Helicobacter pylori: A concise review of the latest treatments against an old foe

ABSTRACT

Helicobacter pylori is a significant public health concern given its high prevalence, growing rates of antibiotic resistance, and carcinogenic effect, all of which create management challenges for internists, gastroenterologists, and other specialty physicians. With almost half of the world’s human population harboring H pylori, carcinogenic sequelae are a concern to many practitioners. Recent guidelines recommend testing high-risk populations for H pylori using noninvasive or invasive methods. H pylori eradication regimens are tailored based on the presence of effective empiric therapy (local cure rates ≥ 90% for a given regimen) or antimicrobial susceptibility testing. When empiric therapy cure rates are not optimal, guidelines recommend antimicrobial susceptibility testing to improve eradication rates and reduce the progression of antibiotic resistance.

KEY POINTS

H pylori infection is a major health concern and is the most common carcinogenic infection worldwide.

Antimicrobial susceptibility testing is recommended when the cure rate of empiric therapy is less than 90%.

The choice of H pylori eradication therapy depends on antimicrobial susceptibility testing, the local antibiogram, cost, pill burden, and patient-related factors.

Helicobacter pylori is a gram-negative spiral microaerophilic bacterium that infects and colonizes the stomach mucosa. Nearly 50% of the world’s human population harbor H pylori, while the overall prevalence in the United States is less than 50%, with notable racial and ethnic disparities. H pylori infection has been linked with low socioeconomic status, poor hygiene, close interpersonal contact, and old age.

About 10% to 20% of persons with H pylori infection will develop duodenal or gastric ulcer disease, and around 80% of non-cardia–type gastric cancers are caused by H pylori. In 1994, the World Health Organization and International Agency for Research on Cancer consensus group designated H pylori as a group 1 carcinogenic organism. Although antibiotic regimens to treat H pylori infection will develop duodenal or gastric ulcer disease, and around 80% of non-cardia–type gastric cancers are caused by H pylori remains a socioeconomic burden and a significant health concern. In 2018, H pylori was the primary cause of cancer in 37% (810,000 cases) of new infection-attributable cancer cases, making it the most common carcinogenic infection worldwide. H pylori eradication therapy reduces the risk of gastric cancer by about 34%.

This review summarizes current evidence and guidelines on H pylori testing and management.

WHO SHOULD BE TESTED?

In 2017, the American College of Gastroenterology (ACG) strongly recommended H pylori testing for patients with active or past peptic ulcer...
TABLE 1
Noninvasive and invasive testing methods for Helicobacter pylori

<table>
<thead>
<tr>
<th>Testing method</th>
<th>Pros</th>
<th>Cons</th>
<th>Cost (approximate)</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Invasive tests</td>
<td></td>
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<tr>
<td>Endoscopic biopsy</td>
<td>Allows direct visualization of <em>H pylori</em> infection</td>
<td>Discomfort and risk of complications</td>
<td>$\sim$–$$\sim$</td>
<td>95%–98%</td>
<td>95%–98%</td>
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<tr>
<td>Allows for histological evaluation</td>
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<tr>
<td>Rapid urease test</td>
<td>Quick results (usually within minutes)</td>
<td>False negatives can occur with recent proton pump inhibitor use or active bleeding</td>
<td>$\sim$</td>
<td>90%–95%</td>
<td>95%–98%</td>
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<tr>
<td>Relatively low cost</td>
<td></td>
<td></td>
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<tr>
<td><em>H pylori</em> culture</td>
<td>Allows for antibiotic susceptibility testing</td>
<td>Time-consuming and labor-intensive</td>
<td>$\sim$–$$\sim$</td>
<td>Variable$^a$</td>
<td>Variable$^a$</td>
</tr>
<tr>
<td>Molecular testing (gastric tissue)</td>
<td>High sensitivity and specificity</td>
<td>Requires specialized equipment and expertise</td>
<td>$\sim$–$$\sim$</td>
<td>90%–95%</td>
<td>90%–95%</td>
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<tr>
<td>Can detect resistance mutations</td>
<td></td>
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<td></td>
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<tr>
<td>Noninvasive tests</td>
<td></td>
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<tr>
<td>Stool antigen test</td>
<td>Easy to collect specimens</td>
<td>May yield false negatives if antigen levels are low</td>
<td>$\sim$</td>
<td>90%–95%</td>
<td>90%–95%</td>
</tr>
<tr>
<td>Molecular testing (stool)</td>
<td>Easy to collect specimens, High sensitivity and specificity</td>
<td>Requires specialized equipment and expertise</td>
<td>$\sim$–$$\sim$</td>
<td>Variable</td>
<td>Variable</td>
</tr>
<tr>
<td>Serology (blood test)</td>
<td>Easy to perform</td>
<td>Cannot distinguish current infection from past exposure</td>
<td>$\sim$</td>
<td>80%–85%</td>
<td>80%–85%</td>
</tr>
<tr>
<td>Urea breath test</td>
<td>Well tolerated, High sensitivity and specificity</td>
<td>Requires abstaining from certain medications (eg, antibiotics, proton pump inhibitors) before the test</td>
<td>$\sim$–$$\sim$</td>
<td>95%–98%</td>
<td>95%–98%</td>
</tr>
<tr>
<td>GastroPanel$^b$</td>
<td>Provides comprehensive information on gastric health</td>
<td>Limited availability, Interpretation may be complex</td>
<td>$\sim$</td>
<td>Variable</td>
<td>Variable</td>
</tr>
</tbody>
</table>

$^a$Depending on DNA extraction method.
$^b$Combination of immunoglobulin G serology coupled with pepsinogen I and II testing.

Based on information from references 8 and 9.

disease (unless a cure is documented), low-grade gastric mucosa–associated lymphoid tissue lymphoma, or a history of early endoscopic resection of gastric cancer, and conditionally recommended nonendoscopic testing for patients under age 60 with uninvestigated dyspepsia who do not have alarm symptoms. Other scenarios in which *H pylori* testing is conditionally recommended include long-term nonsteroidal anti-inflammatory drug therapy, low-dose aspirin use, and unexplained iron deficiency anemia or idiopathic thrombocytopenic purpura.4
In 2018, 11 H pylori management experts suggested additional indications for H pylori testing, such as patients with a family history of gastric cancer, first-generation immigrants from high-prevalence areas, and patients of Latino or African American ethnic or racial groups.7 Table 1 summarizes key aspects of noninvasive and invasive H pylori testing.8,9 The noninvasive urea breath test and stool antigen test are highly specific and sensitive, and are widely available for use in clinical practice in the United States. Invasive molecular testing can be considered to detect infection and assess antibiotic susceptibility.

**WHAT IS STANDARD TREATMENT FOR H PYLORI?**

The ACG guidelines4 recommend treating all patients with positive tests for active H pylori infection. The recommended standard therapy is a combination of a proton pump inhibitor with or without a bismuth-containing product and 1 or more of the following antibiotics: clarithromycin, metronidazole, amoxicillin, or tetracycline, given for 10 to 14 days.10,11 Clarithromycin-based regimens generally should not be offered where H pylori clarithromycin resistance exceeds 15%.4,10,11 Clarithromycin resistance is determined through antimicrobial susceptibility testing and local patterns of resistance, ie, the local antibiogram.

The overall eradication success rate with standard therapy is around 75%, with bismuth quadruple therapy having a higher success rate (about 90%) than other therapies.12 Hence, current guidelines recommend bismuth quadruple (proton pump inhibitor, bismuth, metronidazole, tetracycline) or nonbismuth quadruple (proton pump inhibitor, amoxicillin, metronidazole, clarithromycin) therapies for 10 to 14 days as first-line treatments.4,10

### Treatment failure and antibiotic resistance

H pylori treatment failure can be due to many factors, including systems-, host-, and microbial-related factors.13 Systems-related factors include a lack of surveillance registries and supportive modalities for increasing medication adherence. Host factors include age, smoking history, medication nonadherence, host genetics, drug- or food-drug interaction, and insufficient dose and frequency of proton pump inhibitor or antibiotic therapy. Medication nonadherence is a common and modifiable host risk factor for eradication failure. Nonadherence can be caused by high pill burden, complicated regimens, intolerance, lack of understanding of the impact of treatment on health, and patient-clinician miscommunication. Microbial factors include primary or secondary resistance, H pylori load, and virulence through vacuolating cytotoxin A and cytotoxin-associated antigen A.13

A recent systematic review and meta-analysis showed that in the United States the prevalence of H pylori resistance to clarithromycin is 31%, metronidazole 42%, and levofloxacin 38%; the pooled resistance rates are higher than 30%.14 Resistance rates to amoxicillin, tetracycline, and rifabutin remain low.14 Metronidazole resistance may be overcome by using higher doses.13,14

### WHEN IS ANTIMICROBIAL SUSCEPTIBILITY TESTING RECOMMENDED?

Antimicrobial susceptibility testing examines H pylori cultures against several antibiotics to determine sensitivity.15 Susceptibility testing is an underlying principle of antimicrobial stewardship programs that have been developed to guide treatment and limit antibiotic resistance. Such programs focus on:

- Restricting empiric therapy and tailoring antibiotic choice to locally effective therapy based on the local antibiogram.

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**TABLE 2**

<table>
<thead>
<tr>
<th>Susceptibility testing results</th>
<th>Recommended regimen</th>
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</thead>
<tbody>
<tr>
<td>Clarithromycin-susceptible</td>
<td>Clarithromycin triple therapy for 14 days</td>
</tr>
<tr>
<td>Clarithromycin-resistant, metronidazole-susceptible</td>
<td>Metronidazole triple therapy for 14 days</td>
</tr>
<tr>
<td>Clarithromycin- and metronidazole-resistant, levofloxacin-susceptible</td>
<td>Preferred: empiric therapy with bismuth quadruple therapy for 14 days</td>
</tr>
<tr>
<td></td>
<td>Alternative: levofloxacin triple therapy for 14 days</td>
</tr>
</tbody>
</table>

*If levofloxacin triple therapy is selected and fails, bismuth quadruple therapy is the next step.*

Based on information from reference 15.
H PYLORI

Assessing treatment effectiveness using a test of cure
Evaluating treatment outcomes
Sharing test-of-cure data with local and regional clinicians, to be integrated into their antimicrobial stewardship programs.16

In general, antimicrobial susceptibility testing is recommended when empiric therapy cure rates fall below 90% or after a failed treatment attempt.15 Gastric biopsy culture with drug sensitivity testing is considered the gold standard for antibiotic susceptibility evaluation, with 100% specificity; however, it is difficult and time-consuming to perform, and requires a special medium for transportation and culture.15,17 Molecular-based testing such as polymerase chain reaction or next-generation sequencing is sensitive and specific and offers several other advantages: it can be done using stool samples and fresh or formalin-fixed, paraffin-embedded histological samples; can detect active infection and provide drug resistance information; has a rapid turnaround time (around 5 business days); and does not require special handling and transportation. However, only a limited number of laboratories can perform molecular-based testing, and it may not be covered by health insurance.17

### HOW SHOULD H PYLORI ERADICATION THERAPY REGIMENS BE TAILORED?

If highly effective empiric therapy is available based on local resistance profiles, empiric treatment with bismuth quadruple therapy is recommended (Table 2).15 If empiric therapy fails, antimicrobial susceptibility testing is indicated, with treatment selection based on the results (Table 3).15 Penicillin allergy may hinder \(H\) pylori eradication therapy because most treatment regimens contain amoxicillin.4,18 Even though up to 20% of the general population is labeled as having a penicillin allergy, most can safely take amoxicillin after a thorough history or allergy testing.18 The ACG guidelines recommend allergy testing in individuals with a history of penicillin allergy or failed first-line therapy.4

### PROTON PUMP INHIBITOR OR POTASSIUM-COMPETITIVE ACID BLOCKERS

The ability of \(H\) pylori to survive in an acidic environment necessitates the use of a proton pump inhibitor to maintain the intragastric pH above 6 and enhance the bioavailability of the antibiotics.19,20 Several proton

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**TABLE 3**

<table>
<thead>
<tr>
<th>Effective Helicobacter pylori regimens available in the United States</th>
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<tbody>
<tr>
<td><strong>Regimen</strong></td>
</tr>
<tr>
<td>Empiric therapy</td>
</tr>
</tbody>
</table>
| Bismuth quadruple therapy | Bismuth subsalicylate 300 mg 4 times daily, 30 minutes before meals  
Tetracycline 500 mg 4 times daily, 30 minutes after meals  
Metronidazole 500 mg 4 times daily, 30 minutes after meals  
Proton pump inhibitor (standard dose) twice daily, 30 minutes before meals and at bedtime, or before morning and evening meals | 14 days |
| Bismuth quadruple therapy  
(Pylera) | Combination pill containing bismuth, tetracycline, and metronidazole 4 times daily with meals and at bedtime  
Proton pump inhibitor (standard dose) twice daily, 30 minutes before meals and at bedtime | 14 days |
| Susceptibility-based therapy  |  |  |
| Clarithromycin triple therapy | Clarithromycin 500 mg twice daily, 30 minutes after meals  
Amoxicillin 1 g twice daily, 30 minutes after meals  
Proton pump inhibitor (standard dose) twice daily, 30 minutes before meals | 14 days |
| Metronidazole triple therapy | Metronidazole 500 mg twice daily, 30 minutes after meals  
Amoxicillin 1 g twice daily, 30 minutes after meals  
Proton pump inhibitor (standard dose) 3 times daily, 30 minutes before meals | 14 days |
| Levofloxacin triple therapy | Levofloxacin 500 mg daily, 30 minutes after meal  
Amoxicillin 1 g twice daily, 30 minutes after meals  
Proton pump inhibitor (standard dose) twice daily, 30 minutes before meals | 14 days |

Based on information from reference 15.
pump inhibitor agents are available, but rabeprazole or esomeprazole 20 to 40 mg twice daily is preferable. Rabeprazole metabolism is independent of CYP2C19, which poorly metabolizes other proton pump inhibitors, causing less acid suppression. Esomeprazole exhibits potent inhibition of the proton pump.15

Potassium-competitive acid blockers (P-CAB) directly compete with potassium, which in turn directly inhibits hydrogen-potassium adenosine triphosphatase (proton pump).21 P-CAB agents have the following advantages over proton pump inhibitors:

- Have direct action on the proton pump
- Reversibly bind to the proton pump
- Achieve full effect from the first dose
- Are not affected by CYP2C19 genetic polymorphism
- Have a potent antisecretory effect and a longer half-life.21,22

The US Food and Drug Administration recently approved the P-CAB vonoprazan for treating H pylori infection.25 Vonoprazan is reversible and fast-acting, has a prolonged half-life, and is not affected by diet or genetic polymorphism in drug-metabolizing enzymes.22,24

Studies of P-CAB–based regimens
A recent systematic review and meta-analysis of 8 studies focused on first-line H pylori eradication regimens found that vonoprazan-based regimens were superior to proton pump inhibitor–based therapy as second-line therapy.25 A systematic review and meta-analysis26 that comparing vonoprazan dual (with amoxicillin) therapy with vonoprazan triple (with amoxicillin and clarithromycin) therapy concluded that vonoprazan dual therapy is as effective as vonoprazan triple therapy. More interestingly, a recent systematic review and meta-analysis of randomized controlled trials27 showed eradication rates exceeding 90% in clarithromycin-sensitive strains using P-CAB–based regimens. Notably, the majority of evidence supporting the superiority of vonoprazan-based treatment was from studies conducted outside the United States.

As noted, clarithromycin-based regimens can be used when clarithromycin resistance does not exceed 15%, but with higher resistance rates, bismuth-based quadruple therapy regimens guided by susceptibility testing are preferred.4,10,11 In a multicenter, randomized controlled trial conducted in the United States and Europe, vonoprazan regimens were noninferior to standard therapy (proton pump inhibitor triple therapy).28 Eradication success rates among patients with clarithromycin- and amoxicillin-susceptible organisms were 78.5% for vonoprazan dual therapy and 84.7% for vonoprazan triple therapy, compared with 78.8% for standard therapy. In cases involving clarithromycin-resistant organisms, both vonoprazan regimens (69.6% for dual therapy and 65.8% for triple therapy) showed superiority over standard therapy (31.9%). Despite the superiority of vonoprazan regimens, eradication rates with these

### Table 4

<table>
<thead>
<tr>
<th>Antimicrobial susceptibility information not available</th>
<th>Preferred regimens</th>
<th>Alternative regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clarithromycin resistance &lt; 15%</td>
<td>Vonoprazan triple therapy&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Vonoprazan dual therapy&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Bismuth quadruple therapy</td>
<td>Vonoprazan dual therapy&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Clarithromycin resistance ≥ 15%</td>
<td>Clarithromycin or vonoprazan triple therapy&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Vonoprazan dual therapy&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Antimicrobial susceptibility information available</td>
<td>Metronidazole susceptible</td>
<td>Metronidazole triple therapy</td>
</tr>
<tr>
<td>Levofloxacin susceptible</td>
<td>Levofloxacin triple therapy</td>
<td>Vonoprazan dual therapy&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup>Vonoprazan plus amoxicillin and clarithromycin.

<sup>b</sup>Vonoprazan plus amoxicillin.

Based on information from reference 29.
regimens remained below the desirable threshold of 70% when used against clarithromycin-resistant organisms. As long as clarithromycin resistance rates in the United States exceed 30%, vonoprazan-based regimens may not be optimal. Further studies are warranted to evaluate vonoprazan-based regimens in settings where clarithromycin resistance exceeds 15%.

Table 4 summarizes a proposed treatment approach for H pylori infection based on susceptibility testing and incorporating vonoprazan-based regimens.

**REFERENCES**


**CONCLUSION**

H pylori infection is the most common carcinogenic infection worldwide. Eradication therapy is indicated for all individuals who test positive for active H pylori infection. Due to the rising burden of antibiotic resistance, susceptibility testing for H pylori infection is recommended when local empiric therapy cure rates are less than 90%; testing is also recommended after a failed first treatment attempt. Several H pylori eradication therapies, including vonoprazan-based regimens, are available. Clinicians should tailor the therapy according to antimicrobial susceptibility testing results, the local antibiogram, cost, pill burden, and patient-related factors.

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