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Helicobacter Pylori: A Review of Epidemiology, Treatment, and Management

Yana Thaker[1], Andrew Moon[1] and Anita Afzali[1,2]*

[1]*Department of Internal Medicine, University of Washington, Seattle, Washington, USA*

[2]*Division of Gastroenterology, Harborview Medical Center, University of Washington, Seattle, Washington, USA*

***Corresponding author:** *Anita Afzali, MD, MPH, Harborview Medical Center, University of Washington, 325 Ninth Avenue, Box 359773, USA, Tel: 206-744-7055, Fax 206-744-8698, E-mail: anitaa@medicine.washington.edu*

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Background

Helicobacter pylori, a gram-negative, helical bacilli that live in the gastric epithelium was first isolated in 1983 [1]. It was discovered by Marshall and Warren who cultured Campylobacter pyloridis, which was later reclassified as Helicobacter pylori. It is transmitted via the fecal-oral, gastro-oral, or oral-oral routes [2-4]. H. pylori is able to thrive in the gastric environment due to urease [5], motility [6], and adherence to gastric epithelium [7,8], which allow it to neutralize gastric acid, penetrate through the mucus layer to the gastric epithelium, and colonize. It induces inflammation, leading to peptic ulcer disease (PUD) [9], gastric cancer [10-12], and gastric mucosa associated lymphoid-tissue (MALT) lymphoma [13-14]. Although infection with H. pylori persists without treatment, the majority of infections do not lead to symptoms or gastrointestinal disease [15,16].

Epidemiology

Simulations indicate that H. pylori spread from East Africa around 58,000 years ago, later evolving into many strains with varying degrees of pathogenicity [17,18]. Most individuals acquire infection during childhood [19] and infection is more common in developing countries [20]. In the United States, H. pylori infection is more common in Hispanic and black populations although this may be related to socioeconomic factors, including low income, less education, household crowding, and immigration into the United States [21,22].

Incidence/Prevalence

Infection with H. pylori has a reported annual incidence of 0.3-0.7% in developed countries and 6-14% in developing countries [23]. One study in Italy which followed a cohort of H. pylori-negative individuals from 2002 to 2012 identified four new infections out of 207 individuals (2.5%), equating to a 0.25% (0.10-0.63) yearly incidence rate [24]. H. pylori is the most prevalent bacterial infection in humans, occurring in at least half the world's population [25] and an estimated 30-40% of the US population [11]. Some reports highlight populations with particularly high rates of H. pylori infection including Alaska Native children (86%), [26] adults and children in Bolivia (80%), [27] elderly adults in China (83%), [28] and adults in Poland (84%) [29]. A recent systematic review reported higher prevalence of H. pylori infection in Central/South America and Asia [30]. In several populations, the prevalence of H. pylori appears to be decreasing, including among Korean adults, [31] Brazilian children [32], and Iranians [33]. This observed decline might be due to changing socioeconomic factors, improving hygiene, or increased use of antibiotics or proton pump inhibitors [34-36].

Indications for H. pylori Testing

The American College of Gastroenterology recommends a test-and-treat strategy for H. pylori in patients with active PUD, history of PUD without prior H. pylori treatment, low grade gastric MALT lymphoma, after endoscopic resection of early gastric cancer, and uninvestigated dyspepsia [37].

In the decade following the discovery of H. pylori various studies documented that this bacteria was found in 85-95% of gastric and duodenal ulcers [38,39]. Although all individuals infected with H. pylori have histopathologic evidence of active gastritis, only a subset of these patients develop clinically significant disease [38]. Among patients with H. pylori infection, the estimated lifetime risk of developing PUD is 10-20% and gastric cancer is 1-2% [38]. The factors that determine development of severe disease include environment (e.g. concurrent NSAID use), H. pylori virulence factors (of which there are over 10 virulence factors evaluated), and host determinants (e.g. immune system, level of acid production) [38,40]. Detection of H. pylori infection in ulcer disease and subsequent treatment with antibiotic therapy increases the cure rate, decreases risk of ulcer recurrence, and minimizes clinical complications (e.g. hemorrhage). This strategy has been credited with decreasing rates of PUD in the recent decades [41,42]. A recent Cochrane review reported a mean percentage of re-bleeding in the H. pylori eradication therapy group of 2.9% compared to 20% in the non-eradication anti-secretory therapy group (OR 0.17, 95% CI 0.10-0.32) [43].

Given the bleeding concerns, recent reports suggest benefit of

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diagnosing and treating H. pylori infection before starting non-steroid anti-inflammatory (NSAID) treatment and in those on aspirin (ASA) with history of gastroduodenal ulcer [44].

Diagnosis

The test of choice for diagnosing H. pylori is determined by necessity for endoscopic intervention as 4 of the 6 tests require biopsies (Table 1). Test selection is also determined by cost, availability of equipment and reagents, expertise, and pre-test probability for H. pylori. Diagnostic accuracy for most modalities are affected by medications used for H. pylori treatment since these medications suppress H. pylori infection and thus reduce test sensitivity [37,45,46]. To increase detection of infection, the patient should be off antibiotics for 4 weeks, off proton pump inhibitors (PPIs) for 2 weeks, and off H2-receptor antagonists and bismuth-containing compounds for several days [37,45,46].

Treatment

The first line, Food and Drug Administration (FDA) approved drug regimens for the treatment of H. pylori are listed in table 2. These therapies include proton pump inhibitor (PPI) and two antibiotics or bismuth subsalicylate, acid suppressor, and two antibiotics. However, eradication rates using these regimens are a disappointing 75% in the United States due to increased H. pylori resistance to standard antibiotics [48]. Clarithromycin and metronidazole show the highest rates of resistance and the factors associated with resistance include geographic region, sex, ethnicity, age, and active versus inactive ulcer disease [49]. As a result of the declining eradication rates, other

Table 1: Comparison of testing methods for *H. pylori* infection [37,45-47].

Test	Description of Test	Sensitivity	Specificity	Advantages	Limitations
Rapid urease testing	Gastric biopsies are incubated with urea and the *H. pylori* urease enzyme converts it to ammonia and bicarbonate. The test detects an increase in pH.	85-90%	98-100%	Rapid testing (5 mins-24 hours depending on kit) Inexpensive	Requires endoscopy to obtain samples. Sensitivity is dependent on the number of bacteria present, thus limited by H2-receptor antagonists, PPIs, antibiotics, and presence of blood.
Histology	Hematoxylin and eosin (H&E) staining is typically sufficient for detection of infection but immunohistochemical stain has greater sensitivity and specificity. A variety of other staining methods can be employed if there is severe gastritis but no infection initially detected.	82-95%	99-100%	Allows for concurrent evaluation for inflammation, metaplasia, and malignancy.	Requires endoscopy to obtain samples. Accuracy is dependent on size and site of biopsies, histological staining techniques, use of PPIs, use of antibiotics, and interpretation by pathologist. Expensive Requirement for trained personnel for sample processing and interpretation. Possible false positive results if other *H. pylori* species are present.
Culture	Requires special transport medium (e.g. Stuart's), growth medium (e.g. Pylori agar) and incubation environment (microaerobic environment) for 5-7 days.	70-80%	100%	Determination of antibiotic susceptibility.	Requires endoscopy to obtain samples. Can take a week to detect infection. Test affected by quality of specimens, transportation method, exposure to aerobic conditions, and growth conditions. Affected by use of H2-receptor antagonists, PPIs, and antibiotics. Expensive
Polymerase chain reaction (PCR)	Several genes can be used for DNA amplification.	> 95%	> 95%	Uses a variety of samples: gastric juice and biopsy. Determine mutations causing resistance. Rapid and accurate	Expensive Requires specialized equipment and reagents.
Antibody testing	Detection of IgG antibodies against *H. pylori* using enzyme-linked immunosorbent assay (ELISA) and latex agglutination.	76-84%	79-90%	Least expensive of all tests. Rapid Readily available	Remains positive for years even after eradication of the infection. Influenced by the prevalence of the infection. Requires local validation of reagents. Not appropriate for detection of active infection or confirmation of eradication.
Urea breath test (UBT)	Patient ingests non-radioactive isotope ^{13}C or radioactive isotope ^{14}C labeled urea and the resultant CO_2 is quantified.	> 95%	> 95%	Noninvasive and simple Post treatment testing for eradication. Reproducible	Exposure to radiation with ^{14}C, thus avoided in pregnancy and children. Sensitivity is dependent on the number of bacteria present thus limited by PPIs, antibiotics, and blood. Expensive Equipment requirements
Fecal antigen test	Detects *H. pylori* antigen in stool using either enzyme immunoassay (EIA) or immunochromatography assay (ICA) and antibodies.	94%	97%	Noninvasive Screen and determine eradication of infection. Inexpensive	Sensitivity is dependent on the number of bacteria present, thus limited by PPIs, antibiotics, and blood. Availability Cumbersome for patient to provide sample.

Table 2: FDA approved first line oral therapy for *H. pylori* treatment.

Therapy	Duration (days)	Eradication Rates	Comments
PPI twice a day, clarithromycin 500 mg twice a day, amoxicillin 1g twice a day	10-14	70-85%	Not allergic to penicillin and have not received a macrolide.
PPI twice a day, clarithromycin 500 mg twice a day, metronidazole 500 mg twice a day	10-14	70-85%	Allergic to penicillin and have not received a macrolide.
Bismuth subsalicylate 525 mg four times a day, metronidazole 250 mg four times a day, tetracycline 500 mg four times a day, PPI twice a day for 2 weeks, or H2RA for 4 weeks.	10-14	75-90%	Those allergic to penicillin or failed triple therapy or prevalence of macrolide-resistance is > 20%.

PPI: Proton Pump Inhibitor, Lansoprazole 30 mg twice a day, Omeprazole 20 mg twice a day, H2RA: Histamine 2 receptor antagonist [34,37].

more promising therapies have been proposed. In a recent meta-analysis comprised mostly of trials from Italy, five days of a PPI with amoxicillin followed by five days of a PPI with clarithromycin and tinidazole had an eradication rate of 93.4% [47]. This regimen has not yet been validated in the United States and it is not clear if it is superior to quadruple therapy. Sequential therapy (e.g. five days of PPI + amoxicillin followed by 5 days of PPI + clarithromycin and metronidazole) may increase medication adherence compared to quadruple therapy since it requires fewer medications. Another promising therapy that requires validation in the United States is PPI with levofloxacin and amoxicillin, with a reported 87% eradication rate in a recent meta-analysis [50].

Confirmation of Eradication

Testing for eradication of H. pylori is generally recommended in patients with H. pylori-associated peptic ulcer disease, H. pylori-associated MALT lymphoma, resection of early gastric cancer, or persistent symptoms despite treatment of confirmed H. pylori infection [37]. Urea breath test provides the most reliable means for confirming H. pylori eradication [51-54] but PPI therapy within 1-2 weeks of testing can cause false-negative results [55,56].

Other options for establishing cure of H. pylori after treatment include monoclonal fecal antigen test, which is more sensitive than tests for polyclonal H. pylori antibody, [54] and endoscopic tests including histology or histology plus rapid urease testing. All tests of cure are considered to be most accurate when performed at least 4 weeks after completion of antibiotic therapy. These tests are less accurate in patients taking bismuth-containing compounds or PPIs [37]. To limit costs, endoscopic tests of cure should be limited to patients with other indications for EGD [37]. Lastly, serologic antibody testing should not be used to document cure since serologies remain positive for years after successful eradication of H. pylori [54].

Complications of Untreated Disease

Untreated H. pylori is associated with an increased risk of peptic ulcer disease, gastric adenocarcinoma, and gastric MALT lymphoma. A systematic review of observational studies concluded that H. pylori infection increased the odds of uncomplicated peptic ulcer disease by 18-fold in patients not using NSAIDs [57]. Both NSAID use and smoking in combination with H. pylori synergistically increase the risk of PUD [57,58].

H. pylori infection is associated with increased risk of histologic progression of gastric intestinal metaplasia [59] and gastric adenocarcinoma [60-63]. Furthermore, retrospective studies have identified a strong association between H. pylori infection and MALT lymphoma [64]. In addition, successful treatment of H. pylori causes regression of MALT lymphoma [65]. While dyspepsia is one of the hallmark symptoms of H. pylori infection, most randomized controlled trials have shown that treatment of non-ulcer dyspepsia does not result in statistically significant symptomatic benefit [66,67]. Lastly, some studies have linked H. pylori with unexplained iron-deficiency anemia, idiopathic thrombocytopenic purpura (ITP), and vitamin B12 deficiency [44].

New Frontiers in H. pylori Research

In the decades following the discovery of H. pylori a lot has been learned about this bacterium and its association with PUD and gastric cancer. It is evident that treatment of H. pylori infection decreases complications associated with active disease but rising rates of bacterial resistance to current antibiotic options have increased the frequency of treatment failure. New frontiers in research are focusing on ways to improve eradication rates, including the use of probiotics as an adjuvant to triple and quadruple therapies. There have been multiple promising studies and meta-analyses published on the topic of probiotic supplementation and eradication of H. pylori infection. Specifically, Saccharomyces boulardii and Lactobacillus have been the most frequently studied probiotics and shown to increase eradication rates by 10% when compared to placebo [68-70]. Furthermore, probiotics have been shown to decrease side effects of antibiotic therapy, specifically diarrhea, without significantly increasing adverse effects [68-70]. There are currently no guidelines recommending probiotics in conjunction with antibiotic therapy. However, probiotics are thought to be generally safe in immunocompetent individuals and thus can probably be supplemented in conjunction with antibiotics.

Other research has emerged showing an association between H. pylori and idiopathic thrombocytopenic purpura (ITP). There have been several studies documenting H. pylori infection in adult patients with chronic ITP with subsequent improvement in platelet count following eradication of infection [71,72]. Consequently, the 2011 American Society of Hematology Clinical Practice Guidelines recommend evaluation and treatment of H. pylori in adult patients with ITP [73].

More controversial recent research has suggested an inverse association between H. pylori infection and celiac disease [74,75]. Two cross-sectional studies have shown that patients colonized with H. pylori have a lower prevalence of celiac disease, although it is unclear if these findings are incidental or the result of confounding factors. Study authors suggested that H. pylori might mediate immune responses to gluten.

Other areas of controversy include the evaluation and treatment of H. pylori infection in non-ulcer dyspepsia, unexplained iron deficiency anemia, and those at risk for gastric cancer. Lastly, it is not certain if H. pylori has protective effects against reflux disease.

Conclusions

In summary, patients should be evaluated for H. pylori when they have PUD or gastric cancer and the treatment of choice is either triple or quadruple therapy with subsequent documentation of eradication of infection. However, in the era of antibiotic resistance these treatment options could soon become obsolete; thus new research is focusing on other antibiotic regiments along with vaccine development to combat this pathogen [47,50,76]. Other areas of study are attempting to elucidate the oncogenesis of H. pylori, finding that strains that carry cytotoxin-associated antigen A (cagA) gene are associated with gastric carcinoma [77]. The new frontiers in H. pylori research will provide for better understanding of its impact on human health and allow for the development of targeted therapies.

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