ACG Clinical Guideline: Treatment of *Helicobacter pylori* Infection

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Am J Gastroenterol 2017; 112:212–238; doi: 10.1038/ajg.2016.563; published online 10 January 2017

SUPPLEMENTARY MATERIAL is linked to the online version of the paper at http://www.nature.com/ajg

Abstract

Helicobacter pylori (*H. pylori*) infection is a common worldwide infection that is an important cause of peptic ulcer disease and gastric cancer. *H. pylori* may also have a role in uninvestigated and functional dyspepsia, ulcer risk in patients taking low-dose aspirin or starting therapy with a non-steroidal anti-inflammatory medication, unexplained iron deficiency anemia, and idiopathic thrombocytopenic purpura. While choosing a treatment regimen for *H. pylori*, patients should be asked about previous antibiotic exposure and this information should be incorporated into the decision-making process. For first-line treatment, clarithromycin triple therapy should be confined to patients with no previous history of macrolide exposure who reside in areas where clarithromycin resistance amongst *H. pylori* isolates is known to be low. Most patients will be better served by first-line treatment with bismuth quadruple therapy or concomitant therapy consisting of a PPI, clarithromycin, amoxicillin, and metronidazole. When first-line therapy fails, a salvage regimen should avoid antibiotics that were previously used. If a patient received a first-line treatment containing clarithromycin, bismuth quadruple therapy or levofloxacin salvage regimens are the preferred treatment options. If a patient received first-line bismuth quadruple therapy, clarithromycin or levofloxacin-containing salvage regimens are the preferred treatment options. Details regarding the drugs, doses and durations of the recommended and suggested first-line and salvage regimens can be found in the guideline.

Introduction

Helicobacter pylori infection remains one of the most common chronic bacterial infections affecting humans. Since publication of the last American College of Gastroenterology (ACG) Clinical Guideline in 2007, significant scientific advances have been made regarding the management of *H. pylori* infection. The most significant advances have been made in the arena of medical treatment. Thus, this guideline is intended to provide clinicians working in North America with updated recommendations on the treatment of *H. pylori* infection. For the purposes of this document, we have defined North America as the United States and Canada. Whenever possible, recommendations are based upon the best available evidence from the world's literature with special attention paid to literature from North America. When evidence from North America was not available, recommendations were based upon data from international studies and expert consensus.

This guidance document was developed using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) system (1), which provides a level of evidence and strength of recommendation for statements developed using the PICO (patient population, intervention or indicator assessed, comparison group, outcome achieved) format. At the start of the guideline

development process, the authors developed PICO questions relevant to *Helicobacter pylori* infection. The authors worked with research methodologists from McMaster University to conduct focused literature searches to provide the best available evidence to address the PICO questions. Databases searched included MEDLINE, EMBASE and Cochrane CENTRAL from 2000 to 11 September 2014. Search terms included "pylori, treat*, therap*, manag*, eradicat*". The full literature search strategy is provided as **Supplementary Appendix 1** online. After assessing the risk of bias, indirectness, inconsistency, and imprecision, the level of evidence for each recommendation was reported as "high" (further research is unlikely to change the confidence in the estimate of effect), "moderate" (further research would be likely to have an impact on the confidence in the estimate of effect), "low" (further research would be expected to have an impact on the confidence in the estimate of effect), or "very low" (any estimate of effect is very uncertain). The strength of recommendations was determined to be "strong" or "conditional" based on the quality of evidence, the certainty about the balance between desirable and undesirable effects of the intervention, the certainty about patients' values and preferences, and the certainty about whether the recommendation represents a wise use of resources. A summary of the recommendation statements for this management guideline is provided in **Table 1**. The justification for the assessments of the quality of evidence for each statement can be found in **Supplementary Appendix 2** online.

Table 1. Recommendation statements
What is known about the epidemiology of H. pylori *infection in North America? Which are the high risk groups?*
H. pylori infection is chronic and is usually acquired in childhood. The exact means of acquisition is not always clear. The incidence and prevalence of *H. pylori* infection are generally higher among people born outside North America than among people born here. Within North America, the prevalence of the infection is higher in certain racial and ethnic groups, the socially disadvantaged, and people who have immigrated to North America (Factual statement, low quality of evidence).
What are the indications to test for, and to treat, H. pylori *infection?*
Since all patients with a positive test of active infection with *H. pylori* should be offered treatment, the critical issue is which patients should be tested for the infection (strong recommendation; quality of evidence not applicable).
All patients with active peptic ulcer disease (PUD), a past history of PUD (unless previous cure of *H. pylori* infection has been documented), low-grade gastric mucosa-associated lymphoid tissue (MALT) lymphoma, or a history of endoscopic resection of early gastric cancer (EGC) should be tested for *H. pylori* infection. Those who test positive should be offered treatment for the infection (Strong recommendation; quality of evidence: high for active or history of PUD, low for MALT lymphoma, low for history of endoscopic resection of EGC).
In patients with uninvestigated dyspepsia who are under the age of 60 years and without alarm features, non-endoscopic testing for *H. pylori* infection is a consideration. Those who test positive should be offered eradication therapy (conditional recommendation; quality of evidence: high for efficacy, low for the age threshold).
When upper endoscopy is undertaken in patients with dyspepsia, gastric biopsies should be taken to evaluate for *H. pylori* infection. Infected patients should be offered eradication therapy (strong recommendation; high quality of evidence).

Table 1. Recommendation statements (continued)
What are the indications to test for, and to treat, H. pylori *infection? (continued)*
Patients with typical symptoms of gastroesophageal reflux disease (GERD) who do not have a history of PUD need not be tested for *H. pylori* infection. However, for those who are tested and found to be infected, treatment should be offered, acknowledging that effects on GERD symptoms are unpredictable (strong recommendation; high quality of evidence).
In patients taking long-term, low-dose aspirin, testing for *H. pylori* infection could be considered to reduce the risk of ulcer bleeding. Those who test positive should be offered eradication therapy to reduce the risk of ulcer bleeding (conditional recommendation; moderate quality of evidence).
Patients initiating chronic treatment with a non-steroidal anti-inflammatory drug (NSAID) should be tested for *H. pylori* infection. Those who test positive should be offered eradication therapy (Strong recommendation; Moderate quality of evidence). The benefit of testing and treating *H. pylori* in a patient already taking an NSAID remains unclear (conditional recommendation; low quality of evidence).
Patients with unexplained iron deficiency anemia despite an appropriate evaluation should be tested for *H. pylori* infection. Those who test positive should be offered eradication therapy (conditional recommendation; low quality of evidence).
Adults with idiopathic thrombocytopenic purpura (ITP) should be tested for *H. pylori* infection. Those who test positive should be offered eradication therapy (conditional recommendation; very low quality of evidence).
There is insufficient evidence to support routine testing for and treatment of *H. pylori* in asymptomatic individuals with a family history of gastric cancer or patients with lymphocytic gastritis, hyperplastic gastric polyps, and hyperemesis gravidarum (no recommendation; very low quality of evidence).
What are evidence-based first-line treatment strategies for providers in North America?
Patients should be asked about any previous antibiotic exposure(s) and this information should be taken into consideration when choosing an *H. pylori* treatment regimen (conditional recommendation; moderate quality of evidence).
Clarithromycin triple therapy consisting of a PPI, clarithromycin, and amoxicillin or metronidazole for 14 days remains a recommended treatment in regions where *H. pylori* clarithromycin resistance is known to be <15% and in patients with no previous history of macrolide exposure for any reason (Conditional recommendation; low quality of evidence (for duration: moderate quality of evidence)).
Bismuth quadruple therapy consisting of a PPI, bismuth, tetracycline, and a nitroimidazole for 10–14 days is a recommended first-line treatment option. Bismuth quadruple therapy is particularly attractive in patients with any previous macrolide exposure or who are allergic to penicillin (strong recommendation; low quality of evidence).
Concomitant therapy consisting of a PPI, clarithromycin, amoxicillin and a nitroimidazole for 10–14 days is a recommended first-line treatment option (strong recommendation; low quality of evidence (for duration: very low quality of evidence)).

Table 1. Recommendation statements (continued)
What are evidence-based first-line treatment strategies for providers in North America? (continued)
Sequential therapy consisting of a PPI and amoxicillin for 5–7 days followed by a PPI, clarithromycin, and a nitroimidazole for 5–7 days is a suggested first-line treatment option (conditional recommendation; low quality of evidence (for duration: very low quality of evidence)).
Hybrid therapy consisting of a PPI and amoxicillin for 7 days followed by a PPI, amoxicillin, clarithromycin and a nitroimidazole for 7 days is a suggested first-line treatment option (conditional recommendation; low quality of evidence (For duration: very low quality of evidence)).
Levofloxacin triple therapy consisting of a PPI, levofloxacin, and amoxicillin for 10–14 days is a suggested first-line treatment option (conditional recommendation; low quality of evidence (For duration: very low quality of evidence)).
Fluoroquinolone sequential therapy consisting of a PPI and amoxicillin for 5–7 days followed by a PPI, fluoroquinolone, and nitroimidazole for 5–7 days is a suggested first-line treatment option (conditional recommendation; low quality of evidence (for duration: very low quality of evidence)).
What factors predict successful eradication when treating H. pylori *infection?*
The main determinants of successful *H. pylori* eradication are the choice of regimen, the patient's adherence to a multi-drug regimen with frequent side-effects, and the sensitivity of the *H. pylori* strain to the combination of antibiotics administered (Factual statement; moderate quality of evidence).
What do we know about H. pylori *antimicrobial resistance in the North America?*
Data regarding antibiotic resistance among *H. pylori* strains from North America remains scarce. Organized efforts are needed to document local, regional, and national patterns of resistance in order to guide the appropriate selection of *H. pylori* therapy (strong recommendation; low quality of evidence).
What methods can be used to evaluate for H. pylori *antibiotic resistance and when should testing be performed?*
Although *H. pylori* antimicrobial resistance can be determined by culture and/or molecular testing, (strong recommendation; moderate quality of evidence), these tests are currently not widely available in the United States.
Should we test for treatment success after H. pylori *eradication therapy?*
Whenever *H. pylori* infection is identified and treated, testing to prove eradication should be performed using a urea breath test, fecal antigen test or biopsy-based testing at least 4 weeks after the completion of antibiotic therapy and after PPI therapy has been withheld for 1–2 weeks. (Strong recommendation; Low quality of evidence (for the choice of methods to test for eradication: Moderate quality of evidence)).

Table 1. Recommendation statements (continued)
When first-line therapy fails, what are the options for salvage therapy?
In patients with persistent *H. pylori* infection, every effort should be made to avoid antibiotics that have been previously taken by the patient (unchanged from previous ACG guideline (1)) (Strong recommendation; moderate quality of evidence).
Bismuth quadruple therapy or levofloxacin salvage regimens are the preferred treatment options if a patient received a first-line treatment containing clarithromycin. Selection of best salvage regimen should be directed by local antimicrobial resistance data and the patient's previous exposure to antibiotics (Conditional recommendation; for quality of evidence see individual statements below).
Clarithromycin or levofloxacin-containing salvage regimens are the preferred treatment options, if a patient received first-line bismuth quadruple therapy. Selection of best salvage regimen should be directed by local antimicrobial resistance data and the patient's previous exposure to antibiotics (Conditional recommendation; for quality of evidence see individual statements below).
The following regimens can be considered for use as salvage treatment:
Bismuth quadruple therapy for 14 days is a recommended salvage regimen. (Strong recommendation; low quality of evidence)
Levofloxacin triple regimen for 14 days is a recommended salvage regimen. (Strong recommendation; moderate quality of evidence (For duration: low quality of evidence)
Concomitant therapy for 10–14 days is a suggested salvage regimen. (conditional recommendation; very low quality of evidence)
Clarithromycin triple therapy should be avoided as a salvage regimen. (conditional recommendation; low quality of evidence)
Rifabutin triple regimen consisting of a PPI, amoxicillin, and rifabutin for 10 days is a suggested salvage regimen (conditional recommendation; moderate quality of evidence (For duration: very low quality of evidence)).
High-dose dual therapy consisting of a PPI and amoxicillin for 14 days is a suggested salvage regimen (conditional recommendation; low quality of evidence (For duration: very low quality of evidence)).
When should penicillin allergy testing be considered in patients with H. pylori *infection?*
Most patients with a history of penicillin allergy do not have true penicillin hypersensitivity. After failure of first-line therapy, such patients should be considered for referral for allergy testing since the vast majority can ultimately be safely given amoxicillin-containing salvage regimens (strong recommendation; Low quality of evidence).

Table 2. Recommended and Suggested first-line therapies for *H pylori* infection

Recommended				
Regimen	**Drugs (doses)**	**Dosing frequency**	**Duration (days)**	**FDA approval**
Clarithromycin triple	PPI (standard or double dose)	BID	14	Yes[a]
	Clarithromycin (500 mg)			
	Amoxicillin (1 grm) or Metronidazole (500 mg TID)			
Bismuth quadruple	PPI (standard dose)	BID	10-14	No[b]
	Bismuth subcitrate (120–300 mg) or subsalicylate (300 mg)	QID		
	Tetracycline (500 mg)	QID		
	Metronidazole (250–500 mg)	QID (250)		
		TID to QID (500)		
Concomitant	PPI (standard dose)	BID	10-14	No
	Clarithromycin (500 mg)			
	Amoxicillin (1 grm)			
	Nitroimidazole (500 mg)[c]			
Suggested				
Regimen	**Drugs (doses)**	**Dosing frequency**	**Duration (days)**	**FDA approval**
Sequential	PPI (standard dose)+Amoxicillin (1 grm)	BID	5-7	No
	PPI, Clarithromycin (500 mg)+Nitroimidazole (500 mg)[c]	BID	5-7	
Hybrid	PPI (standard dose)+Amox (1 grm)	BID	7	No
	PPI, Amox, Clarithromycin (500 mg), Nitroimidazole (500 mg)[c]	BID	7	
Levofloxacin triple	PPI (standard dose)	BID	10-14	No
	Levofl oxacin (500 mg)	QD		
	Amox (1 grm)	BID		
Levofloxacin sequential	PPI (standard or double dose)+Amox (1 grm)	BID	5-7	No
	PPI, Amox, Levofloxacin (500 mg QD), Nitroimidazole (500 mg)[c]	BID	5-7	
LOAD	Levofloxacin (250 mg)	QD	7-10	No
	PPI (double dose)	QD		
	Nitazoxanide (500 mg)	BID		
	Doxycycline (100 mg)	QD		

BID, twice daily; FDA, Food and Drug Administration; PPI, proton pump inhibitor; TID, three times daily; QD, once daily; QID, four times daily.
[a]Several PPI, clarithromycin, and amoxicillin combinations have achieved FDA approval. PPI, clarithromycin and metronidazole is not an FDA-approved treatment regimen.
[b]PPI, bismuth, tetracycline, and metronidazole prescribed separately is not an FDA-approved treatment regimen. However, Pylera, a combination product containing bismuth subcitrate, tetracycline, and metronidazole combined with a PPI for 10 days is an FDA-approved treatment regimen.
[c]Metronidazole or tinidazole.

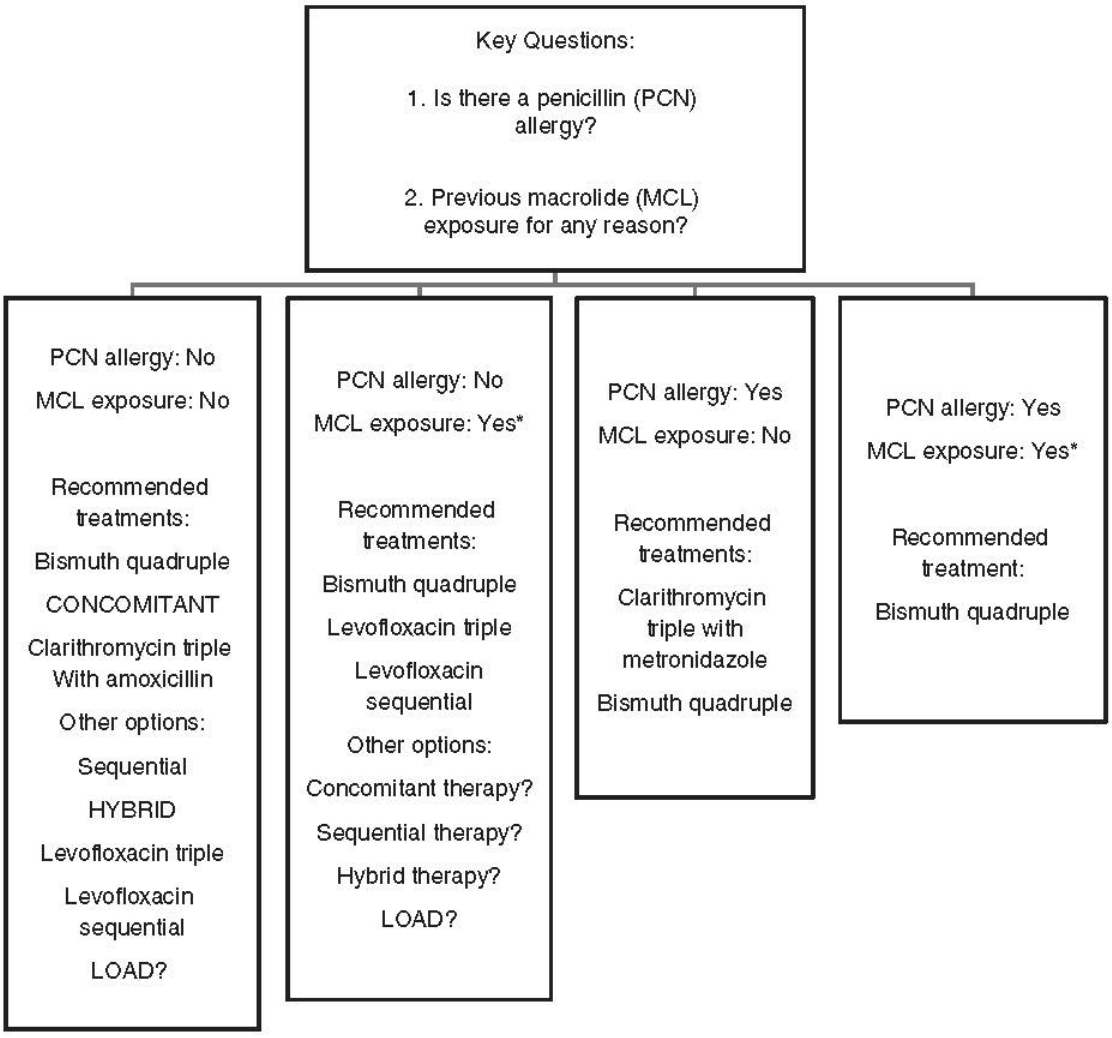

Figure 1. Selection of a first-line *H. pylori* treatment regimen.

Table 4. Salvage therapies for *H pylori* infection

Regimen	Drugs (doses)	Dosing frequency	Duration (days)	FDA approval
Bismuth quadruple	PPI (standard dose)	BID	14	No[a]
	Bismuth subcitrate (120–300 mg) or subsalicylate (300 mg)	QID		
	Tetracycline (500 mg)	QID		
	Metronidazole (500 mg)	TID or QID		
Levofloxacin triple	PPI (standard dose)	BID	14	No
	Levofloxacin (500 mg)	QD		
	Amox (1 grm)	BID		
Concomitant	PPI (standard dose)	BID	10-14	No
	Clarithromycin (500 mg)	BID		
	Amoxicillin (1 grm)	BID		
	Nitroimidazole (500 mg)	BID or TID		
Rifabutin triple	PPI (standard dose)	BID	10	No
	Rifabutin (300 mg)	QD		
	Amox (1 grm)	BID		
High-dose dual	PPI (standard to double dose)	TID or QID	14	No
	Amox (1 grm TID or 750 mg QID)	TID or QID		

BID, twice daily; FDA, Food and Drug Administration; PPI, proton pump inhibitor; TID, three times daily; QD, once daily; QID, four times daily.

[a]PPI, bismuth, tetracycline, and metronidazole prescribed separately is not an FDA-approved treatment regimen. However, Pylera, a combination product containing bismuth subcitrate, tetracycline, and metronidazole combined with a PPI for 10 days is an FDA-approved treatment regimen.

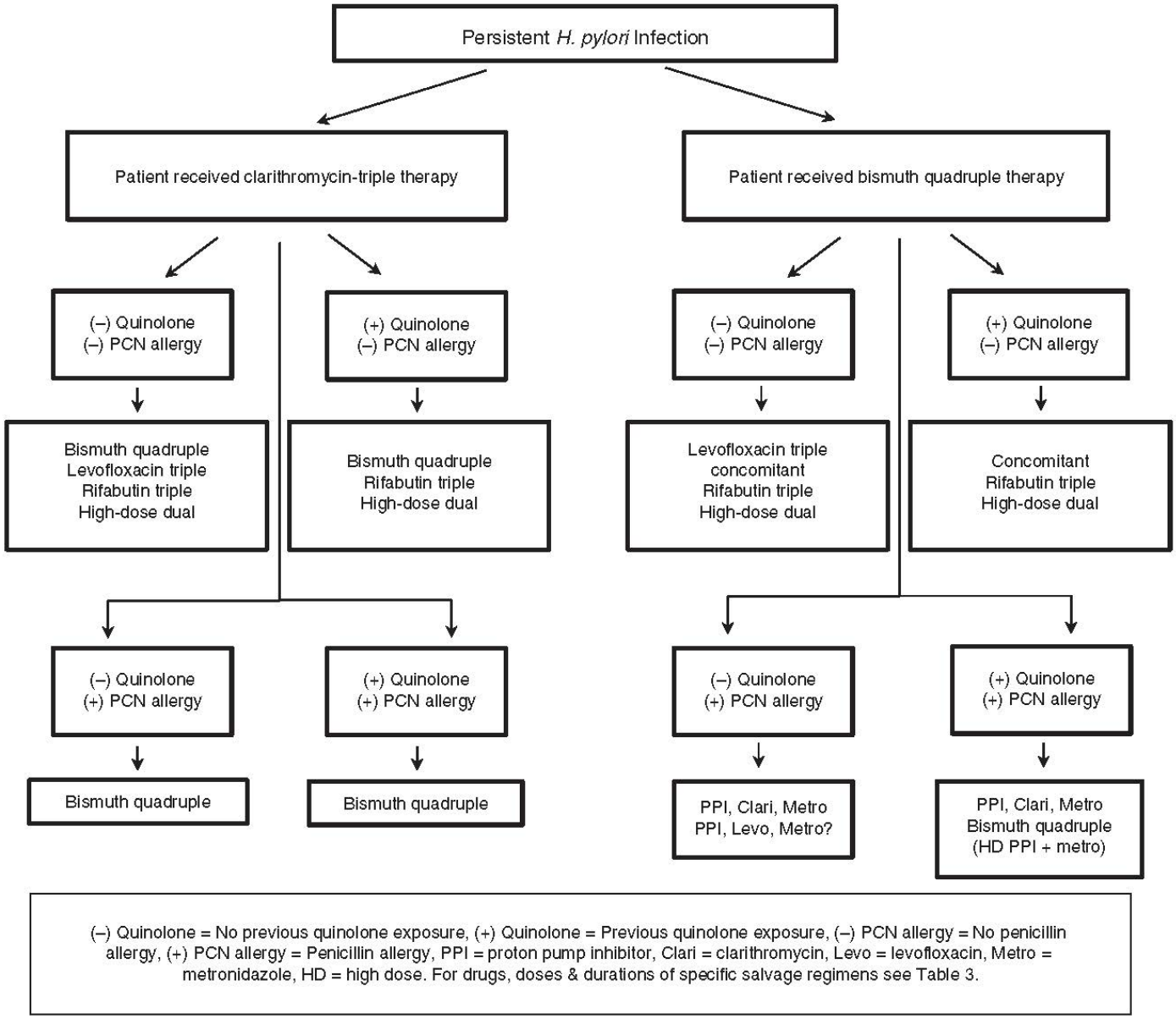

Figure 3. Selection of a salvage treatment regimen for persistent *H. pylori* infection.

Summary

The number of treatment options for *H. pylori* infection has substantially increased since publication of the 2007 ACG guideline (**Tables 2** and **4**). All of the modern treatment regimens, including concomitant therapy, hybrid therapy, and levofloxacin-containing regimens, which have been found to be most effective in international trials, have not been evaluated in North America. Thus it is impossible to make confident, evidence-based recommendations regarding the relative efficacy of these regimens in North America. As concomitant, sequential and hybrid therapies are generally composed of the same four drugs, and the available data suggest that they provide similar efficacy and tolerability, practical issues such as simplicity of the regimen take on greater importance. Using this logic, concomitant therapy seems the best choice of the clarithromycin quadruple therapies for both first-line and salvage therapy. Of the levofloxacin treatment regimens, none of which has been evaluated in North America, we feel that levofloxacin sequential therapy offers the most robust first-line efficacy data based upon available international trials. At present, levofloxacin triple therapy remains an evidence-based salvage treatment option. Clinicians are encouraged to make decisions based upon local antibiotic resistance data, whenever available. Acknowledging that these data are not readily available in most parts of North America, we recommend that clinicians ask about previous exposure to antibiotics as well as allergy to penicillin. This information can be leveraged to narrow the treatment options for an individual patient.