

REVIEW

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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 $\geq 90\%$ 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.^{1,2} Nearly 50% of the world's human population harbor *H pylori*,² while the overall prevalence in the United States is less than 50%, with notable racial and ethnic disparities.^{1,3} *H pylori* infection has been linked with low socioeconomic status, poor hygiene, close interpersonal contact, and old age.^{1,2,4}

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*.^{2,5} In 1994, the World Health Organization and International Agency for Research on Cancer consensus group designated *H pylori* as a group 1 carcinogenic organism.²

Although antibiotic regimens to treat *H pylori* infection are available, disease related to *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.⁵ *H pylori* eradication therapy reduces the risk of gastric cancer by about 34%.^{5,6}

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)⁴ strongly recommended *H pylori* testing for patients with active or past peptic ulcer

doi:10.3949/ccjm.91a.24031

TABLE 1
Noninvasive and invasive testing methods for *Helicobacter pylori*

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

^aDepending on DNA extraction method.

^bCombination 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

TABLE 2

Recommended susceptibility-based *Helicobacter pylori* eradication therapy after failure of empiric therapy

Susceptibility testing results	Recommended regimen
Clarithromycin-susceptible	Clarithromycin triple therapy for 14 days
Clarithromycin-resistant, metronidazole-susceptible	Metronidazole triple therapy for 14 days
Clarithromycin- and metronidazole-resistant, levofloxacin-susceptible	Preferred: empiric therapy with bismuth quadruple therapy for 14 days Alternative: levofloxacin triple therapy for 14 days ^a

^aIf levofloxacin triple therapy is selected and fails, bismuth quadruple therapy is the next step.

Based on information from reference 15.

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

TABLE 3
Effective *Helicobacter pylori* regimens available in the United States

Regimen	Drug and dosing	Duration
Empiric therapy		
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.

- 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

TABLE 4

Proposed approach for *Helicobacter pylori* eradication therapy incorporating vonoprazan

		Preferred regimens	Alternative regimens
Antimicrobial susceptibility information not available	Clarithromycin resistance < 15%	Vonoprazan triple therapy ^a	Vonoprazan dual therapy ^b Clarithromycin triple therapy Bismuth quadruple therapy
	Clarithromycin resistance ≥ 15%	Bismuth quadruple therapy	Vonoprazan dual therapy ^b
Antimicrobial susceptibility information available	Clarithromycin susceptible	Clarithromycin or vonoprazan triple therapy ^a	Vonoprazan dual therapy ^b
	Metronidazole susceptible	Metronidazole triple therapy	Vonoprazan dual therapy ^b
	Levofloxacin susceptible	Levofloxacin triple therapy	Vonoprazan dual therapy ^b Bismuth quadruple therapy

^aVonoprazan plus amoxicillin and clarithromycin.^bVonoprazan plus amoxicillin.

Based on information from reference 29.

pump inhibitor agents are available, but rabeprazole or esomeprazole 20 to 40 mg twice daily is preferable. Unlike omeprazole, lansoprazole, esomeprazole, and pantoprazole, which are mainly metabolized in the liver by CYP2C19, rabeprazole is mainly metabolized by a nonenzymatic pathway and to a lesser extent by CYP2C19.²¹ CYP2C19 metabolism is based on genetic predisposition (normal, intermediate, poor, rapid or ultra-rapid metabolizer), resulting in more or less acid suppression, depending on the patient. Information on the type of metabolism is only available with genetic testing. Because rabeprazole metabolism is not dependent on enzyme CYP2C19 metabolism, acid suppression is more consistent and not patient dependent.²² 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).²³ 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.^{23,24}

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.^{24,26}

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.²⁶ Another systematic review and meta-analysis showed that vonoprazan-based regimens were superior to proton pump inhibitor–based therapy as second-line therapy.²⁷ A systematic review and meta-analysis²⁸ 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 trials²⁹ 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).³⁰ 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 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%,¹⁴ 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.³¹

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CONCLUSION

H pylori infection is the most common carcinogenic infection worldwide. Eradication therapy is indicated for all individuals who test positive for active 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.

Acknowledgment: The authors thank Dr. Ahmed Salih for his valuable support throughout the writing of this manuscript.

DISCLOSURES

Dr. Wallace has disclosed consulting for Boston Scientific Corporation, Cosmo Pharmaceuticals, and Fujifilm, and ownership interest (stock, stock options in a publicly traded company) in Verily. The other authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

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Treatment of *H pylori* infection

In the August 2024 issue, an error appeared in Aldhalei WA, Wallace MB, Harris DM, Bi Y. *Helicobacter pylori*: A concise review of the latest treatments against an old foe. *Cleve Clin J Med* 2024; 91(8):481–487. doi:10.3949/ccjm.91a.24031. The first paragraph in the section titled “Proton pump inhibitor or potassium-competitive acid blockers” (pages 484–485 in print) should have read as follows: “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 pump inhibitors are available, but rabeprazole or esomeprazole 20 to 40 mg twice daily is preferable. Unlike omeprazole, lansoprazole, esomeprazole, and pantoprazole, which are mainly metabolized in the liver by CYP2C19, rabeprazole is mainly metabolized by a nonenzymatic pathway and to a lesser extent by CYP2C19.²¹ CYP2C19 metabolism is based on genetic predisposition (normal, intermediate, poor, rapid or ultra-rapid metabolizer), resulting in more or less acid suppression, depending on the patient. Information on the type of metabolism is only available with genetic testing. Because rabeprazole metabolism is not dependent on enzyme CYP2C19 metabolism, acid suppression is more consistent and not patient-dependent.²² Esomeprazole exhibits potent inhibition of the proton pump.¹⁵”

References 21 and 22 were added to the article and the subsequent references renumbered accordingly.

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The corrected article is available at www.ccjm.org.