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Diagnosis and Management of *Helicobacter pylori*

Uni Wong and Leon P McLean*

Department of Medicine, Division of Gastroenterology and Hepatology, University of Maryland, Baltimore, USA

***Corresponding author:** *Leon P McLean, Department of Medicine, Division of Gastroenterology and Hepatology, University of Maryland, 100 North Greene Street, Lower Level, Baltimore, MD 21201, USA, Tel: 410 706-3387, Fax: 410 706-4330, E-mail: lmclean@medicine.umaryland.edu*

Abstract

Helicobacter pylori is a common infection linked to dyspepsia, peptic ulcer disease, gastritis, gastric cancer, and MALT lymphoma. Endoscopic and nonendoscopic options may be used to diagnose *H. pylori* and confirm its eradication. Fourteen days of triple or quadruple therapy may be used as initial therapy, although clarithromycin-based triple therapy has become less effective over time. Quadruple therapy or sequential therapy have been increasingly utilized. Previously prescribed antibiotics should be avoided in management of persistent *H. pylori* infection. Eradication should be confirmed in patients with peptic ulcer disease, MALT lymphoma, or gastric cancer.

Keywords

Helicobacter pylori, Peptic ulcer disease, MALT lymphoma, Gastric cancer, Dyspepsia, Triple therapy, Quadruple therapy, Sequential therapy

Introduction

Helicobacter pylori (H. pylori) is a common bacterial infection, affecting up to 40% of the United States (US) population [1] with up to two-thirds of the world population infected [2]. *H. pylori* has been linked to a variety of gastrointestinal (GI) conditions including gastritis, peptic ulcer disease (PUD), mucosa associated lymphoid tissue (MALT) lymphoma, and gastric cancer [3]. In fact, it is classified as a Group 1 carcinogen by the International Agency for Research on Cancer due to its association with gastric cancer [4]. Interestingly, although it is a carcinogen, *H. pylori* may be protective against esophageal adenocarcinoma [5-9].

H.pylori is a gram-negative, spiral-shaped, pathogenic bacterium that resides within the mucus layer that coats the gastric mucosa [1]. The bacterium was first isolated by Robin Warren and Barry Marshall in 1982 [10]. It was originally called *Campylobacter pylori*, but was later renamed *Helicobacter pylori*. *H. pylori* is microaerophilic, surviving in the presence of relatively low oxygen tension [11]. It is also able to tolerate the acidic environment of the stomach through production of ureases, which catalyze a chemical reaction producing ammonia that surrounds the organism [1]. The ammonia produced neutralizes the acid environment around the bacterium, allowing it to survive within the stomach.

H. pylori eradication is typically advised in cases where infection is confirmed. Classic triple-therapy, utilizing clarithromycin and amoxicillin in conjunction with a proton-pump inhibitor (PPI), has become less effective over time [12,13]. Prolonged courses of therapy, quadruple-therapy, and/or sequential therapy may be required for eradication [14]. Confirmation of eradication is advised in certain clinical scenarios, such as PUD, MALT lymphoma, and in patients with gastric cancer [14].

The following manuscript discusses the epidemiology of and risk factors for *H. pylori* infection. We also discuss its clinical significance, strategies for diagnosis, and current treatment options.

Epidemiology

Although *H. pylori* infection is common, the precise mechanism underlying its transmission is not definitively established. Suggested methods of transmission include ingestion of contaminated water [15], fecal-oral means [16], and even periodontal pockets serving as a reservoir [17]. Other possibilities include transmission by flies [18,19], iatrogenic spread with unsterile endoscopes [18,20] and use of pH probes [18]. Most children in developing countries are infected before age 10, but in the US and other developed countries infection more commonly occurs in adulthood [1]. *H. pylori* infection is less common in developed countries with a prevalence of approximately 20-30% [21]. In developing countries disease burden is higher with prevalence rates approaching 90% [21].

Demographic variation exists in *H. pylori* infection within the US population [1]. In a cross-sectional study of 1200 Veterans Affairs patients between 40 and 80 years of age who underwent esophagogastroduodenoscopy (EGD) with gastric biopsies, *H. pylori* infection was more common in Hispanics (adjusted odds ratio [OR] 3.0; 95% CI 1.7 - 5.3) and African Americans (adjusted OR 2.6; 95% CI 0.2 - 0.9) than in non-Hispanic whites [22]. Similarly, African American and Hispanic military personnel have higher rates of *H. pylori* seropositivity at 44% and 38%, respectively, compared to their Caucasian counterparts at 14% ($p < 0.05$) [23]. The higher prevalence of *H. pylori* seropositivity in African Americans and Hispanics may be driven by socioeconomic factors such as income, education, household crowding, and birth outside of the US [24,25].

Males have a higher prevalence of *H. pylori* infection than females. In a cross-sectional study of 556 healthy adults between 20 and 30 years of age, males were twice as likely to have antibodies against *H. pylori* than females (OR 2.0, 95% CI 1.2–3.1) across all strata of age, race, education, and household income [25]. These findings were

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confirmed in a meta-analysis examining 18 population-based studies, with a combined OR of 1.2 (95% CI 1.1–1.2) [26]. Whether males are more susceptible to infection with *H. pylori* remains unclear. It is also possible that males are exposed to *H. pylori* more often or that the immune system in females is more effective at preventing or clearing *H. pylori*.

Risk factors

Smoking: It is possible that a relationship between *H. pylori* infection and smoking exists. In case-control studies, subjects who were seropositive for *H. pylori* were more likely to be current smokers than those who were seronegative (OR 7.9, 95% CI 2.0–30) [27,28]. In a survey study in Northern Ireland of 4742 randomly selected subjects, *H. pylori* seropositivity was more common in current smokers and ex-smokers than never smokers (OR 1.2, 95% CI 1.0–1.5) [29]. Others, however, have found a negative association between smoking and *H. pylori* infection. In a retrospective study of 8836 subjects, current smokers had lower risk of *H. pylori* seropositivity (OR 0.8, 95% CI 0.7–0.9) than those who had never smoked [30]. Another retrospective study of 545 subjects found no difference in *H. pylori* seropositivity between smokers (current and ex-smokers) and non-smokers (40% vs. 40%, p = 0.98). [31]. Socioeconomic class may have played a role in these conflicting data as this was not consistently controlled for in studies examining this topic [30]. Other potential confounding factors include alcohol consumption and use of medications such as PPI and antibiotics.

Alcohol: Although the relationship between smoking and *H. pylori* infection remains somewhat murky, habitual alcohol consumption does appear to protect against *H. pylori* [30-32]. In a German cross-sectional study of 6545 subjects, the seroprevalence of *H. pylori* was highest among subjects who reported no alcohol consumption and lowest among subjects consuming 25–50 g of alcohol per day (OR 0.6, 95% CI 0.5–0.8) [32]. While these data suggest a protective role for alcohol, factors that would influence *H. pylori* eradication such as recent use of antibiotics or PPI therapy were not controlled in this analysis. Interestingly, daily alcohol consumption is associated with greater success of eradication therapy with failure rate of only 12%, compared to 30% in those not consuming alcohol on a daily basis (OR 3.2, 95% CI 1.1 - 9.2) [33].

Clinical significance

H. pylori infection is linked to dyspepsia, gastritis, PUD, gastric adenocarcinoma, and MALT lymphoma. Up to 20% of *H. pylori*-infected individuals can develop one or more of these sequelae [34]. *H. pylori* infection may also protect against symptoms of gastro-esophageal reflux disease (GERD) and the development of esophageal adenocarcinoma, but this relationship has not been definitively established.

Dyspepsia: Symptoms of dyspepsia often include epigastric pain, postprandial fullness, and/or early satiety [35]. EGD must reveal no structural disease that could explain symptoms and patients must have at least one of the following - bothersome postprandial fullness, early satiety, epigastric pain, or epigastric burning [36]. While ulcers and gastritis can cause these symptoms, up to 70% of patients with dyspepsia have no evidence of mucosal injury [37]. In a prospective cohort study, *H. pylori* eradication was associated with improvement of epigastric pain [38]. Therefore, in patients under the age of 55 years without alarm features (bleeding, anemia, early satiety, unexplained weight loss, dysphagia, odynophagia, recurrent vomiting, family history of gastrointestinal cancer, previous esophago-gastric cancer), a "test and treat" strategy with *H. pylori* eradication is recommended [14]. Those with alarm features should undergo EGD to exclude underlying pathology such as PUD or esophageal or gastric malignancy.

Gastritis: In early infection, *H. pylori* gastritis preferentially causes inflammation at the gastric antrum, but later migrates proximally toward the body and cardia of the stomach. Unless treated early, acute gastritis will evolve into chronic gastritis. *H. pylori* organisms are most frequently detected at the gastric antrum [39]. In some cases, however, the organisms can be detected only in the body of the stomach, particularly during PPI use or in the presence of marked atrophy or gastric intestinal metaplasia. With chronic inflammation, there is a loss of gastrin producing G cells and acid producing parietal cells resulting in decreased acid secretion and the development of gastric atrophy with intestinal metaplasia [40]. The decrease in gastric acid secretion may lessen GERD symptoms and is the reason it has been suggested that *H. pylori* infection may protect against the development of esophageal adenocarcinoma. Patients with *H. pylori* associated atrophic gastritis are often asymptomatic, but these individuals are at increased risk of developing gastric carcinoma [41].

Peptic ulcer disease: *H. pylori* is present in 70–85% of patients with gastric ulcers and 90–95% of those with duodenal ulcers [42]. Nonetheless, it is important to obtain a detailed history to exclude nonsteroidal anti-inflammatory drugs as an additional cause of PUD. Early in infection, *H. pylori* preferentially colonizes the antrum resulting in exaggerated gastrin release and reduced somatostatin release, causing increased acid secretion contributing to the formation of duodenal ulcers [43]. If left untreated, *H. pylori* migrates proximally to the body of the stomach where it may cause diffuse gastritis and gastric ulcers.

Gastric adenocarcinoma: As mentioned previously, duodenal ulcers develop in the setting of antral predominant gastritis, minimal atrophy, and increased acid secretion. Gastric ulcers and gastric carcinoma, on the other hand, are associated with extensive gastritis, widespread intestinal metaplasia, and decreased acid secretion [44]. Gastric cancer was the fourth most common malignancy worldwide in 2008 with approximately 72% of new cases occurring in developing countries [45]. Based on Surveillance, Epidemiology, and End Results (SEER) data between 2005–2011, the five-year relative survival rate for gastric cancer in the US is 29% [46].

The majority of gastric cancers are adenocarcinomas [47]. Gastric adenocarcinoma can be subdivided into two morphologic types: intestinal-type and diffuse-type. Diffuse-type gastric adenocarcinomas are typically less well differentiated, with sheets of cells without gland formation with occasional signet ring cells and mucin. *H. pylori* infection, chronic gastritis, atrophy, and intestinal metaplasia can all contribute to the development of intestinal-type gastric adenocarcinomas [48]. *H. pylori* infection can also drive the development of diffuse-type gastric carcinomas, but gastric atrophy and intestinal metaplasia have not been shown to contribute to its development [49].

Mucosal associated lymphoid tissue lymphoma: Extranodal marginal zone B cell lymphoma, also known as low grade B cell lymphoma of MALT, is an extranodal lymphoma that arises from mucosa associated lymphoid tissue, often in the stomach. MALT lymphoma can develop in other mucosal sites besides the stomach. *H. pylori* is present in the gastric mucosa in up to 92% of patients with MALT lymphoma [50]. *H. pylori* gastritis contributes directly to the pathogenesis of this gastric malignancy [50,51] with eradication essential for successful treatment of low grade MALT lymphoma. In a large cohort follow-up study of 420 patients with gastric low grade MALT lymphoma, up to 77% responded to *H. pylori* eradication [52].

GERD and Barrett's adenocarcinoma: Given its effect on acid production in the stomach, *H. pylori* infection has been hypothesized to impact GERD symptoms and potentially the development of esophageal adenocarcinoma. Early *H. pylori* infection causes increased gastrin release, but decreased somatostatin release. This has a net effect of increasing gastric acid secretion. In patients with a predisposition for GERD, increased acid production due to *H. pylori* infection may further exacerbate reflux symptoms.

The pathophysiology underlying chronic *H. pylori* gastritis differs considerably from acute *H. pylori* gastritis. In chronic *H. pylori* infection patients suffer from a loss of gastrin producing G cells and acid producing parietal cells, resulting in decreased acid production.

This effect may protect against GERD, Barrett's esophagus and the development of esophageal adenocarcinoma [5-9]. Although these features suggest a protective role for *H. Pylori*, studies have been limited by the fact that subject have been classified as either *H. pylori* infected or uninfected, but whether *H. pylori* was localized to the gastric antrum or body has not been consistently examined.

Diagnosis

Endoscopic testing

H. pylori can be diagnosed during EGD with biopsy using rapid urease test (RUT), histology, bacterial culture, or polymerase chain reaction (PCR) (Table 1) [14]. Indications for EGD are multiple and are delineated in the 2012 guideline from the American Society for Gastrointestinal Endoscopy. Although EGD can be utilized to determine if a patient is infected with *H. pylori*, it should not be performed for the sole purpose of establishing the diagnosis given the availability of several non-invasive testing techniques [14].

Rapid urease test

If EGD is to be performed, the test of choice for detecting *H. pylori* is the RUT performed on antral biopsy specimens. In patients who have taken PPI, antibiotics, or bismuth within 2 weeks of EGD, distribution of *H. pylori* infection can be patchy, therefore biopsies from both the antrum and the gastric body are needed for RUT [14]. In a prospective study of 620 patients undergoing EGD for gastrointestinal symptom, biopsies obtained from both the antrum and gastric body revealed the presence of *H. Pylori* in 307 (50%) patients, either by RUT or histology [53]. In this study, performing RUT on gastric body biopsies in addition to antral biopsies increased the detection rate of *H. pylori* by 6.3% [53]. Overall, RUT has a sensitivity of 90 - 95% and a specificity of 95 - 100% for detection of *H. pylori* [54,55].

Histology

Gastric biopsy histology testing for *H. pylori* also has a high sensitivity and specificity with both exceeding 95% [14]. However, testing is expensive and requires trained personnel [14]. In addition, its accuracy depends on the site biopsied, number of biopsies obtained, and size of biopsies submitted. Similar to RUT, test performance may be impaired in the setting of antibiotic, bismuth, or PPI use [14]. Combining gastric body biopsies with antral biopsies increases the detection rate of *H. pylori* [53]. Whether the patients in this study who had isolated positive gastric body histology with *H. pylori* were on PPI, antibiotics, or bismuth is unclear.

Bacterial culture and PCR

Bacterial culture and PCR are not widely available and are therefore rarely used in the clinical setting. While bacterial culture is useful for determining the susceptibility of *H. pylori* to antibiotics, it is not effective for detecting the presence or absence of *H. pylori* with a sensitivity of only 53%, although its specificity approaches 100% [14,56]. PCR is a DNA amplification technique that makes use of the multiple copies of a target DNA sequence to identify *H. pylori*. PCR is able to detect *H. pylori* not identified on histology [57] with sensitivity greater than 90% [58,59]. PCR also has the added benefit of being able to detect mutations associated with antimicrobial resistance [60], allowing clinicians to tailor their eradication strategy accordingly. However, PCR is currently limited to research settings and is not available for routine clinical practice.

Table 1: Strategies for Diagnosing *H. Pylori* Infection.

Endoscopic testing	Non-endoscopic testing
Rapid urease test	Antibody testing
Histology	Urea breath test
Bacterial culture	Fecal antigen testing
Polymerase chain reaction	

Nonendoscopic testing

Antibody testing, urea breath testing, and the fecal antigen test are three noninvasive diagnostic tests available for determining if a patient is infected with *H. pylori* (Table 1).

Antibody testing: Serum *H. pylori* IgG is generally detectable approximately 21 days after infection and remains positive long after eradication [61]. It has a sensitivity of up to 85% with a specificity of 79% [62]. Antibody testing is inexpensive and widely available, but is limited by the fact that it cannot distinguish between active and past infection.

Urea breath test: The urea breath test is another non-invasive testing option. Its major drawback is that it requires the patient to ingest urea, labeled with either non-radioactive (^{13}C) or radioactive carbon (^{14}C). If *H. pylori* is present, urease produced by the bacteria breaks down ingested urea releasing labeled carbon dioxide, which is measured in exhaled air [63]. The sensitivity and specificity of urea breath testing exceeds 95% [14,63]. Antibiotics and bismuth should be avoided for at least one month and PPI for 7–14 days prior to performing the urea breath test. Performing the test on these medications is associated with an increased false negative rate [14,63]. The requirement for appropriate testing equipment and the cost of obtaining labeled urea limits the availability of this test [14].

Fecal antigen test: Fecal antigen testing identifies *H. pylori* antigen in stool through immunologic techniques using a polyclonal antibody directed against *H. pylori* [14]. Because this test detects active infection, it can be used as a screening test as well as for confirming eradication. If used for documentation of cure after *H. pylori* therapy, it should be performed 8 weeks after completion of therapy [64]. Similar to the urea breath test, patients should avoid PPI for at least 14 days prior to undergoing fecal antigen test to minimize the chance of obtaining a false negative result.

Treatment

Multiple options exist for the treatment of patients with active *H. pylori* infection (Table 2 and Table 3). Determining which regimen is most appropriate depends on several factors including local susceptibility patterns, whether a patient is undergoing initial treatment, likelihood of patient adherence, and patient factors such as the presence or absence of drug allergies.

Adherence to therapy is an important factor with non-adherence contributing to treatment failure as well as antibiotic resistance. As a result, regimens that are "easier" to take are generally preferred. Eradication regimens that require the patient to take drugs twice a day are more likely to be followed when compared to more frequent dosing regimens. Both three and four drug regimens are acceptable first-line therapies to eradicate *H. pylori* (Table 2). Triple therapy consists of a PPI, clarithromycin, and amoxicillin or metronidazole and is taken twice daily. Triple therapy should be administered for 14 days [65,66]. Quadruple therapy utilizes a PPI or H_2 receptor antagonist, bismuth, metronidazole, and tetracycline. These medications are taken up to four times daily for 10–14 days [14]. Although both triple and quadruple therapies have been recommended as first-line options for the treatment of *H. Pylori*, the complexity of four times daily dosing and the high pill count in quadruple therapy may be challenging for

Table 2: First-line regimens for *H. Pylori* Eradication [14].

	Medications	Duration	Efficacy
Standard triple therapy	PPI bid, clarithromycin 500 mg bid, amoxicillin 1000 mg bid	10-14 days	70-85%
For PCN allergic patients	PPI bid, clarithromycin 500 mg bid, metronidazole 500 mg bid	10-14 days	70-85%
Quadruple therapy	Bismuth subsalicylate 525 mg qid, metronidazole 250 mg qid, tetracycline 500 mg qid, PPI bid or ranitidine 150 mg bid	10-14 days	75-90%

Table 3: Salvage regimens for *H. Pylori* Eradication [14].

	Medications	Duration
Alternative triple therapy	If no allergy, can use one of the triple therapies that have not been used previously.	10-14 days
Alternative triple therapy	PPI bid, levofloxacin renally dosed, amoxicillin 1000 mg bid	10 days
Quadruple therapy	Bismuth subsalicylate 525 mg qid, metronidazole 250 mg qid, tetracycline 500 mg qid, PPI bid or ranitidine 150 mg bid	10-14 days
Sequential therapy	PPI + amoxicillin 1000 mg bid followed by PPI + clarithromycin 500 mg bid + tinidazole 500 mg bid	5+5 days

*Avoid antibiotics that have been used previously

PPI = Proton Pump Inhibitor

Bid = Twice daily, Qid = Four times daily

PCN = Penicillin

patients to take and has the potential to be associated with decreased patient adherence.

Eradication rates vary according to the strategy utilized. Clarithromycin-based triple therapy has become less effective over time. Previously, eradication rates with triple therapy and quadruple therapy were as high as 93% and 80%, respectively [13,67,68]. In a recent meta-analysis examining 104 studies of 42,124 patients treated with triple therapy for *H. pylori*, the overall eradication rate was 75% (95% CI 72-77%) by intention-to-treat analysis and 82% (95% CI 81-83%) by per-protocol analysis [12]. A prospective study of 37 patients found that the eradication rate associated with 14 days of quadruple therapy administered twice daily was 92% (95% CI 79-98%) [69]. Although these data suggest that quadruple therapy is more effective than triple therapy, the study sizes vary considerably and this should be considered while interpreting these data.

Sequential therapy can also be used to treat *H. pylori*. This strategy differs in that not all medications are taken at the same time. Sequential therapy includes a PPI taken with amoxicillin for 5 days followed by a PPI, clarithromycin, and tinidazole (or metronidazole) for an additional 5 days [14]. In a prospective randomized study of 213 patients, sequential therapy was found to be more effective than either 7 or 10 days of triple therapy (94% vs. 76% vs. 82%, respectively, $p < 0.05$) [70]. In this study, adherence was determined by pill count at follow-up visit. Only 6 patients (3%) withdrew from the study due to side effects [70]. There was no difference in the incidence in side effect among the treatment arms studied [70]. In a meta-analysis of 10 randomized controlled trials with 3,006 adults, sequential therapy was shown to be more effective for *H. pylori* eradication than both 7 day triple therapy (OR 3.0, 95% CI 2.5-3.6) and 10 day triple therapy (OR 2.9, 95% CI 2.0-4.4) without a difference in side effects (OR 1.2, 95% CI 0.8-1.3) [71]. Adherence to sequential therapy exceeded 90% [70,72-74].

In cases of persistent *H. pylori* infection, bismuth-based quadruple therapy, levofloxacin-based triple therapy, or sequential therapy are acceptable salvage options (Table 3). Previously utilized antibiotics should be avoided in cases of persistent infection, as bacteria may be resistant to prior medications. Due to expense and lack of availability, culture and antimicrobial sensitivity testing are not routinely recommended [14].

Documentation of Eradication

Documentation of *H. pylori* eradication is recommended in patients who have undergone resection of early gastric cancer and those with *H. pylori* associated ulcer, *H. pylori* associated MALT lymphoma, or in patients who have persistent dyspeptic symptoms [14]. Testing for eradication should not be performed earlier than 4 weeks after completion of therapy. Confirmation of eradication can be performed using nonendoscopic testing. EGD should only be performed if other clinical indications exist, not solely for determining whether *H. pylori* has been eradicated [14]. If EGD were to be performed, biopsies for histology should be obtained from both the antrum and the gastric body as histology on antral biopsies alone can miss up to 5% of *H. pylori* infection after triple therapy [75]. If endoscopic follow-up is not necessary, either urea breathe test or fecal antigen test can be used to confirm *H. pylori* eradication. Serum *H. pylori* IgG testing should not be used to document eradication as this can remain positive long after infection has cleared.

Conclusion

H. pylori is a common infection and can be associated with clinical symptoms and diagnoses including dyspepsia, PUD, gastritis, gastric cancer, and MALT lymphoma. EGD is not indicated for diagnosing *H. pylori* infection alone, but can be used to diagnose *H. pylori* when other indications for upper endoscopy exist. Both endoscopic and nonendoscopic options are available for the diagnosis of *H. pylori* and confirmation of its eradication. A 14 day course of triple therapy or quadruple therapy can be used as initial therapy. Clarithromycin-based triple therapy has become less effective over time. As a result, quadruple therapy or sequential therapy has been increasingly utilized. Previously prescribed antibiotics should be avoided in management of persistent *H. pylori* infection. If not previously used, quadruple therapy, levofloxacin-based triple therapy, or sequential therapy can be used as salvage therapy.

Disclosures

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