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CONSENSUS STATEMENT

The Toronto Consensus for the Treatment of *Helicobacter pylori* Infection in Adults

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This article has an accompanying continuing medical education activity, also eligible for MOC credit, on page e25. Learning Objective: Upon completion of this examination, successful learners will be able to establish a treatment plan for patients with *H pylori* infection.

BACKGROUND & AIMS: *Helicobacter pylori* infection is increasingly difficult to treat. The purpose of these consensus statements is to provide a review of the literature and specific, updated recommendations for eradication therapy in adults. **METHODS:** A systematic literature search identified studies on *H pylori* treatment. The quality of evidence and strength of recommendations were rated according to the Grading of Recommendation Assessment, Development and Evaluation (GRADE) approach. Statements were developed through an online platform, finalized, and voted on by an international working group of specialists chosen by the Canadian Association of Gastroenterology. **RESULTS:** Because of increasing failure of therapy, the consensus group strongly recommends that all *H pylori* eradication regimens now be given for 14 days. Recommended first-line strategies include concomitant nonbismuth quadruple therapy (proton pump inhibitor [PPI] + amoxicillin + metronidazole + clarithromycin [PAMC]) and traditional bismuth quadruple therapy (PPI + bismuth + metronidazole + tetracycline [PBMT]). PPI triple therapy (PPI + clarithromycin + either amoxicillin or metronidazole) is restricted to areas with known low clarithromycin resistance or high eradication success with these regimens. Recommended rescue therapies include PBMT and levofloxacin-containing therapy (PPI + amoxicillin + levofloxacin). Rifabutin regimens should be restricted to patients who have failed to respond to at least 3 prior options. **CONCLUSIONS:** Optimal treatment of *H pylori* infection requires careful attention to local antibiotic resistance and eradication patterns. The quadruple therapies PAMC or PBMT should play a more prominent role in eradication of *H pylori* infection, and all treatments should be given for 14 days.

Keywords: Helicobacter pylori; Eradication; Resistance; Proton Pump Inhibitor; Amoxicillin; Bismuth; Clarithromycin; Metronidazole; Tetracycline; Levofloxacin; Rifabutin.

Although the prevalence of *H pylori* is decreasing in some parts of the world, the infection remains present in 28% to 84% of subjects depending on the population tested.[1] Even studies in Western nations, which tend to have the lowest general prevalence,[1–4] report high proportions of infected individuals in certain communities (eg, 38%–75% of Alaskan or Canadian aboriginal populations).[2,3,5–8]

H pylori is implicated in the development of and its eradication is recommended in the treatment of duodenal or gastric ulcers, early gastric cancer, and gastric mucosa-associated lymphoid tissue lymphomas (in <0.01%).[4,9–14] Treatment has been suggested for prevention of gastric cancer in high-risk individuals,[11–13,15] as well as in patients with uninvestigated[16] and functional dyspepsia,[17] given evidence that eradication of the infection leads to sustained improvements in symptoms in a proportion of patients.[10,16,17]

The increasing prevalence of antibiotic-resistant strains of *H pylori* has led to reduced success with traditional *H*

Abbreviations used in this paper: **BPAL, bismuth compounds + proton pump inhibitor + amoxicillin + levofloxacin; CAG, Canadian Association of Gastroenterology; CI, confidence interval; GRADE, Grading of Recommendation Assessment, Development and Evaluation; ITT, intention-to-treat; NNT, number needed to treat; PA, proton pump inhibitor + amoxicillin; PAC, proton pump inhibitor + amoxicillin + clarithromycin; PAL, proton pump inhibitor + amoxicillin + levofloxacin; PAM, proton pump inhibitor + amoxicillin + metronidazole; PAMC, proton pump inhibitor + amoxicillin + metronidazole + clarithromycin; PAR, PPI + amoxicillin + rifabutin; PBMT, proton pump inhibitor + bismuth compounds + metronidazole + tetracycline; PICO, Population, Intervention, Comparator, Outcomes; PMC, proton pump inhibitor + metronidazole + clarithromycin; PPI, proton pump inhibitor; RCT, randomized controlled trial; RD, risk difference.**

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pylori treatments.[18–24] Proton pump inhibitor (PPI) triple therapies (a PPI plus two of the following antibiotics: clarithromycin, amoxicillin, or metronidazole) for 7 to 10 days were once standard and recommended as first-line therapy[11–13,25] but have become increasingly ineffective, with some studies reporting eradication in less than 50% of cases.[21,22,26–28] Suboptimal patient compliance may be another cause of treatment failure.[4,29–31]

It has been suggested that the goal of *H pylori* therapy should now be eradication in ≥90% of treated patients.[32] This arbitrary threshold is not easily achieved, especially in real-world settings. However, the most efficacious therapies available should be used first to avoid the cost, inconvenience, and risks associated with treatment failure.

Some of the more common regimens for *H pylori* eradication include bismuth quadruple therapy (PPI + bismuth compounds + metronidazole + tetracycline [PBMT]), nonbismuth quadruple therapy (concomitant [PPI + amoxicillin + metronidazole + clarithromycin {PAMC}] or sequential [PPI + amoxicillin {PA} followed by PPI + metronidazole + clarithromycin {PMC}]), PPI triple therapy (PPI + amoxicillin + clarithromycin [PAC], PMC, or PPI + amoxicillin + metronidazole [PAM]), and quinolone-containing regimens (PPI + amoxicillin + levofloxacin [PAL]). Definitions of these and other regimens discussed in this consensus paper are shown in Table 1, with suggested doses listed in Table 2.

The increasing prevalence of antibiotic-resistant strains and evidence of more frequent failures of triple therapies suggest the need for more effective therapies given for a longer duration (14 days instead of 10 or 7 days) than were recommended in prior consensus statements.[11,12] For this reason, as well as the existence of new therapies, the Canadian Association of Gastroenterology (CAG) and the Canadian *Helicobacter* Study Group determined that an update was needed. The purpose of this consensus process was to systematically review the literature relating to the management of *H pylori* infection and to provide specific, updated recommendations for eradication therapy in adults. This consensus was limited to adults, because updated pediatric recommendations are currently in progress from the European Society for Paediatric Gastroenterology, Hepatology and Nutrition and North American Society for Pediatric Gastroenterology, Hepatology and Nutrition.

Methods

Scope and Purpose

The consensus development process was initiated in the summer of 2013 with the first meeting of the steering committee and lasted approximately 2 years, with the meeting of the full consensus group taking place in June 2015.

Sources and Searches

The Editorial Office of the Cochrane Upper Gastrointestinal and Pancreatic Diseases Group at McMaster University

Table 1. Recommendations for Regimens Used for the Eradication of *H pylori*

Recommendation	Regimen	Definition (see dose table)
First line		
Recommended option	Bismuth quadruple (PBMT)	PPI + bismuth + metronidazole[a] + tetracycline
Recommended option	Concomitant nonbismuth quadruple (PAMC)	PPI + amoxicillin + metronidazole[a] + clarithromycin
Restricted option[b]	PPI triple (PAC, PMC, or PAM)	PPI + amoxicillin + clarithromycin PPI + metronidazole[a] + clarithromycin PPI + amoxicillin + metronidazole[a]
Not recommended	Levofloxacin triple (PAL)	PPI + amoxicillin + levofloxacin
Not recommended	Sequential nonbismuth quadruple (PA followed by PMC)	PPI + amoxicillin followed by PPI + metronidazole[a] + clarithromycin
Prior treatment failure		
Recommended option	Bismuth quadruple (PBMT)	PPI + bismuth + metronidazole[a] + tetracycline
Recommended option	Levofloxacin-containing therapy (usually PAL)	PPI + amoxicillin + levofloxacin[c]
Restricted option[d]	Rifabutin-containing therapy (usually PAR)	PPI + amoxicillin + rifabutin
Not recommended	Sequential nonbismuth quadruple therapy (PA followed by PMC)	PPI + amoxicillin followed by PPI + metronidazole[a] + clarithromycin
Undetermined	Concomitant nonbismuth quadruple therapy (PAMC)	PPI + amoxicillin + metronidazole[a] + clarithromycin

[a]Tinidazole may be substituted for metronidazole.
[b]Restricted to areas with known low clarithromycin resistance (<15%) or proven high local eradication rates (>85%) (see statement 5).
[c]There is some evidence that adding bismuth to this combination may improve outcomes.
[d]Restricted to cases in which at least 3 recommended options have failed (see statement 13).