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GUIDELINES

ACG Guideline on Treatment of *Helicobacter pylori*: New Recommendations… Will Practice Change?

Dr Philip Schoenfeld
Editor-in-Chief

Philip Schoenfeld, MD, MSEd, MSc (Epi)

Chief (Emeritus), Gastroenterology Section, John D. Dingell VA Medical Center, Detroit, MI.

This summary reviews Chey W, Howden C, Moss S, et al. ACG Clinical Guideline: Treatment of *Helicobacter pylori* infection. Am J Gastroenterol. 2024;119:1730-53.

Correspondence to Philip Schoenfeld, MD, MSEd, MSc. Editor-in-Chief. Email: EBGI@gi.org

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STRUCTURED ABSTRACT

Question: What is the optimal approach to treatment of *Helicobacter pylori* infection in North America?

Design: The Patient Intervention Comparison and Outcomes (PICO) format was used to develop key questions of clinical relevance to be addressed in the guideline. A health services librarian performed literature searches of PubMed (MEDLINE), EMBASE, and the Cochrane Library. GRADE methodology was used to assess benefits and risks of therapies in a North American population. For clinically relevant topics that were not amenable to formal evidence-based recommendations, key concepts based on expert consensus were presented.

Patients: Adults (≥18 years old) with *H. pylori* infection

Interventions/Exposure: Proton pump inhibitor (PPI)-clarithromycin triple therapy, bismuth quadruple therapy (BQT), concomitant therapy, rifabutin-

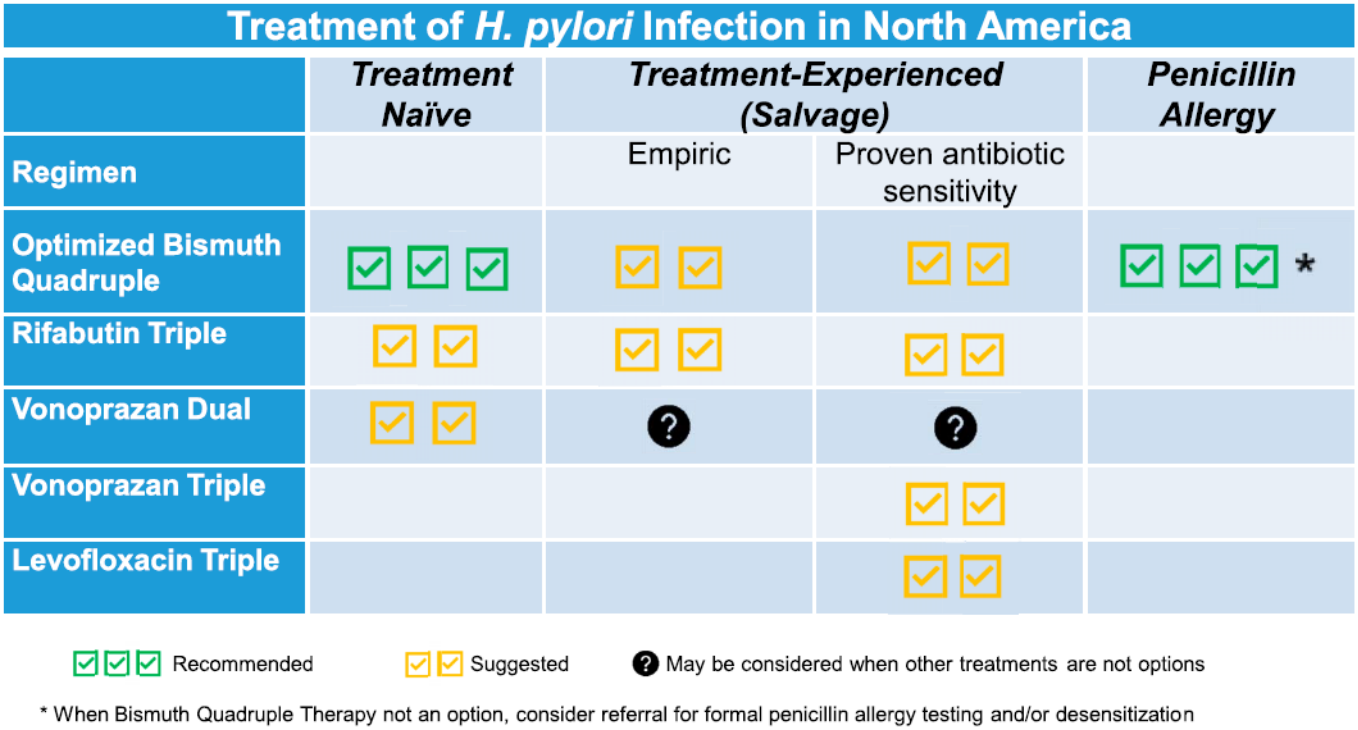

Figure 1. ACG Clinical Guideline on the treatment of *Helicobacter pylori.*

triple therapy, potassium-competitive acid blocker (PCAB) dual therapy, PCAB triple therapy, quinolone-based therapy, high-dose PPI dual therapy, susceptibility-guided therapy, and probiotics. Comparators included PPI-clarithromycin triple therapy, BQT, and empiric (i.e., non–susceptibility-guided) therapy. Respective dosing and frequency of each regimen was also recorded.

Outcome: *H. pylori* eradication rates in intention-to-treat (ITT) analyses and per-protocol analyses, compliance with treatment, and rates of adverse events.

Data Analysis: Guideline methodologists performed meta-analysis when appropriate with RevMan software and the Cochrane Risk of Bias tool to assess risk of biased results based on use of concealment of allocation, blinding, incomplete outcome data reporting, selective reporting and other potential biases. The GRADE process[1] uses 2 types of guideline recommendations based on the quality of evidence, risks vs benefits, feasibility, and costs while taking into account patient-based and population-based factors.

Strong Recommendation: Providers should recommend this intervention for most patients. A strong recommendation is usually accompanied by "High" or "Moderate" level of evidence from well-designed randomized controlled trials (RCTs), or RCTs with mild methodologic limitations.

Conditional Recommendation/Suggestion: Many providers might suggest this therapy, while other providers would consider other therapy in similar patients. Conditional recommendations/suggestions are usually accompanied by "Low" or "Very Low" quality of evidence.

The quality of evidence is categorized based upon an assessment of study methodology, including risk of bias, evidence of publication bias, heterogeneity among studies, and precision of the estimate of eradication rates. High quality evidence rating infers that the guideline authors are confident in the accuracy of research data to support a particular recommendation and further research is unlikely to change this recommendation. Low or Very Low quality evidence infers that the guideline authors have less confidence in the accuracy of research data to support a particular recommendation and future research may alter this recommendation.

Funding: The American College of Gastroenterology.

Results: Optimized bismuth-based quadruple therapy (BQT) for 14-days is the recommended therapy for treatment-naïve patients **(Figure 1, Table 1**) as well as treatment-experienced patients who failed to eradicate *H. pylori* with an initial course of PPI-clarithromycin triple therapy. Optimized BQT consists of PPI twice daily, tetracyclince 500 mg 4 times daily, metronidazole 500 mg 3 or 4 times daily, and bismuth subcitrate or bismuth subsalicylate 4 times daily for 14 days. Rifabutin-based triple therapy and vonoprazan-amoxicillin dual therapy are alternative suggested regimens. The guideline specifically recommends against using PPI-clarithromycin triple therapy unless antibiotic sensitivity has been performed and clarithromycin-sensitivity has been proven.

In the key concepts section, the guideline authors' note that clarithromycin-resistance and levofloxacin-resistance has risen precipitously, which greatly reduces the efficacy of these clarithromycin-based and levofloxacin-based regimens when used as empiric therapies. This is particularly important since PPI-clarithromycin triple therapy (i.e., PrevPac; Takeda Pharmaceuticals, Bannockburn, IL) remains the most commonly prescribed *H. pylori* infection treatment, although eradication rates drop to approximately 30% in clarithromycin-resistant strains of *H. pylori*.

The key concepts section also emphasizes that proof of *H. pylori* eradication is required in all patients after treatment by obtaining a fecal antigen test, urea breath testing, or gastric biopsy. Importantly, this testing should not be done until at least

4 weeks after the patient has completed antibiotics and after the patient has been off PPIs/PCABs for at least 2 weeks, although the patient can be bridged with H2 receptor antagonists and antacids during that period.

Finally, the authors recommend expanding the indications for testing and treating *H. pylori* to include individuals at increased risk of gastic cancer, individuals with atrophic gastritis, gastric intestinal metaplasia, and household members of adults with *H. pylori* infection based on non-serologic testing. This expanded list of indications reflects recognition of *H. pylori's* role in increasing the risk of gastric cancer as well as being classified by the World Health Organization as a Class I carcinogen due to its causative role in the development of mucosa-associated lymphoid tissue (MALT) lymphoma.

Regimen	Drugs (doses)	Dosing frequency	FDA Approval	Recommendation
Optimized bismuth quadruple	PPI (standard dose)	b.i.d.	No	Strong (moderate quality of evidence)
	Bismuth subcitrate (120 - 300 mg) or subsalicylate (300 mg)	q.i.d.		
	Tetracycline (500 mg)	q.i.d.		
	Metronidazole (500 mg)	t.i.d. or q.i.d.		
Rifabutin triple (Talicia)	Omeprazole (10 mg)	4 capsules t.i.d.	Yes	Conditional (low quality of evidence)
	Amoxicillin (250 mg)			
	Rifabutin (12.5 mg)			
PCAB dual (Voquezna DualPak)	Vonoprazan (20 mg)	b.i.d	Yes	Conditional (moderate quality of evidence)
	Amoxicillin (1,000 mg)	t.i.d		
PCAB triple (Voquezna TriplePak)	Vonoprazan (20 mg)	b.i.d	Yes	Conditional (moderate quality of evidence)
	Clarithromycin (500 mg)			
	Amoxicillin (1,000 mg)			

Table 1. Recommended regimens for treatment-naïve patients with *H.pylori* infection.

b.i.d., twice daily; PCAB, potassium channel acid blocker; PPI, proton pump inhibitor; q.i.d., 4-times daily; t.i.d., 3-times daily.

COMMENTARY

Why Is This Important?

This guideline makes substantial changes from the 2017 guideline recommendations[2] because of rising resistance rates to clarithromycin and levofloxacin, which reduces the efficacy of commonly-used regimens, and also because of the publication of RCTs since 2017 that demonstrated the efficacy of rifabutin-based triple therapy and vonoprazan-amoxicillin dual therapy. I commend the authors for the huge effort required to produce this well-designed guideline.

Key Study Findings

Optimized bismuth-based quadruple therapy for 14 days is the recommended therapy for treatment-naïve patients **(Figure 1, Table 1**) as well as treatment -experienced patients who failed to eradicate *H. pylori* with PPI-clarithromycin triple therapy. PPI-clarithromycin triple therapy should not be used unless antibiotic sensitivity has been performed and demonstrated clarithromycin-sensitivity.

Caution

The GRADE methodology provides transparency about how recommendations were made, although the authors' subjective opinions may influence assessments about the strength of recommendations and quality of evidence. For example, given that the prevalence of amoxicillin-resistant *H. pylori* strains is approximately 1%, I might have provided a Strong recommendation based on moderate quality of evidence for vonoprazan-amoxicillin duel therapy among treatment-naïve patients without penicillin allergies. However, I also understand the authors' rationale for only providing a Conditional recommendation here.

My Practice

I agree that optimized BQT should be the preferred *H. pylori* treatment regimen in the compliant patient. Unfortunately, I've found that my patients at the VA have difficulty complying with this regimen because of its complexity (4 medications taken up to 4 times per day while obtaining tablets from 4 different pill bottles) and the potential for dyspepsia and altered bowel habits. Also, there have been intermittent shortages of tetracycline, and the guideline recommends against substituting doxycycline. Therefore, I prefer to use PCAB-based dual therapy with vonoprazan and amoxicillin, which enhances compliance with its blister packaging and is well-tolerated, despite the additional cost to our pharmacy. Shared decision-making with individual patients may be particularly helpful here.

For patients who were previously treated with clarithromycin-based triple therapy or in treatment-naïve patients with a penicillin allergy, I prefer to use

optimized BQT. My personal tips are to proactively educate the patient about potential side effects (change in stool color, mild dyspepsia), emphasize the importance of compliance, engage a family member to help if possible, and help the patient set an alarm or even use a phone application to remember to take their medications. There is simply no substitute for spending extra time with the patient to educate them.

With my GI fellows, I emphasize the basics: don't order a *H. pylori* test unless you intend to treat, don't use PPI-clarithromycin based triple therapy, always plan to confirm eradication 4 weeks after antibiotic therapy has been completed, but, remember that the patient has to be off PPIs/PCABs for 2 weeks prior to testing.

For Future Research

As noted by the guideline authors, comparative RCTs performed in North America of optimized BQT versus rifabutin-based triple therapy and vonoprazan-based dual/triple therapy in both treatment-naïve and treatment-experienced patients would be helpful. I'd also emphasize the importance of implementation research to minimize the continued use of PPI-clarithromycin triple therapy. Again, this is by far the most commonly prescribed *H. pylori* treatment regimen, although the guideline explicitly states that it should only be used when the specific strain of *H. pylori* has demonstrated susceptibility to clarithromycin (which is quite rare).

Conflict of Interest

Dr. Schoenfeld reports serving on advisory boards, consultant and speakers bureau for Phathom Pharmaceuticals.

Note: The authors of this ACG Guideline are active on social media. Tag them to discuss their work and this EBGI summary.

@umfoodoc
William Chey

@shailjashahmd
Shailja Shah)

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