Helicobacter pylori: The Past, Present, and Future in Management

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Abstract

Helicobacter pylori is a common bacterial pathogen responsible for substantial gastrointestinal morbidity worldwide. *Helicobacter pylori* infection can be clinically challenging, given the numerous diagnostic and therapeutic options available. In this article, we provide a systematic review of *H pylori* epidemiology and pathogenesis. In addition, we provide a simplified approach to the diagnosis and treatment of *H pylori* infection, suitable for application in the primary care setting. On completion of this article, one should be able to (1) state the indications for *H pylori* testing; (2) identify noninvasive and invasive tests to diagnose *H pylori* infection; and (3) describe the advantages and disadvantages of various treatment regimens.

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elicobacter pylori is one of the most common bacterial pathogens, affecting more than half of the population worldwide.[1] This bacterium was first described as a member of the genus *Campylobacter*; however, because of differences in taxonomy, it was classified as a member of the genus *Helicobacter* in 1989.[2] Despite its widespread prevalence, clinical manifestations of the organism develop in a minority of cases. *Helicobacter pylori* is the most common cause of gastric and duodenal ulcers, especially when nonsteroidal anti-inflammatory drug use has been ruled out.[3] In individuals infected with *H pylori*, there is a 10% to 20% lifetime risk of peptic ulcer disease

(PUD) and 1% to 2% risk of gastric cancer.[3] Specifically, patients infected with cytotoxin-associated gene A *H pylori* strains are at higher risk of PUD and gastric cancer because of greater inflammation.[3] Recognizing *H pylori* in the right clinical circumstances is crucial, as treatment can greatly decrease morbidity. For example, eradication of *H pylori* in patients with gastric mucosa-associated lymphoid tissue (MALT) lymphoma can lead to 60% to 80% regression of the lymphoma.[3]

EPIDEMIOLOGY

In developing countries, infection commonly develops in children and chronic infection continues into adulthood; in the developed world, infection is rare in children and develops more commonly in adulthood.[3] Early exposure to *H pylori* is associated with gastric pathologic changes, progressing from atrophic gastritis to gastric ulcers and carcinoma.[4] Later-onset infection most commonly presents with duodenal pathology.[4] The most common route of transmission is person-to-person spread through fecal-oral and oral-oral exposures.[4] The prevalence of infection generally increases with age and is higher in blacks and Hispanics than in whites.[5,6] The seroprevalence of *H pylori* is approximately 30% in individuals younger than 30 years and 63% for individuals aged 55 to 65 years.[5] In addition, *H pylori* prevalence varies by ethnic groups: whites, 26%; blacks, 53%; and Mexican Americans, 62%.[6] Risk factors for transmission are related to living conditions that promote close person-to-person contact such as crowded homes and sharing of beds.[5] The association of these factors with socioeconomic status may explain some of the racial differences in *H pylori* prevalence in the United States.

PATHOGENESIS

Helicobacter pylori is a spiral, microaerophilic, gram-negative bacterium with flagella that have urease, catalase, and oxidase activity.[3] These characteristics are vital to its survival in the harsh acidic gastric environment. Specifically, urease helps convert urea to ammonia, which aids in neutralizing gastric acid and promoting bacterial protein synthesis.[7] The gene *urel* encodes for a hydrogen ion–gated urea channel that promotes urea uptake and urease secretion in response to a decrease in gastric pH.[7] Urease can account for up to 10% of the total protein content of *H pylori*.[8] *Helicobacter pylori* infection triggers an intense release of phagocytic cells that attempt to kill the organism by releasing oxygen metabolites.[9] However, catalase activity enables *H pylori* to survive this oxidative stress.[9] In turn, the inflammatory response damages the gastric epithelial lining and allows *H pylori* to flourish. In addition, flagella-mediated motility allows for the colonization of the stomach mucosa and facilitates initial infection. *Helicobacter pylori* infection predominantly affecting the gastric corpus is associated with hypochlorhydria because of damage to parietal cells, whereas infection localized to the gastric antrum is associated with duodenal ulceration given an increase in gastrin production may be seen.[3]

DIAGNOSIS

Because of the strong association of *H pylori* with PUD and MALT lymphoma, *H pylori* testing is recommended for patients with a history of or active PUD and MALT lymphoma (Figure).[10] In addition, *H pylori* testing should be performed in patients with dyspepsia if the local *H pylori* prevalence exceeds 10%.[11] In such patients who are younger than 60 years and without alarm features, a test-and-treat approach to *H pylori* is effective.[10] Alarm features include fevers, weight loss, anemia, gastrointestinal bleeding, dysphagia, and personal or family history of malignant neoplasm. In patients aged 60 years or older and in those with alarm features, esophagogastroduodenoscopy is the most appropriate first step. Regional *H pylori* prevalence patterns are poorly described in the literature. In the United States, estimates of *H pylori* prevalence approach 30%.[12] Patients from lower socioeconomic backgrounds, those from poor living conditions, or those immigrated from a region with high prevalence are at higher risk and should have a lower threshold for being tested. Testing should not be performed in asymptomatic family members unless there are known risk factors, such as a family history of gastric malignant neoplasm.[10]

Helicobacter pylori infection can be diagnosed using noninvasive and invasive methods. In general, both noninvasive and invasive tests are equally accurate.[13]

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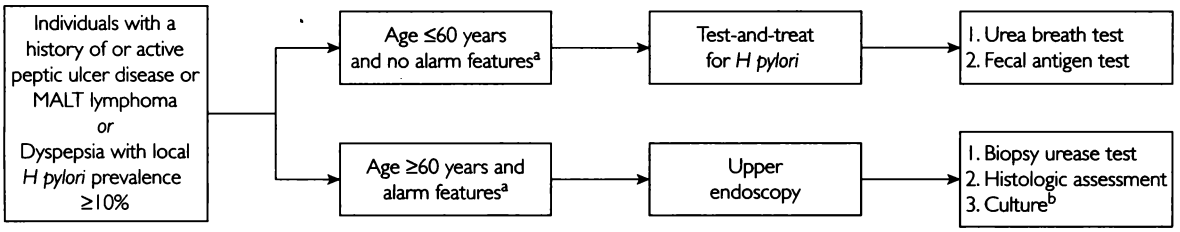

[a]Alarm features include fevers, weight loss, anemia, gastrointestinal bleeding, dysphagia, and personal or family history of malignant neoplasm.
[b]This test is rarely used in clinical practice.

FIGURE. Indications for testing and diagnosis of *Helicobacter pylori*. MALT = mucosa-associated lymphoid tissue.

Noninvasive tests include the urea breath test, fecal antigen test, and serologic test. The preferred noninvasive tests in the outpatient setting are the urea breath test and fecal antigen test given their excellent accuracy and ability to diagnose active infection. The fecal antigen test relies on identifying *H pylori* antigens in the stool using an enzymatic immunoassay.[13] In the urea breath test, urea labeled with 13C or 14C is given to patients. Urease, if present, converts urea into ammonia and labeled CO_2 that is exhaled, indicating a positive result.[13] Before testing, proton pump inhibitors (PPIs) and antibiotics should be discontinued at least 2 and 4 weeks, respectively, as these can interfere with the urea test.[10] Pretreatment sensitivity and specificity of both these tests are approximately 95%.[13] Although the cost of testing varies by location and laboratory, the estimated cost of the urea breath test and fecal antigen test is $102.80 and $19.70, respectively.[14] Serologic testing is not recommended to detect active infection, as it cannot distinguish between active disease and previous exposure. Antibodies to *H pylori* can remain elevated for a long time even after treatment, potentially increasing the number of false-positive results.[13] The 1 positive aspect of serologic testing is that it is the only test for *H pylori* that is not affected by PPI therapy, antibiotics, or by the presence of blood in the stomach.

Invasive testing strategies require upper endoscopy and include the biopsy urease (campylobacter-like organism) test, histologic assessment, and culture. The biopsy urease test is a good first-line test, as it is accurate, rapid, and inexpensive. This test relies on *H pylori* urease to convert urea into ammonia, increase the pH, and change the color of the pH indicator.[15] Although the specificity is excellent with this test (>95%), the sensitivity can vary from 75% to 98%.[15] The urease test is preferred in patients without recent use of PPIs and antibiotics, as outlined above.[10] However, in patients with recent PPI or antibiotic use, histologic assessment of biopsy samples is the better choice, although these medications can interfere with bacterial density.[10] Traditionally, histologic assessment is the criterion standard for the diagnosis of *H pylori* infection. One advantage of the histological test over other modalities is that it allows for the examination of inflammation, metaplasia, dysplasia, and malignant neoplasm. The results of the histological test can vary depending on the number and location of biopsy samples obtained, the experience of the gastroenterologist and pathologist, and the type of stain used. Immunostaining for *H pylori* can be done in addition to routine hematoxylin and eosin staining to improve the yield from histologic assessment. Although culture and sensitivity testing is routinely performed for most bacterial infections, it is rarely performed for *H pylori* because of a prolonged incubation period of up to 2 weeks.[15] However, the use of culture can play an important role in certain circumstances, such as in the patient who has failed to respond to therapy in order to identify potential antibiotic resistance and select an alternative treatment regimen.

TREATMENT

There are various proposed treatment regimens for *H pylori* infection. The 2007 American College of Gastroenterology guidelines[10] recommend first-line treatment with a

10- to 14-day course of standard triple therapy, which consists of a PPI, amoxicillin, and clarithromycin. In patients with penicillin allergy, the recommended treatment options include a 10- to 14-day course of bismuth quadruple therapy, which consists of a PPI, bismuth, metronidazole, and tetracycline (PBMT) or a 10- to 14-day course of a PPI, clarithromycin, and metronidazole.[10]

Over the past several years, clarithromycin resistance is increasing worldwide while *H pylori* eradication rates are decreasing.[16] Data on clarithromycin resistance in the United States remains limited, but estimates approach 30%.[16] Consequently, alterative regimens have been suggested to counteract this increase in resistance. One proposed regimen is sequential therapy, which consists of a PPI and amoxicillin for the first half of treatment duration and a PPI, metronidazole, and clarithromycin for the second half. The principle behind sequential therapy is that amoxicillin first weakens the bacterial cell wall, which then allows clarithromycin and metronidazole to directly attack the bacteria and prevent efflux of antibiotics through drug efflux channels. Although this principle makes theoretical sense, a 10-day course of reverse sequential therapy (5 days of a PPI, clarithromycin, and metronidazole followed by 5 days of a PPI and amoxicillin) had an eradication rate similar to that of a 10-day course of standard sequential therapy.[17] Another regimen is concomitant nonbismuth therapy, which consists of a PPI, amoxicillin, metronidazole, and clarithromycin (PAMC). The notion with this therapy is that the addition of a third antibiotic compared with standard triple therapy should result in higher eradication rates.

Several studies have analyzed the various treatment regimens in different populations over the past decade. A pooled data analysis[18] comparing a 7- to 10-day course of standard triple therapy with a 10-day course of sequential therapy revealed higher rates of eradication in the sequential therapy group, consistently greater than 90%. A multicenter randomized controlled trial (RCT)[19] compared 7-day courses of standard triple therapy and concomitant (PAMC) therapy with a 10-day course of sequential therapy and found that concomitant therapy had the highest eradication rates. Intention-to-treat (ITT) eradication rates with PPI, amoxicillin, and clarithromycin therapy; sequential therapy; and concomitant therapy were 76.2%, 84.4%, and 94.4%, respectively.[19] Another RCT[20] compared 10- and 14-day sequential therapy with 10- and 14-day concomitant PAMC therapy and found ITT rates of 91.7%, 91.2%, 94.2%, and 98.5%, respectively. More recently, a multicenter, open-label, RCT[21] comparing the efficacy of 10-day bismuth quadruple PBMT therapy, 10-day concomitant PAMC therapy, and 14-day standard triple therapy found eradication rates of 90.4%, 85.9%, and 83.7%, respectively. There was a statistically significant difference between quadruple PBMT therapy and standard triple therapy but not between quadruple PBMT therapy and concomitant PAMC therapy.[21] However, not all studies have reported a difference in eradication between various treatment options. A Cochrane Database Systematic Review[22] found no differences in efficacy between 10-day regimens of sequential therapy and standard triple therapy.

New guidelines have also been proposed to reflect the increasing clarithromycin resistance patterns. The 2016 Toronto Consensus guidelines[23] recommend first-line treatment with a 14-day course of either concomitant PAMC therapy or bismuth quadruple PBMT therapy. The 2016 Maastricht V/Florence Consensus Report[24] recommends first-line treatment with a 14-day course of bismuth quadruple PBMT therapy or concomitant PAMC therapy in areas of high clarithromycin resistance (>15% resistance). However, standard triple therapy and bismuth quadruple PBMT therapy are acceptable first-line regimens in areas of low clarithromycin resistance (<15% resistance).[24] Both guidelines[23,24] recommend all treatment regimens be 14 days in duration and standard triple therapy be abandoned in areas of high clarithromycin resistance. A Cochrane Database Systematic Review[25] analyzed the optimal duration of the treatment of *H pylori* infection and determined that 14-day therapy was ideal. Compared with 7-day regimens, 14-day regimens achieved significantly higher rates of eradication (72.9% versus 81.9%), with a relative risk of *H pylori* persistence of 0.66 (95% CI 0.60-0.74).[25] Given the increase in

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clarithromycin resistance worldwide and limited knowledge about local antibiotic resistance patterns, we believe that first-line treatment should consist of a 14-day course of concomitant PAMC therapy or bismuth quadruple PBMT therapy, consistent with these newer guidelines (Table).

Recent research has continued to explore new potential treatment options for *H pylori* infection. Vonoprazan is a new potassium-competitive acid suppressing medication. A multicenter retrospective study[26] found considerably higher eradication rates with vonoprazan-based triple therapy (vonoprazan, amoxicillin, and clarithromycin) than with standard triple therapy: 87.2% vs 72.4%, respectively. Another proposed approach to the treatment of *H pylori* infection is based on culture-based antimicrobial susceptibility-guided therapy. One study compared concomitant PAMC therapy with susceptibility-guided triple therapy with a PPI, amoxicillin, and one of the following: clarithromycin, levofloxacin, and metronidazole. The last one achieved higher eradication rates with ITT analysis: 94% vs 87%.[27] Moreover, the addition of probiotics to *H pylori* antibiotic regimens has resulted in better treatment efficacy as compared with placebo (87.4% vs 72.6%) and fewer medication adverse effects.[28]

The American College of Gastroenterology[10] recommends eradication confirmation testing in the following groups of patients: those with persistent symptoms despite treatment, *H pylori*–induced ulcer, MALT lymphoma, and early resection for gastric cancer. However, given the increasing *H pylori* resistance worldwide, eradication confirmation testing should ideally be performed in all patients undergoing treatment, at least 4 weeks after the completion of therapy. This time frame is critical, as enough time is necessary for any surviving bacteria to populate the gastric environment and become detectable on repeat testing. In addition to antibiotic resistance, other causes of treatment failure include nonadherence to drug therapy and short treatment duration. In addition, eradication confirmation testing, when performed universally, has been found to be cost-effective.[14] Because noninvasive tests are both accurate and relatively inexpensive, repeat testing should be performed with a urea breath test or fecal antigen test, because they are the 2 noninvasive tests that detect active infection. Serologic testing is not appropriate for eradication confirmation, as it does not distinguish between active and previous infections. Invasive testing with upper endoscopy should rarely be considered for eradication confirmation and should be limited to instances in which there are other indications for upper endoscopy (such as documenting healing of a large ulcer or sampling of a gastric ulcer not previously sampled).

TABLE. Clinical Pearls for *Helicobacter pylori* Infection[a]

1. *Helicobacter pylori* is a leading cause of gastritis, peptic ulcers, and gastric lymphoma worldwide.
2. *Helicobacter pylori* testing is recommended for
   - Patients with current or previous peptic ulcer disease or MALT lymphoma and
   - Patients younger than 60 years with dyspepsia, in the absence of alarm features, if local *H pylori* prevalence exceeds 10%.
3. The preferred noninvasive tests are the urea breath test and fecal antigen test given their excellent accuracy and ability to diagnose active infection.
4. Invasive testing options during EGD include biopsy urease test, histologic assessment, and culture (rarely used).
5. Testing is most effective when patients avoid PPIs or antibiotics in the preceding 2 and 4 weeks, respectively.
6. Serologic testing is seldom used, as it cannot distinguish between active disease and previous exposure. However, it is the only test that is not affected by medication use.
7. The 2007 American College of Gastroenterology Guidelines recommend first-line treatment with a 10- to 14-d course of a PPI, amoxicillin, and clarithromycin.
8. Newer guidelines[b] recommend first-line treatment with a 14-day course of either a PPI, amoxicillin, metronidazole, and clarithromycin or a PPI, bismuth, metronidazole, and tetracycline because of an increase in worldwide antibiotic resistance to traditional treatment regimens for *H pylori* infection.
9. Eradication confirmation testing should be performed in all patients who undergo the treatment of *H pylori* infection, at least 4 weeks after the completion of therapy.

[a]EGD = esophagogastroduodenoscopy; MALT = mucosa-associated lymphoid tissue; PPI = proton pump inhibitor.

[b]2016 Toronto Consensus Guidelines and 2016 Maastricht V/Florence Consensus Report.

CONCLUSION

Helicobacter pylori is a complex bacterial pathogen and a leading causative agent of gastritis, PUD, and gastric lymphoma worldwide. Infection is common in both developing and developed countries. Its unique characteristics, including urease activity, allow it to thrive in the harsh acidic gastric environment. In the outpatient setting, the diagnosis can be easily and accurately performed with the urea breath test or fecal antigen test. With increasing *H pylori* resistance to traditional antibiotic

regimens, new treatment regimens have been proposed. All treatment regimens should be 14 days, and eradication testing should be performed in all patients.

Abbreviations and Acronyms: **ITT** = intention-to-treat; **MALT** = mucosa-associated lymphoid tissue; **PAMC** = proton pump inhibitor, amoxicillin, metronidazole, and clarithromycin; **PBMT** = proton pump inhibitor, bismuth, metronidazole, and tetracycline; **PPI** = proton pump inhibitor; **PUD** = peptic ulcer disease; **RCT** = randomized controlled trial

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