CME

ACG Clinical Guideline: Treatment of *Helicobacter pylori* Infection

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***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.**

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

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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

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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.

QUESTION 1: WHAT IS KNOWN ABOUT THE EPIDEMIOLOGY OF *H. PYLORI* INFECTION IN NORTH AMERICA? WHICH ARE THE HIGH-RISK GROUPS?

Recommendation

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).

H. pylori infection is usually acquired during childhood (2–6) although the exact means of acquisition is not always clear. Risk factors for acquiring the infection include low socioeconomic status (6–8) increasing number of siblings (9) and having an infected parent—especially an infected mother (10). In the Ulm (Germany) Birth Cohort Study, the odds ratio (OR) for acquiring *H. pylori* infection if a child's mother was infected was 13.0 (95% confidence interval (CI) 3.0–55.2) (10) Apart from intrafamilial spread, the infection may also be transmitted through contaminated water supplies (11) particularly in developing countries.

Although infection rates for male and female children are similar (3,12) there may be a slight male preponderance of the infection in adulthood. In a meta-analysis of observational, population-based studies, men were slightly more likely to be *H. pylori*-positive than women; OR=1.16 (95% CI 1.11–1.22) (12) This was confirmed in a study of adults in Ontario, Canada, in which the overall seroprevalence was 23.1% but higher in men (29.4%) than women (14.9%) (13). One explanation that has been proposed for the lower seroprevalence in women is that they may be more likely to clear *H. pylori* infection because of higher rates of incidental antibiotic use for other indications (12).

There is evidence for a birth cohort effect on *H. pylori* prevalence; for example, people who were born in the 1930s are more likely to have been infected during childhood than people born in the 1960s. In a study conducted among 7310 US veterans with gastrointestinal symptoms, seroprevalence was 73% among those born before 1920 and 22% in those born after 1980 (14). The overall prevalence of the infection in these US veterans fell from 70.8% in 1997 to a plateau of around 50% after 2002.

Within North America, the prevalence of *H. pylori* infection varies with socioeconomic status and race/ethnicity (14–17). In general, the prevalence is lower among non-Hispanic whites than among other racial/ethnic groups including African Americans, Hispanic Americans, Native Americans, and Alaska natives (5,14,15,18). African Americans with a higher proportion of African ancestry have been reported to have higher rates of *H. pylori* infection than African Americans with a lower proportion of African ancestry suggesting that racial/genetic factors may have some role in predisposition to the infection unrelated to socioeconomic factors (16). Higher prevalence rates have been found among those living close to the US/Mexico border (19,20); in one study (19), prevalence of *H. pylori* assessed by stool antigen testing was 38.2%. Prevalence has also been reported to be high among Alaska natives (18) and Canadian First Nations populations (21).

The prevalence of *H. pylori* infection is generally lower in the United States than in many other parts of the world, particularly in comparison to Asia and Central and South America (8,22). There is, however, preliminary evidence that it may be falling in some previously high prevalence areas (22). People immigrating to North America from Asia and other parts of the world have a much higher prevalence of the infection than people born in North America (23). In one study, the seroprevalence among immigrants from East Asia was 70.1% (24). Hispanic immigrants to North America have higher rates of the infection than first- or second-generation Hispanics who were born here (25).

QUESTION 2: WHAT ARE THE INDICATIONS TO TEST FOR, AND TO TREAT, *H. PYLORI* INFECTION?

Recommendations

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).

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).
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)).
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?*

Table 1 continued on following page

Table 1. Continued

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 teatment 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)).
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).

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).

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 (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 (strong recommendation, moderate quality of evidence). Those who test positive should be offered eradication therapy. The benefits of testing and treating *H. pylori* in patients already taking NSAIDs remains unclear (conditional recommendation, low quality of evidence).

Patients with unexplained iron deficiency (ID) anemia despite an appropriate evaluation should be tested for *H. pylori* infection. Those who test positive should be offered eradication therapy (conditional recommendation, high 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 and treating 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).

The ACG's 2007 treatment guideline on the management of *H. pylori* infection (26) listed the following as established indications for diagnosis and treatment:

- Active PUD (gastric or duodenal).
- Confirmed history of PUD (not previously treated for *H. pylori*).
- Gastric MALT lymphoma (low grade).
- After endoscopic resection of EGC.

The current guideline extends the list of potential indications to test patients for *H. pylori* infection. There are varying levels of evidence in support of the different potential indications for testing that are listed below. For some of these, the decision to test an individual patient for *H. pylori* will be influenced by clinical judgment and considerations of a patient's general medical condition. Not all of these potential indications are given a definite recommendation, so that clinicians may exercise their judgment for individual patients. There is no justification in North America for universal or population-based screening.

PUD

The evidence in support of the 2007 recommendation was substantive at that time and these broad recommendations are still pertinent. All patients with a new diagnosis or a past history of PUD should be tested for *H. pylori* infection. Ideally, tests which identify active infection such as a urea breath test, fecal antigen test, or when endoscopy is performed, mucosal biopsy-based testing should be utilized. Because of the higher pretest probability of infection, patients with documented PUD represent a rare group, where it is acceptable to utilize an IgG *H. pylori* antibody test. In most other circumstances where the pretest probability of infection is lower, tests which identify active disease are preferred over antibody testing. Patients with a history of PUD who have previously been treated for *H. pylori* infection should undergo eradication testing with a urea breath test or fecal antigen test. Patients with evidence of ongoing infection should be treated appropriately.

Gastric mucosa-associated lymphoid tissue (MALT) lymphoma

The term "MALT lymphoma" has largely been supplanted by "marginal zone B-cell lymphoma of MALT type". Identification of this neoplasm remains a key indication to test for, and to eradicate, *H. pylori* infection.

A review published in 2009 identified and summarized six prospective cohort studies of treatment for *H. pylori* infection in patients with gastric MALT lymphoma (also referred to as "localized B-cell lymphoma of the stomach") but found no systematic reviews or randomized controlled trials (27). Tumor regression was reported in 60–93% of patients after eradication of *H. pylori* infection, but response was inconsistent, with some patients showing a delayed response and some showing tumor relapse within a year of treatment.

More recent studies have confirmed these observations. In a Japanese series, 77% out of 420 patients treated for *H. pylori* infection showed either complete histological response or probable minimal residual disease (the investigators' definition of response), although 10 (3%) responders relapsed in a mean of 6.5 years (28). Among infected patients who did not respond to eradication treatment, there was progression of the disease in 27%. Among 120 patients in Germany followed for a median of 122 months, there was initial complete remission in 80% following treatment of *H. pylori* infection (29). Out of these, 3% had macroscopic recurrence of disease within 24 months, and another 17% had histological residual disease found after a median of 48 months.

A recent review has suggested that treatment of *H. pylori* infection may also be beneficial for patients diagnosed with diffuse large B-cell lymphoma of the stomach (30).

Early gastric cancer

Three recent meta-analyses have each found that the incidence of metachronous gastric cancer following the endoscopic resection of a gastric neoplasm was reduced by the eradication of *H. pylori* infection (31–33). The most inclusive analysis by Yoon *et al.* (33) included 13 studies (three prospective and 10 retrospective) comprising 6687 patients. The pooled OR of gastric cancer in patients successfully cured of *H. pylori* was 0.42 (95% CI 0.32–0.56); in a subgroup analysis of the three prospective studies, the OR was 0.39 (95% CI 0.20–0.75) (33,34). The other two meta-analyses yielded similar results (31,32). Most recently, a meta-analysis comprising 24 studies (22 out of which were conducted in Asia) confirmed a lower rate of metachronous EGC following treatment of *H. pylori* infection; the incidence rate ratio was 0.54 (95% CI 0.46–0.65) (34).

Dyspepsia (uninvestigated)

Dyspepsia (defined as pain or discomfort centered in the upper abdomen) is highly prevalent in North America and elsewhere. In North America, most patients with dyspepsia will not have serious underlying, organic disease to explain their symptoms. That is, most will be found to have functional dyspepsia (FD), which is discussed elsewhere in this guideline. The ACG's 2007 guideline on *H. pylori* management (26) included uninvestigated dyspepsia (depending upon *H. pylori* prevalence) in its list of established indications for diagnosis and treatment of *H. pylori* infection. The test and treat strategy for *H. pylori* infection was endorsed for patients under age 55 with dyspeptic symptoms and without alarm features.

In the UK, the Bristol Helicobacter Project randomized 1517 *H. pylori*-positive adults to treatment for *H. pylori* infection or placebo and followed them prospectively (35). Among those treated for the infection, of whom over 90% achieved successful eradication, there was a small but statistically significant ($P<0.05$) reduction in subsequent consultations at the primary care level for dyspeptic complaints.

The Cochrane Collaboration's review on initial management strategies for dyspepsia was published in 2005 (36). As of early 2016, it had not been updated. A "test and treat" strategy for *H. pylori* had been found to be more effective than empirical acid suppression with either a proton pump inhibitor (PPI) or

H_2-receptor antagonist in managing dyspepsia (relative risk (RR) 0.59; 95% CI 0.42–0.83). This conclusion differs from an individual patient data meta-analysis which included three RCTs of 1537 patients randomized to the "test and treat" strategy or empirical acid suppression for the management of dyspepsia in the primary care setting (37). Although there was no significant difference between the groups in terms of symptom cure at 12 months, there was a trend for reduced overall costs in those assigned to "test and treat".

An individual patient data meta-analysis included five RCTs of 1924 patients randomized to "test and treat" or to prompt upper endoscopy for the evaluation of dyspeptic symptoms (38). After 1 year, the RR of remaining symptomatic was 0.95 (95% CI 0.92–0.99) in favor of prompt endoscopy. However, costs were lower with the "test and treat" approach. Prompt endoscopy for all patients with dyspepsia is neither feasible nor cost-effective.

Functional dyspepsia

A Cochrane systematic review published in 2006 concluded that there was a small but statistically significant benefit of treating *H. pylori* infection in patients with FD (39). In 17 RCTs comprising over 3500 patients, the RR reduction seen with treatment of *H. pylori* infection was 10% (95% CI 6–14%) and the number needed to treat (NNT) to cure one patient with FD was 14 (95% CI 10–25) (39). A subsequent update of that Cochrane review included 21 trials comprising 4331 patients (40). Most trials assessed patients' symptoms 12 months after treatment. This study validated the NNT of 14 but with a narrower 95% CI (10–20).

The Rome IV criteria have suggested subgrouping patients with FD into two groups, epigastric pain syndrome (epigastric pain and/or burning) or post-prandial distress syndrome (meal-related early satiation and/or fullness), while acknowledging that there may be considerable overlap between these (41). Although treatment trials have not utilized these newest criteria, improvement has been shown for patients with either predominant epigastric pain or predominant dysmotility-type symptoms following eradication of *H. pylori* infection (40).

Since some FD patients with *H. pylori* infection experience durable benefit following eradication therapy, we recommend testing for, and treating, *H. pylori* in patients with FD. This aligns with a recent guideline by the American Gastroenterological Association, which recommends collecting biopsies of normal-appearing gastric mucosa to test for *H. pylori* when performing endoscopy in patients with dyspeptic symptoms (42).

At the time of preparing this guideline, the ACG and the Canadian Association of Gastroenterology were in the process of preparing a joint guideline on management of uninvestigated dyspepsia and FD (43).

Gastroesophageal reflux disease (GERD)

There is no proven causal association between *H. pylori* infection and GERD. On a geographical basis, there is a negative association between the prevalence of *H. pylori* infection and the prevalence and severity of GERD (44). Barrett's esophagus is more common among individuals who are not infected with *H. pylori* (45). The risk of esophageal adenocarcinoma among patients with Barrett's esophagus is lower among those with *H. pylori* infection (45).

The ACG's 2007 guideline on *H. pylori* (26) reviewed the evidence for any change in GERD symptoms or severity following eradication of *H. pylori* infection. In North Americans who acquire *H. pylori* infection, the most likely phenotype is antral-predominant gastritis, hypergastrinemia, parietal cell hyperplasia, and increased gastric acid secretion. Such individuals who also have GERD may experience an improvement in GERD symptoms following eradication of *H. pylori* infection as gastric acid secretion slowly decreases in association with resolution of antral-predominant gastritis and hypergastrinemia (46). In a *post hoc* analysis of eight RCTs of the treatment of *H. pylori* infection in duodenal ulcer patients, there was no significant difference in the development of erosive esophagitis or GERD symptoms between those with successful and failed eradication (47). Among patients with pre-existing GERD, there was a worsening of symptoms in 7% of those cured of the infection and in 15% of those with persistent infection (OR=0.47; 95% CI 0.24–0.91; *P*=0.02).

It is theoretically possible, however, that patients with corpus-predominant gastritis may experience onset or worsening of GERD symptoms following *H. pylori* eradication as a consequence of restitution of parietal cell mass and increased gastric acid secretion. However, this scenario should be relatively uncommon in North America.

In a community-based study from the UK (the Bristol Helicobacter Project), treatment for *H. pylori* infection was not associated with an increase in the prevalence of heartburn or other reflux symptoms (48). Similarly, treatment for *H. pylori* infection did not improve reflux symptoms in patients with pre-existing symptoms.

A systematic review of 27 published studies concluded that eradication of *H. pylori* infection from patients with duodenal ulcer did not predispose to the development of GERD (49) or worsen symptoms in patients with established GERD (49).

Others have reported that cure of *H. pylori* infection in patients with erosive esophagitis before starting PPI therapy does not influence healing rates or symptom response (50–52).

Therefore, based upon currently available evidence, there is no indication to test a patient with typical GERD symptoms for *H. pylori* infection unless that patient also has a history of PUD or dyspeptic symptoms. Patients with GERD who are tested for *H. pylori* infection for any reason and who are found to be positive should be offered treatment for the infection acknowledging that GERD symptoms are unlikely to improve. Long-term treatment with PPIs in *H. pylori*-positive individuals with corpus-predominant gastritis may promote the development of atrophic gastritis (53,54). Although eradication of the infection before initiating PPI therapy may prevent the progression to atrophic gastritis (55), the clinical relevance of this is unclear.

Low-dose aspirin use

Aspirin (acetylsalicylic acid, ASA) is frequently recommended for patients with cardiovascular risk factors or following a major

cardiovascular event (56). ASA use increases the risk of upper GI tract ulceration. *H. pylori* infection is a recognized risk factor for the development of ulcers and for ulcer bleeding during low-dose ASA treatment (57,58).

In a study conducted in Canada, Australia, the UK and Spain, the prevalence of peptic ulcer at endoscopy among 187 middle-aged and elderly patients taking ASA in doses of 75–325 mg daily was 10.7% (95% CI 6.3–15.1%) (59). *H. pylori* infection was a significant risk factor for ASA-related duodenal ulcer (OR=18.5; 95% CI 2.3–149.4) but not for gastric ulcer (OR=2.3; 95% CI 0.7–7.8).

In a study from Hong Kong, patients with an episode of peptic ulcer bleeding while on low-dose ASA were studied according to *H. pylori* status (60). Those who were cured of *H. pylori* infection and subsequently re-started on ASA, had a similar rate of recurrent ulcer bleeding as in a previously ASA-naive cohort without bleeding who were started on low-dose ASA. Thus, eradication of *H. pylori* infection from patients with ASA-associated ulcer bleeding reduces the risk of recurrent bleeding.

Regarding other anti-platelet agents, the 2010 expert consensus document jointly prepared by the ACG, the American College of Cardiology Foundation and the American Heart Association acknowledged that *H. pylori* infection was an established risk factor for upper GI bleeding among patients using thienopyridine anti-platelet agents (61) but made no specific recommendations concerning testing for, or treating, the infection in patients taking these medicines. However, testing for *H. pylori* will commonly be indicated in patients using these agents since most will also be taking ASA.

In the absence of a prospective randomized study addressing *H. pylori* eradication in North American patients at increased risk for adverse cardiovascular outcomes, we suggest testing for *H. pylori* when starting prophylactic low-dose aspirin, while acknowledging that the evidence base for this recommendation is weak.

Non-steroidal anti-inflammatory drug (NSAID) use

H. pylori infection is an independent risk factor for NSAID-induced ulcers and ulcer bleeding (62,63). Eradication of *H. pylori* infection before starting NSAID treatment reduces the development of ulcers and risk of ulcer bleeding (64,65).

A 2005 meta-analysis of five RCTs suggested that eradication of *H. pylori* infection among patients taking NSAIDs was associated with a 57% reduction in the incidence of peptic ulcer (OR=0.43; 95% CI 0.20–0.93) (66). The benefits of *H. pylori* eradication were greatest in patients who were previously NSAID-naive. Eradication of *H. pylori* infection before starting NSAID therapy may be the single most cost-effective strategy for the primary prevention of NSAID-associated ulcers in adult patients (67).

The benefit of *H. pylori* eradication in patients already taking NSAIDs is less clear (68). RCTs suggest that *H. pylori* eradication does not reduce the incidence of new peptic ulcers in chronic NSAID users (69) and that PPI therapy provides a more effective ulcer risk reduction strategy than *H. pylori* eradication in patients on chronic NSAIDs (66).

The ACG's most recent practice guideline on the prevention of NSAID-related ulcer complications (63) concluded that *H. pylori* infection increases the risk of NSAID-related GI complications, that there would be at least a potential advantage of testing for the infection in patients requiring long-term NSAID therapy, and that the infection should be eradicated when identified.

Iron deficiency anemia

H. pylori infection has been associated with ID and iron deficiency anemia (IDA). In a meta-analysis of observational studies, the pooled ORs for ID and IDA in *H. pylori*-infected individuals were 1.4 (95% CI 1.2–1.6) and 2.0 (95% CI 1.5–2.9), respectively. A separate meta-analysis of 15 observational studies also found that IDA was more prevalent in *H. pylori*-infected individuals compared with *H. pylori*-negative controls (OR=2.2; 95% CI 1.5–3.2) (70). Adolescents with IDA have been reported to have a higher prevalence of *H. pylori* infection than non-anemic controls (71).

H. pylori-infected adolescents and adults with IDA respond to oral iron therapy whether or not accompanied by treatment for *H. pylori* infection. However, the response to iron therapy in *H. pylori*-infected patients with IDA may be enhanced by the concomitant eradication of the infection (71,72). A meta-analysis of 16 RCTs conducted among patients with IDA and *H. pylori* infection found statistically significant differences in favor of *H. pylori* eradication with oral iron over oral iron alone for increases in hemoglobin (Hgb), serum iron and serum ferritin (SF) levels ($P<0.00001$ for each) (73). In a separate meta-analysis of four interventional trials, the weighted mean difference in Hgb levels in favor of combined eradication treatment and oral iron vs. oral iron alone was 4.1 g/dl (95% CI −2.6–10.7); that for SF levels in five trials was 9.5 µg/l (95% CI −0.5–19.4) (70).

A Cochrane systematic review is being conducted on the topic of the eradication of *H. pylori* infection for ID but its findings have not yet been reported (74).

Idiopathic thrombocytopenic purpura (ITP)

There is evidence from small randomized and non-randomized trials for a sustained improvement in platelet counts after eradication of *H. pylori* infection in a proportion of adult patients with ITP (75–77). The evidence is less compelling for children with ITP (78).

A systematic review of 25 studies (1555 adult patients), all of which included at least 15 patients, found that platelet counts in ITP patients tended to increase after *H. pylori* eradication (79). Among 696 evaluable patients, 43% achieved a complete response (defined as a platelet count $\geq 100\times10^9$/l), and an additional 50% had an overall response (defined as a platelet count $\geq 30\times10^9$/l and at least a doubling of the baseline platelet count). Response rates were lower in patients with a baseline platelet count of $<30\times10^9$/l. In general, response rates were higher in regions with high background *H. pylori* prevalence and in patients with mild degrees of thrombocytopenia.

In their practice guideline published in 2011 (80), the American Society of Hematology (ASH) suggested that "screening for

H. pylori infection be considered in adults with ITP in whom eradication therapy would be used if testing is positive" (evidence grade 2C). The ASH also recommended that eradication therapy be administered to adults with ITP who were found to have *H. pylori* based on a test of active infection (evidence grade 1B). The ASH has recommended against testing children with ITP for *H. pylori* infection (80).

Asymptomatic individuals and the risk of gastric cancer

Evidence that eradication of *H. pylori* infection reverses the gastric premalignant changes of gastric atrophy and intestinal metaplasia is conflicting. A meta-analysis of 12 studies (2658 patients) published up until 2009 reported that eradication was associated with a significant reduction in atrophic gastritis in the corpus (P=0.006) but not in the antrum (P=0.06); there was no evidence for a significant effect on intestinal metaplasia in either the corpus (P=0.42) or antrum (P=0.76) (81).

A Cochrane systematic review and meta-analysis examined six RCTs (five of which were in Asian populations) that studied the effects of *H. pylori* eradication treatment against either placebo or no treatment on the subsequent development of gastric cancer among asymptomatic and otherwise healthy-infected adults (82). All trials followed subjects for at least 2 years. The quality of evidence was assessed as moderate. The subsequent incidence of gastric cancer was 1.6% among 3294 treated individuals and 2.4% among 3203 untreated controls (RR=0.66; 95% CI 0.46–0.95). The overall NNT was 124 (95% CI 78–843). However, assuming that the benefits of *H. pylori* eradication persist for life, the NNT could be as low as 15 among Chinese men. Since the lifetime risk of gastric cancer is lower in the United States, the corresponding NNT to prevent one case here would be 95 for men and 163 for women.

A recent meta-analysis of 24 studies, 22 of which were conducted in Asia, showed that treatment of *H. pylori* infection in asymptomatic, infected adults led to a reduced incidence of gastric cancer. The greatest benefit was seen in people living in regions with the highest incidence of gastric cancer; reported RRs for regions of low, intermediate and high incidence of gastric cancer were, respectively, 0.80, 0.49, and 0.45 (34).

Other gastrointestinal and non-gastrointestinal disorders

Associations have been proposed between *H. pylori* infection and numerous other disorders (83). In most cases, biological plausibility and the level of evidence to support a causal association has been weak to non-existent. Thus, no formal recommendation can be offered.

Controlled trials have suggested a benefit of *H. pylori* eradication in healing lymphocytic gastritis (84) and inducing regression of hyperplastic gastric polyps (85).

There is some data to suggest a weak association between *H. pylori* infection and hyperammonemia and hepatic encephalopathy (HE) in patients with cirrhosis (86); trials evaluating *H. pylori* therapy in patients with HE have yielded conflicting results.

In a meta-analysis of observational studies, the prevalence of *H. pylori* infection in pregnant women with hyperemesis gravidarum was higher than in matched controls (87).

An association between *H. pylori* infection and major cardiovascular events including myocardial infarction and stroke has been postulated. However, evidence is of low quality and insufficient to establish causality (88).

A Cochrane systematic review of *H. pylori* infection in Parkinson's disease (89) identified three clinical trials and concluded that there was insufficient evidence to support screening for *H. pylori* infection in this population. Limited evidence suggests that symptoms of Parkinson's may improve with *H. pylori* eradication, perhaps due to increases in the absorption and bioavailability of levodopa. Further randomized, controlled trials were encouraged.

An evidence-based review of treating *H. pylori* infection in patients with urticaria found only low-quality evidence (90); nine out of 10 trials identified showed no benefit from *H. pylori* eradication.

A meta-analysis has reported higher levels of glycosylated hemoglobin in *H. pylori*-positive patients with type 1 diabetes compared with non-infected patients (91). However, glycemic control did not improve in the short term following eradication of *H. pylori*.

An inverse association has been reported between the prevalence of *H. pylori* infection and obesity (92). There may also be a weak inverse association between *H. pylori* infection and allergic or atopic disorders (93,94) including eosinophilic esophagitis (95–100) as well as celiac disease (101) and inflammatory bowel disease (102).

QUESTION 3: WHAT ARE EVIDENCE-BASED FIRST-LINE TREATMENT STRATEGIES FOR PROVIDERS IN NORTH AMERICA?

Recommendations

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 option 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)).

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)).

H. pylori is an infectious disease that is typically treated with combinations of 2–3 antibiotics along with a PPI, taken concomitantly or sequentially, for periods ranging from 3 to 14 days. In clinical practice, the initial course of eradication therapy, heretofore referred to as "first-line" therapy, generally offers the greatest likelihood of treatment success. Thus, careful attention to the selection of the most appropriate first-line eradication therapy for an individual patient is essential. There is no treatment regimen which guarantees cure of *H. pylori* infection in 100% of patients. Indeed, there are currently few, if any regimens which consistently achieve eradication rates exceeding 90% (103). In developing this guideline for North America, we conducted comprehensive literature searches to identify randomized, controlled trials which have evaluated the efficacy of treatment regiments in the United States and Canada. Wherever possible, we have tried to highlight these data and use them to develop treatment recommendations. Unfortunately, although *H. pylori* was the subject of many randomized, controlled trials conducted in North America during the first decade of this century, the number of treatment trials assessing modern regimens is modest to non-existent. As such, we were forced to rely upon clinical trial data generated in other parts of the world when considering a number of regimens. Development of this guideline has made clear the need for clinical trials to evaluate the efficacy of modern treatment regimens and organized efforts to monitor *H. pylori* antibiotic resistance in North America. To provide readers a sense of the author's preferences, we have taken the liberty of utilizing the words "recommended" vs. "suggested" in the italicized statements that address each of the treatment regimens. A listing of available first-line treatment options can be found in **Table 2**. A schema to assist providers to choose the best therapy for an individual patient can be found in **Figure 1**.

With very few exceptions, the most common adverse events associated with antibiotics used to treat *H. pylori* infection are gastrointestinal in origin (for example: nausea, dysgeusia, dyspepsia/abdominal pain, diarrhea). As such, we have not listed adverse events for most of the therapies. Where unusual adverse events can occur with a specific therapy, we have tried to point that out.

Clarithromycin triple therapy

The previous ACG guideline from 2007 recommended 14 days of treatment with a PPI, clarithromycin, and amoxicillin (clarithromycin-based triple therapy) or—in patients with an allergy to penicillin—metronidazole as an alternative to amoxicillin. At that time, eradication rates for clarithromycin triple therapy were reported to be 70–85% and were highly influenced by the underlying rate of clarithromycin resistance (26). However, there has been growing concern regarding the efficacy of clarithromycin triple therapy. Key questions which were considered while preparing this document included the expected eradication rate of clarithromycin triple therapy in North America, the most appropriate duration of therapy, and whether eradication rates have been dropping over time.

There are data from other parts of the world to suggest that eradication rates for clarithromycin triple therapy are below 80% (103). In preparing this updated guideline, we identified all randomized, controlled trials conducted in the United States or Canada which have assessed the efficacy of this regimen since 2000 (100,104–119). Consistent with other meta-analyses, eradication rates with 7 or 10 days of clarithromycin triple therapy in studies from the US or Canada were indeed below 80%. Eradication rates with 14 days of triple therapy were higher, but only two study arms with 195 subjects were included. This finding is consistent with the most recent and most complete meta-analysis or the world's literature on this topic which was published by the Cochrane Collaboration (120). For clarithromycin triple therapy, higher eradication rates were reported with 14 vs. 7 days of treatment (34 studies, RR 0.65, 95% CI 0.57–0.75; NNT 12, 95% CI 9–16), and with 14 vs. 10 days (10 studies, RR 0.69, 95% CI 0.52–0.91). Based upon the available data, when triple therapy is utilized in North America, it should be given for 14 days.

The lack of recent RCT data on clarithromycin triple therapy makes it difficult to confidently report on temporal trends in eradication rates. To address this issue, we conducted a retrospective analysis of eradication rates for clarithromycin triple therapy at the University of Michigan from 2001–15. Data was divided into 5-year blocks and eradication rates for 10–14 days of triple therapy when given first-line were calculated. In 662 patients, the overall eradication rate was 79.5% (95% CI 77.2–82.4%) with no significant difference in eradication rates for the 3, 5-year blocks (**Figure 2**, unpublished data).

The impact of clarithromycin resistance on the efficacy of clarithromycin triple therapy is well documented. A 2010 meta-analysis reported an eradication rate of 22% for clarithromycin-resistant *H. pylori* strains compared with 90% for clarithromycin-sensitive strains (121). As such, clarithromycin triple therapy should not be utilized in areas where the rate of clarithromycin resistance is known to be high. The Maastricht/Florence Consensus document published in 2012 recommended against using triple therapy when the rate of underlying clarithro-

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

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]			
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
	Levofloxacin (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.

mycin resistance exceeds 15–20% (55). Although current large scale data on *H. pylori* antibiotic resistance in North America are unavailable, recent data from Houston suggest that clarithromycin resistance rates may now fall within that range (122). In the absence of local or even regional *H. pylori* antibiotic resistance data, it is very important to ask patients about previous exposure to antibiotics for any reason, particularly macrolides and fluoroquinolones, as this provides a proxy for underlying *H. pylori* antibiotic resistance (123,124). A recent study confirmed an association between number of previous antibiotic exposures and an increasing risk for antibiotic resistance (125). Similarly, duration of previous macrolide therapy for greater than 2 weeks is also associated with a greater risk of treatment failure with clarithromycin triple therapy (126).

Based upon the available data, we conclude that clarithromycin triple therapy consisting of a PPI, clarithromycin, and amoxicillin or metronidazole for 14 days remains a first-line treatment option in regions where *H. pylori* clarithromycin resistance is known to be low. In regions where clarithromycin resistance exceeds 15%, as may well be the case in many parts of North America, clarithromycin triple therapy should be avoided. All patients should be asked about previous macrolide exposure for any reason. In those with previous macrolide exposure, clarithromycin triple therapy should be avoided.

Bismuth quadruple therapy

The previous ACG guideline also endorsed the use of 10–14 days of bismuth quadruple therapy composed of a PPI or histamine-2

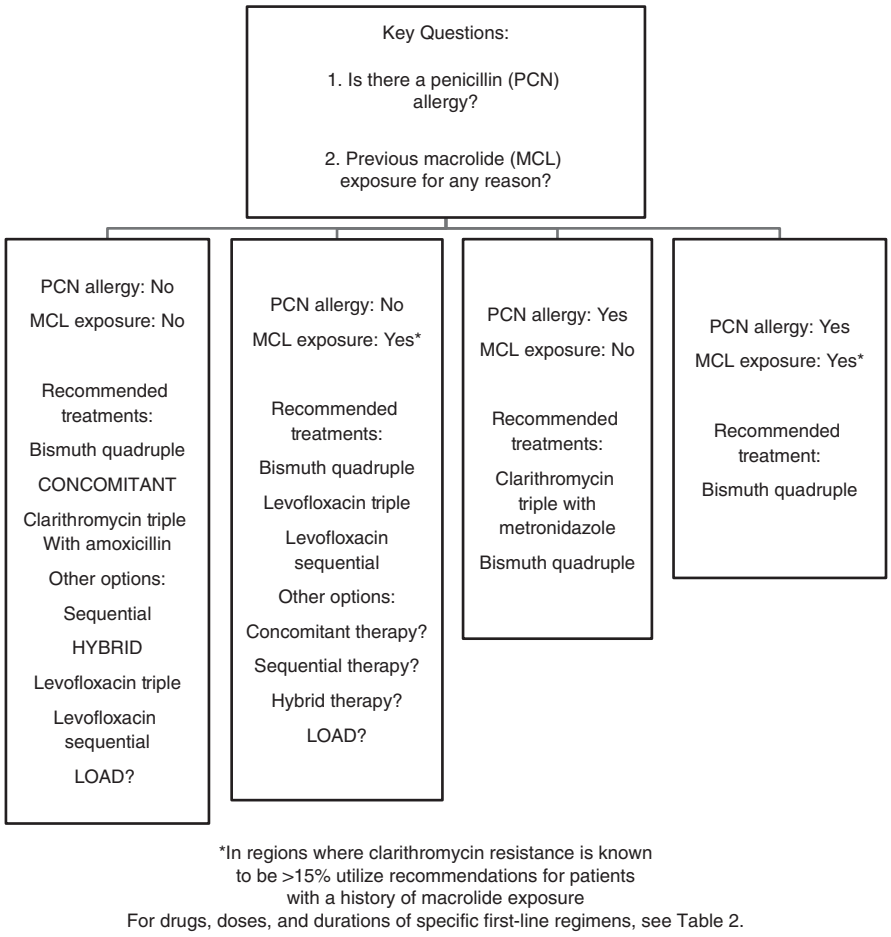

Figure 1. Selection of a first-line *H. pylori* treatment regimen.

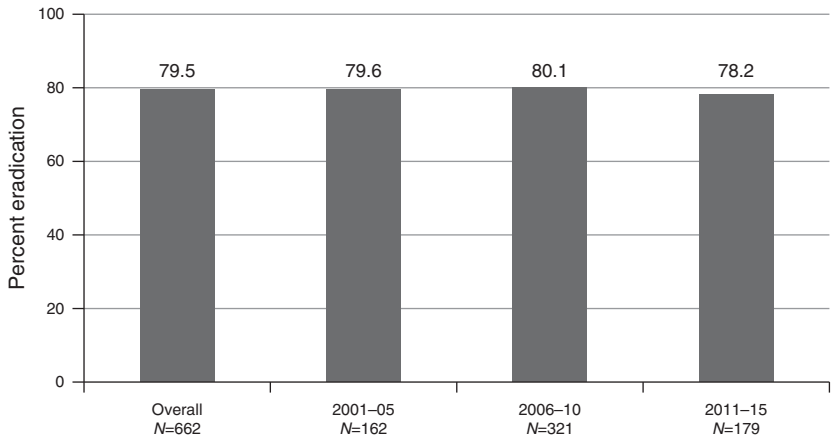

Figure 2. Eradication rates with first-line clarithromycin triple therapy at the University of Michigan (2001–2015).

receptor antagonist, bismuth, metronidazole, and tetracycline. There is very limited data on the efficacy or comparative effectiveness of bismuth quadruple therapy in North America. A literature search identified only two RCTs which included a bismuth quadruple therapy arm (n=172). The mean eradication rate with this regimen given for 10 days was 91% (95% CI; 81–98%).

A meta-analysis of studies from around the world comparing clarithromycin triple and bismuth quadruple therapies suggested

that the two treatments had similar efficacy, compliance, and tolerability (121). An updated meta-analysis, which included 12 RCTs and 2753 patients, reported intention-to-treat (ITT) eradication rates of 77.6% with bismuth quadruple therapy vs. 68.9% with clarithromycin triple therapy (risk difference=0.06, 95% CI; −0.01 to 0.13). There was significant heterogeneity in the data set, in part attributable to differences in treatment duration, drug dosing, and location. Ten days of bismuth quadruple therapy was found to be more effective than 7 days of clarithromycin triple therapy. However, no significant differences in efficacy of the two regimens were identified when given for 10–14 days (127). The most recent network meta-analysis of *H. pylori* regimens also found that 10–14 days of bismuth quadruple therapy was superior to 7 days of clarithromycin triple therapy (85 vs. 73%, RR=1.17; 95% CI=1.12–1.21) (103). Based upon these data, a treatment duration of 10–14 days is recommended for bismuth quadruple therapy. For a time, there were supply issues with tetracycline in the United States which limited access to bismuth quadruple therapy. These issues have now been resolved.

Unlike clarithromycin triple therapy, the efficacy of bismuth quadruple therapy is not affected by clarithromycin resistance. Further, although metronidazole resistance does have an impact on the efficacy of bismuth quadruple therapy, it is not nearly as profound as that of clarithromycin resistance on clarithromycin triple therapy (127). As such, in regions where the rate of clarithromycin resistance is known to be high or if a patient has previously been treated with macrolides for any reason, bismuth quadruple therapy should be strongly considered as the initial treatment choice.

Concomitant therapy

So-called "concomitant therapy" consists of a PPI, amoxicillin, clarithromycin, and a nitroimidazole (tinidazole or metronidazole) given together for 3–10 days (128). No RCTs from North America have assessed the efficacy of concomitant therapy. A meta-analysis of 19 clinical trials of concomitant therapy which included 2070 patients with *H. pylori* infection revealed a mean cure rate of 88% (95% CI, 85–91%). In RCTs which compared concomitant therapy (481 patients) with clarithromycin triple therapy (503 patients), the ITT cure rates were 90% and 78%, respectively (OR, 2.36; 95% CI, 1.67–3.34)(129). Nearly all of the trials evaluated were performed in Europe or Asia, with one study performed in Latin America. A recent network meta-analysis yielded very similar results (103). In a comprehensive meta-analysis of sequential therapy, no differences were found in the efficacy of sequential therapy for 10 days (81.3%, 95% CI, 74.9–87%) vs. concomitant therapy for 5–10 days (81.7%, 95% CI, 76.1–86.7%) based upon data from six studies with over 2000 patients (130).

In the meta-analysis by Gisbert, longer durations of therapy were associated with a trend toward higher cure rates (129). A recent large, multicenter, randomized trial in Latin America reported that 14 days of clarithromycin triple therapy yielded higher cure rates than 5 days of concomitant therapy (82.2 vs. 73.6%, respectively; difference=8.6%, 95% CI, 2.6–14.5%) (131) indirectly supporting a duration for concomitant therapy of at least 7 days. At present, there are no RCTs which have evaluated the efficacy of concomitant therapy for 14 days. Limited data suggest that the efficacy of concomitant therapy may be reduced in patients with clarithromycin-resistant *H. pylori* infection but to a lesser degree than with clarithromycin triple therapy (129). The tolerability and compliance reported in trials with concomitant therapy is similar to clarithromycin triple therapy or sequential therapy (103,130).

Acknowledging the lack of data from North America, we conclude that concomitant therapy is a promising treatment option that has produced high cure rates in international studies but awaits validation in North America. Because concomitant therapy is at least as effective as clarithromycin triple therapy with similar tolerability, it can be considered as a recommended first-line treatment option for North America. If concomitant therapy is recommended, a duration of at least 10–14 days seems appropriate. Studies to assess whether extending the duration of concomitant therapy to 14 days results in improved eradication are eagerly awaited.

Sequential therapy

Sequential therapy, consisting of a PPI plus amoxicillin for 5 days, followed by a PPI, clarithromycin, and a nitroimidazole for an additional 5 days, was introduced in 2000 as an alternative to clarithromycin triple therapy (132). A recent systematic review and meta-analysis identified 46 RCTs including 13,532 patients which compared sequential therapy to established and newer therapies (130). The overall eradication rate for sequential therapy was 84.3% (95% CI, 82.1–86.4%). Sequential therapy was superior to 7 days of clarithromycin triple therapy (RR 1.21; 95% CI, 1.17–1.25). However, sequential therapy was only marginally superior to 10 days of clarithromycin-based triple therapy (RR, 1.11; 95% CI, 1.04–1.19) and was not superior to 14 days of clarithromycin-based triple therapy (RR, 1.00; 95% CI, 0.94–1.06) or 10–14 of bismuth quadruple therapy (RR, 1.01; 95% CI, 0.95–1.06).

The efficacy of sequential therapy is subject to significant geographic variation. Although studies from Italy have reported high eradication rates (133), a multicenter trial which enrolled 1463 adults from six Latin American countries found that 14 days of clarithromycin triple therapy yielded a higher eradication rate than 10 days of sequential therapy (82.2 vs. 76.5%, difference, 5.6%; 95% CI, −0.04% to 11.6%) (131). Another large study from Taiwan identified reduced eradication rates with sequential therapy when clarithromycin resistance was present, although to a lesser degree than with clarithromycin triple therapy. This study was also one of the first to suggest that eradication rates might be improved by extending the duration of sequential therapy to 14 days (134).

A literature search identified only two RCTs which have evaluated sequential therapy in the United States and Canada (100,104). In an abstract presented in 2014, investigators from Dallas, Texas randomized 134 patients with *H. pylori* infection to 10 days of sequential therapy or clarithromycin triple therapy. No significant difference in eradication rates between the two treatments

was observed (RR 0.95; 95% CI 0.79–1.15). In a second trial from Canada, 126 patients were randomized to 10 days of sequential therapy or clarithromycin triple therapy. This trial also failed to identify a significant difference in the efficacy of the two regimens (RR 0.83, 95% CI 0.62–1.06). A random effects meta-analysis of these two trials revealed a pooled RR of 0.91 (95% CI, 0.78–1.06). Tolerability and compliance with sequential therapy appear to be similar to clarithromycin triple therapy (103).

On the basis of the available data, 10 day sequential therapy appears to be a viable alternative to 14 day clarithromycin triple therapy. However, 10 day sequential therapy cannot be endorsed as superior to 14 day clarithromycin triple therapy in North America. Also, the complexity of sequential therapy detracts from its relevance as a first-line treatment option in North America. Extending sequential therapy to 14 days may improve the eradication rate but further research is necessary to confirm the encouraging preliminary results reported in other parts of the world.

Hybrid therapy

Hybrid therapy represents a cross between sequential and concomitant therapies. Hybrid therapy consists of a PPI and amoxicillin for 7 days followed by another 7 days of PPI, amoxicillin, clarithromycin, and a nitroimidazole (135).

To date, there have been no RCTs which have evaluated the efficacy or tolerability of hybrid therapy in North America. Several recent meta-analyses have summarized results from RCTs conducted in other parts of the world (103,136,137). A meta-analysis by Wang *et al.* (136) identified six RCTs which assessed hybrid therapy vs. sequential and/or concomitant therapy. When data from the hybrid therapy treatment arms were pooled, the ITT eradication rate was 88.6%. This ITT eradication rate was confirmed by two other recent meta-analyses (Li 89% (95% CI, 81–94%); He 86.6% (95% CI, 82–91%)(103,137). Hybrid therapy appears to be more effective than the 7-day clarithromycin triple therapy (89 vs. 73%, Network meta-analysis RR 1.22; 95% CI 1.11–1.29) (103). Tolerability of hybrid therapy is similar to clarithromycin triple therapy (103). Further, there appear to be no significant differences in the efficacy, tolerability, or compliance observed with hybrid, sequential, or concomitant therapies (136,137).

Acknowledging the lack of data from North America, we conclude that a 14 day course of hybrid therapy is a promising treatment option that has produced high cure rates in international studies but awaits validation in North America. Because hybrid therapy is at least as effective as clarithromycin triple therapy with similar tolerability, it is a suggested treatment alternative to clarithromycin triple therapy. Though hybrid and concomitant therapies perform similarly in RCTs, the complexity of hybrid therapy may dampen enthusiasm for its use in clinical practice.

Levofloxacin-based therapies

Levofloxacin is a fluoroquinolone which has *in vitro* antimicrobial activity against Gram-positive and Gram-negative bacteria including *H. pylori* and has been utilized in first-line and salvage regimens. Levofloxacin has primarily been used as first-line therapy in three types of regimens: triple therapy with a PPI and amoxicillin, modified sequential therapy consisting of 5–7 days of a PPI and amoxicillin followed by 5–7 days of a PPI, levofloxacin, and a nitroimidazole, or quadruple therapy composed of levofloxacin, a PPI, nitazoxanide, and doxycycline administered for 7 or 10 days.

There are no RCTs which have assessed the efficacy of first-line levofloxacin triple therapy in North America. A meta-analysis of seven trials from other parts of the world found that levofloxacin triple therapy for 7 days and clarithromycin triple therapy for 7 days yield similar eradication rates (79 vs. 81%, respectively, risk ratio 0.97, 95% CI, 0.93–1.02) (138). Another meta-analysis which included nine studies and 2502 patients confirmed these results and identified significant regional variation in eradication rates with levofloxacin triple therapy favored in Europe and clarithromycin triple therapy favored in Asia (139). On the other hand, in the network meta-analysis by Li *et al.* (103), levofloxacin triple therapy for 10–14 days proved superior to clarithromycin triple therapy for 7 days (90%, 95% CI, 84–94 vs. 73%, 95% CI, 71–75%; RR 1.23, 95% CI, 1.16–1.29). Although not formally compared, the pooled eradication rate of levofloxacin triple therapy was also higher than clarithromycin triple therapy for 10–14 days (81%, 95% CI, 78–84%). Tolerability of levofloxacin triple therapy appears to be similar to clarithromycin triple therapy (103,138).

Levofloxacin and ciprofloxacin have also been utilized in modified versions of sequential therapy consisting of a PPI and amoxicillin for 5–7 days followed by a PPI, fluoroquinolone, and nitroimidazole for 5–7 days. There are no studies from North America which have evaluated the efficacy or tolerability of fluoroquinolone sequential therapy. A meta-analysis which included six trials and 738 treatment-naive patients with *H. pylori* infection from other parts of the world compared the efficacy of flouroquinolone sequential therapy for 10–14 days vs. clarithromycin triple therapy for 7–14 days or standard sequential therapy for 10 days. Using a random effects model, the pooled eradication rate with fluoroquinolone sequential therapy was 87.8% vs. 71.1% for clarithromycin triple and standard sequential therapies (RR 1.21, 95% CI, 1.09–1.35). A subgroup analysis demonstrated superiority of levofloxacin sequential therapy vs. clarithromycin triple therapy (83.6% vs. 64%, RR 1.32, 95% CI, 1.09–1.60) or standard sequential therapy (87.4% vs. 78.9%, RR 1.12, 95% CI, 1.04–1.21). Fluoroquinolone sequential therapy eradication rates were not sensitive to duration of therapy, choice of PPI, or fluoroquinolone dose. The incidence of total adverse events and study discontinuations was similar between groups (140).

A first-line quadruple regimen, referred to as "LOAD" consists of levofloxacin, omeprazole, nitazoxanide (*Alinia*), and doxycycline. In an open-label, randomized study of 270 patients conducted in the United States, LOAD given for 7 or 10 days, yielded eradication rates of 89 and 90% compared with 73% with a 10-day course of lansoprazole, amoxicillin, and clarithromycin (106). No data were provided in the manuscript regarding the impact of levofloxacin resistance on the efficacy of LOAD therapy, and additional trials using this unconventional and expensive regimen are awaited.

Similar to many of the other newer therapies for *H. pylori*, there is a paucity of North American data addressing the efficacy of levofloxacin-containing first-line treatment regimens. There is little data to guide clinicians on either fluoroquinolone resistance rates in North America or the impact of resistance on the efficacy of fluoroquinolone-containing treatment regimens. The little data that exist, suggest that fluoroquinolone resistance may be as high—or perhaps even higher—than clarithromycin resistance in North America (122,141,142). Levofloxacin triple therapy for 10–14 days appears to provide a comparable alternative to clarithromycin triple therapy. Of the available options, fluoroquinolone-containing sequential therapy for 10–14 days or LOAD therapy for 7–10 days appear most promising.

Role of probiotics in first-line therapy

There is growing interest in the United Statese of probiotics as adjuvant therapy in the treatment of *H. pylori* infection. Emerging evidence suggests an inhibitory effect of *Lactobacillus* and *Bifidobacterium* species on *H. pylori*. Furthermore, these probiotic strains may also help to reduce the side effects of eradication therapies and improve compliance with therapy (143,144).

A recent meta-analysis of 10 clinical trials of adjuvant probiotics in patients with *H. pylori* infection demonstrated increased cure rates with probiotic supplementation (pooled OR, 2.07; 95% CI, 1.40–3.06) (143). Probiotics also reduced the incidence of total side effects (pooled OR, 0.31; 95% CI, 0.12–0.79). However, most of these studies were performed in China, and were at high risk of bias due to lack of blinding, and inadequate concealment of allocation. Furthermore, there was great variability in the probiotics used, as well as in the treatment regimens employed. Although probiotic therapy for *H. pylori* infection seems promising, many important questions remain, including the optimal dose, the time of dosing (before, during, or after eradication therapy), and the duration of therapy.

QUESTION 4: WHAT FACTORS PREDICT SUCCESSFUL ERADICATION WHEN TREATING *H. PYLORI* INFECTION?

Recommendation

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).

Determinants of successful *H. pylori* eradication can be divided into host and *H. pylori*-related factors. Of host-related variables, adherence was identified as an important factor predicting *H. pylori* eradication in an early report of a triple bismuth-tetracycline-metronidazole combination (145). Subsequent studies have found that drop-out rates in clinical trials are linked to the number of medication doses given per day (146). The likelihood and severity of adverse events also influence adherence. However, patients are more likely to comply with a regimen if they are aware of potential adverse events that might occur and understand which ones warrant discontinuation of therapy. (147). For these reasons, it is important to have a full and frank discussion with the patient about the benefits and challenges of the *H. pylori* eradication regimen to maximize the likelihood of adherence.

Genetic factors may also influence the success of *H. pylori* eradication therapy (148). For example, PPIs are an important component of *H. pylori* eradication regimens. Multiple mechanisms have been proposed to explain their inhibitory effects on *H. pylori* therapy, including direct antibacterial properties, as well as decreasing intragastric acidity to enhance antibiotic effects within the gastric mucosa and lumen. Polymorphisms of *CYP2C19*, a component of the hepatic cytochrome P450 system, determine the rate at which PPIs are metabolized. They have been especially associated with the success of PPI-containing regimens in studies from Southeast Asia where loss of function *CYP2C19* variants are relatively common (10–20% of the population, compared with <5% in the United States). The "poor metabolizer" variants result in increased bioavailability of the PPI, more profound acid inhibition and significantly improved *H. pylori* eradication rates. Effects of *CYP2C19* polymorphisms in North America have not been systematically evaluated.

A variety of other clinical variables have been suggested to play a role in the success of eradication therapy. Chief among these are cigarette smoking and diabetes mellitus which have been associated with treatment failure in separate meta-analyses (149,150). The summary ORs for treatment failure were 1.95 for smoking and 2.19 for diabetes. However, there were only eight studies in the diabetes analysis, including four from Turkey and none from North America. It is conceivable that these results might be confounded by reduced medication adherence or greater prior antibiotic exposure leading to antibiotic resistance since neither of these analyses controlled for these important factors.

Of *H. pylori*-related factors, antibiotic sensitivity has emerged as the single most important and consistent predictor of success in clinical trials and in population-based studies of *H. pylori* eradication (151–153). Resistance to clarithromycin, metronidazole and, increasingly, levofloxacin limits the success of the common eradication regimens in use today. The frequency of multi-drug resistance to these antibiotics appears to be increasing in prevalence. In general, *H. pylori* resistance to amoxicillin, tetracycline and rifabutin remains rare (under 5% for each currently).

As has already been mentioned, the presence of clarithromycin resistance reduces the success of clarithromycin triple therapy by ~50% (151,152). Levofloxacin resistance lowers success rates of levofloxacin-containing regimens by ~20–40%, although data addressing the clinical impact of levofloxacin resistance are very limited (154,155). For metronidazole, where *in vitro* resistance to *H. pylori* is quite high worldwide, the effect on *H. pylori* eradication is less predictable. Metronidazole resistance reduces eradication rates by ~25% in triple therapies but less so in quadruple therapies and when PPIs are included in the regimen (152). Increasing the dose and duration of metronidazole also improves outcomes in metronidazole-resistant strains, demonstrating that,

unlike clarithromycin and levofloxacin, *in vitro* metronidazole resistance is not an absolute predictor of eradication failure (156). Indeed, multiple mechanisms of metronidazole resistance in *H. pylori* have been described and the definition and measurement of metronidazole resistance among *H. pylori* strains remain to be adequately standardized.

QUESTION 5: WHAT DO WE KNOW ABOUT *H. PYLORI* ANTIMICROBIAL RESISTANCE IN THE NORTH AMERICA?

Recommendation

Data regarding antibiotic resistance among *H. pylori* strains from North America remain 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).

A multicenter European survey conducted in 2008–9, reported resistance rates of 35% for metronidazole, 17.5% for clarithromycin (double from 10 years earlier) and 14% for levofloxacin (124). Resistance was associated with outpatient use of quinolones and long-acting macrolides in individual European countries, suggesting that *H. pylori* antibiotic resistance is causally connected to community antibiotic utilization. Similarly, high resistance rates to clarithromycin and even higher resistance rates for metronidazole have been observed in some parts of South America (157) and most other regions of the world from which data exist (158). Generally speaking, antibiotic resistance rates have tended to increase over time (158) with rates as high as 50% for clarithromycin, 65% for metronidazole and 50% for levofloxacin reported recently in other parts of the world (158).

In comparison with the efforts of many countries to carefully sample strains and document antibiotic resistance rates in order to guide more rational treatment selection, there have been no organized attempts to track *H. pylori* resistance patterns in North America. The most recent US national sampling study, which included 347 strains collected from 11 hospitals during 1998–2002, reported resistance rates of 21% for metronidazole and 13% for clarithromycin (159). A decade later, among 128 cultured strains from the Houston VA Medical Center a similar 20% resistance rate for metronidazole was observed whereas resistance to clarithromycin had risen to 16% and levofloxacin resistance was at 31%. Multiple resistance was noted for 17% of strains and only half were susceptible to all five antibiotics tested (122). In an Alaskan native population sampled from 2000–8, resistance to metronidazole was 42%, clarithromycin 30% and levofloxacin 19% (141). Thus the sparse available data from North America suggest concerning rates of resistance to many of the antibiotics currently in use against *H. pylori.* (**Table 3**). This is perhaps not all that surprising given that Americans receive, on average, one outpatient antibiotic prescription per person per year, with the macrolide azithromycin the most frequently prescribed antibiotic (160). Caution should be exercised when considering the extension of this limited data set to a wider audience of people living in North America. These preliminary data emphasize the desperate need for organized surveillance of antibiotic resistance patterns in North America.

Table 3. Antibiotic resistance rates of *H. pylori* strains in the United States, 2009–2011

Antibiotic	Resistance rate (%)
Metronidazole	20
Clarithromycin	16
Levofloxacin	31
Tetracycline	<2
Amoxicillin	<2
Rifabutin	<2

Data based on single center study of 128 strains of *H. pylori* obtained from US veterans by Shiota *et al.* (122), and for rifabutin from review by Gisbert *et al.* (200).

QUESTION 6: WHAT METHODS CAN BE USED TO EVALUATE FOR *H. PYLORI* ANTIBIOTIC RESISTANCE AND WHEN SHOULD TESTING BE PERFORMED?

Recommendation

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.

Antibiotic resistance testing for *H. pylori* can be performed on isolates cultured from gastric biopsies. *H. pylori* culture takes several days and can be difficult to perform, even in experienced hands. The success of culturing *H. pylori* is further complicated by the recent use of PPIs or antibiotics. For these reasons, such testing is not available in most North American medical centers. When *H. pylori* culture is successful, several different methods exist to measure antibiotic sensitivity including agar dilution, disk diffusion and the E-test, with pros and cons described for each (156).

As an alternative, faster and simpler molecular methods have been developed and validated for fresh, frozen, or paraffin-embedded gastric mucosal biopsies; such testing has also been successfully applied to fecal samples, thus obviating the need for endoscopy. Molecular methods such as polymerase chain reaction or fluorescently-labeled nucleic acid hybridization can be used to identify many of the mutations known to be responsible for antibiotic resistance (161). Current testing focuses on a small number of mutations known to account for clarithromycin and levofloxacin resistance since these are currently felt to be the most important clinically. Clarithromycin resistance is usually due to point mutations in one of two sites in *H. pylori's* 23S ribosomal subunit RNA, although multiple other mutations elsewhere in 23SrRNA or other genes have been more rarely implicated. Levofloxacin resistance is normally caused by one of two point mutations within DNA gyrase subunit A. On the other hand, molecular techniques are

not suitable for identifying metronidazole resistance which can be due to multiple mechanisms. At present, molecular testing is not FDA- or CLIA-approved in the United States.

Usual treatment of a bacterial infection involves the selection of an antibiotic based upon the organism's *in vitro* sensitivity, or at least its likely sensitivity from knowledge of local microbiological data. In contrast, the treatment of *H. pylori* relies upon empiric trials of antibiotic therapies. Outside of the US, the increasing difficulty in eradicating *H. pylori* has prompted some experts to advocate for more liberal antibiotic resistance testing, especially after one or more failed treatments and particularly when antibiotic resistance is prevalent in the population. Thus, the Maastricht guidance document has recommended clarithromycin resistance testing before prescribing clarithromycin triple therapy when clarithromycin resistance is common (as it is in many regions) and especially after a second-line treatment has failed (55).

The merits of susceptibility-based vs. empiric antibiotic treatment for first-line or subsequent therapies have been much debated. A recent meta-analysis of 12 publications favored the susceptibility-guided approach for choosing first-line therapies over standard 7–10 day triple therapy after endoscopy and culture (162). Other studies have shown a high eradication rate with susceptibility-guided second-line (163) and third-line therapies (164), but the cost-effectiveness of such strategies has not been rigorously evaluated. The need for repeat endoscopy for the sole purpose of obtaining biopsies may render this approach cost-prohibitive after failed therapy in the United States. The development of non-invasive (fecal or other) sensitivity testing could favorably alter this calculus. In the meantime, clinicians should review patient history of antibiotic use in general and assume previous exposure provides a surrogate measure of resistance to levofloxacin, clarithromycin, or metronidazole.

There seems little doubt that profiling and tracking *H. pylori* antibiotic susceptibility within North America, and more specifically, the US would prove invaluable when deciding upon the most appropriate first-line and salvage treatment regimens for infected individuals and populations. A Europe-wide effort is currently registering thousands of cases per year, thereby providing real-time data on *H. pylori* antibiotic resistance which can be leveraged to guide the most appropriate treatment recommendations (165). The dearth of knowledge about antibiotic resistance in the United States is in sharp contrast to this approach and remains an unfortunate barrier to making evidence-based treatment recommendations.

QUESTION 7: SHOULD WE TEST FOR TREATMENT SUCCESS AFTER *H. PYLORI* ERADICATION THERAPY?

Recommendation

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).

With declining success rates for *H. pylori* eradication therapy, many patients will be persistently infected after treatment and will therefore remain at risk for the complications of *H. pylori*-related disease, such as peptic ulceration and gastric malignancy. The widespread availability of relatively inexpensive, non-endoscopic breath or stool testing allows for easy monitoring for treatment success, albeit with the caveat that patients should be tested at least 4 weeks after the end of eradication therapy and should have been off PPIs for 1–2 weeks when testing is performed (166,167). When conducted properly, the urea breath test, fecal antigen test, and endoscopic tests all are highly sensitive and specific at detecting persistent *H. pylori* infection. Thus, the choice of test in an individual patient is dependent upon a number of other variables including the need for a repeat endoscopy, local availability, cost, and third party payment.

The arguments supporting routine post-treatment testing are intuitively obvious when there is already a clear indication for *H. pylori* treatment. However, the scientific evidence to support such a strategy from a cost-effectiveness viewpoint is less than robust. An exception is for bleeding peptic ulcers associated with *H. pylori* where modeling studies do support the cost-effectiveness of routinely testing to confirm *H. pylori* eradication (168,169). In contrast, such a strategy may not be cost-effective for uncomplicated duodenal ulcers, even when eradication rates are as low as 70% (170).

In the case of FD, where symptoms usually persist even after successful *H. pylori* eradication, post-treatment testing can be especially helpful in deciding whether to pursue alternative diagnoses or empiric therapies aimed at etiologies other than *H. pylori* infection. In the ~10% of patients with FD who achieve sustained symptom resolution after successful therapy, it could be argued that the benefit of re-testing may be outweighed by the onus of re-treating an asymptomatic patient, or even creating "*H. pylori* neurosis". Patients' own desires on the need to confirm eradication should also be taken into consideration, as their wish to be rid of what is a potentially carcinogenic bacterium may ultimately drive shared decision-making in favor of re-testing.

A final argument in favor of post-treatment testing is to provide data on which to make rational community-based decisions. Without re-testing it is impossible to obtain information on a practitioner's or community's eradication success and on the need to modify antibiotic regimens.

We acknowledge that in clinical practice, circumstances may arise in which the performance of eradication testing may be impractical or deemed by the provider or patient to be unnecessary. However, in the overwhelming majority of situations where treatment for *H. pylori* is offered, eradication testing should be offered to the patient.

QUESTION 8: WHEN PRIMARY THERAPY FAILS, WHAT ARE THE OPTIONS FOR SALVAGE THERAPY?

Recommendations

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 (26)). (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 the 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 the 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)).

The selection of a salvage regimen for a patient with persistent *H. pylori* infection after one or more attempts at eradication is an increasingly common scenario facing practicing gastroenterologists. Not unlike first-line therapy, we have had to make empiric selections of salvage therapy rather than base our recommendations on the results of culture and antimicrobial sensitivity testing. Although most trials of salvage regimens have been conducted outside North America, we have, wherever possible, based our recommendations on North American studies conducted since 2000. Absent those, we have highlighted the most relevant international studies. It is notable that reported eradication rates for salvage regimens from Asian studies have been consistently higher than those from North America or Europe. All eradication rates listed below are from ITT analyses.

As explained elsewhere in this document, the most important determinant of the success of eradication therapy is the sensitivity or resistance of *H. pylori* to the antibiotics used; resistance to antibiotics is, in turn, strongly correlated to prior use of these specific antibiotics (for *H. pylori* or other infections) (153). This applies mainly to clarithromycin, fluoroquinolones and rifabutin (an antibiotic that is not currently used first-line) which should not be re-used empirically, because resistance to these antibiotics cannot be overcome by increasing dose, duration of treatment or frequency of administration (151–153). However, amoxicillin or tetracycline can be re-used, because resistance remains rare even after their prior use (122). In general, re-use of metronidazole should be avoided, although resistance to it can be partially overcome by increasing its dose, duration of use or frequency of administration (151,152). Therefore, if alternative regimens are predicted to be clearly inferior, metronidazole could be re-used as a component of a 14-day course of bismuth-based quadruple therapy, especially if its previous use was brief or at a low dose. A listing of available salvage treatment options can be found in **Table 3**. **Figure 3** provides a recommended construct to assist the choice of therapy in an individual patient with persistent *H. pylori* infection.

Bismuth—quadruple regimen

Since 2000, 30 RCTs have compared bismuth quadruple therapy with other regimens or with a bismuth quadruple regimen of different duration as salvage treatment after one or more failed eradication attempts (**Supplementary Appendix 3**). Of those, 23 studies included only patients who had failed a first-line treatment; of those, 20 studies included only patients who had failed clarithromycin triple regimens. The remaining three RCTs did not specify which regimens were used first-line (although in one (171), patients were specifically excluded if they had received bismuth quadruple therapy previously).

With regards to the optimal duration of the salvage bismuth quadruple therapy, the meta-analysis by Marin *et al.* (172) found a non-significant trend in subgroup analyses (between-study comparisons) for increasing eradication rates with longer duration of treatment from 7 days (76%) to 10 days (77%) to 14 days (82%) after failure of clarithromycin triple therapy. The systematic review conducted for this guideline identified four RCTs comparing 14-day bismuth quadruple therapy with 7-day bismuth quadruple therapy that were published since 2000, two from Asia (173,174) and two from Europe (175,176). Meta-analysis of these four RCTs showed a significantly higher eradication rate with 14-day bismuth quadruple therapy (RR 1.14; 95% CI 1.02–1.28). Given the above evidence and the fact that resistance to metronidazole can be partially overcome by increasing treatment duration (151,152), it is reasonable to encourage a 14-day duration for the bismuth quadruple salvage regimen.

We found eleven RCTs, published since 2000, that had compared 14-day bismuth quadruple therapy with other regimens as salvage treatment; one was conducted in the United States (177), three in Europe (175,176,178) and the remaining seven in Asia (173,179–184). Eight of these studies only included patients who failed eradication once, after treatment with clarithromycin triple therapy. The only study from the US (177) included patients who had failed once after treatment with one of several regimens (67% of the patients had failed either bismuth quadruple therapy or ranitidine bismuth citrate, metronidazole,

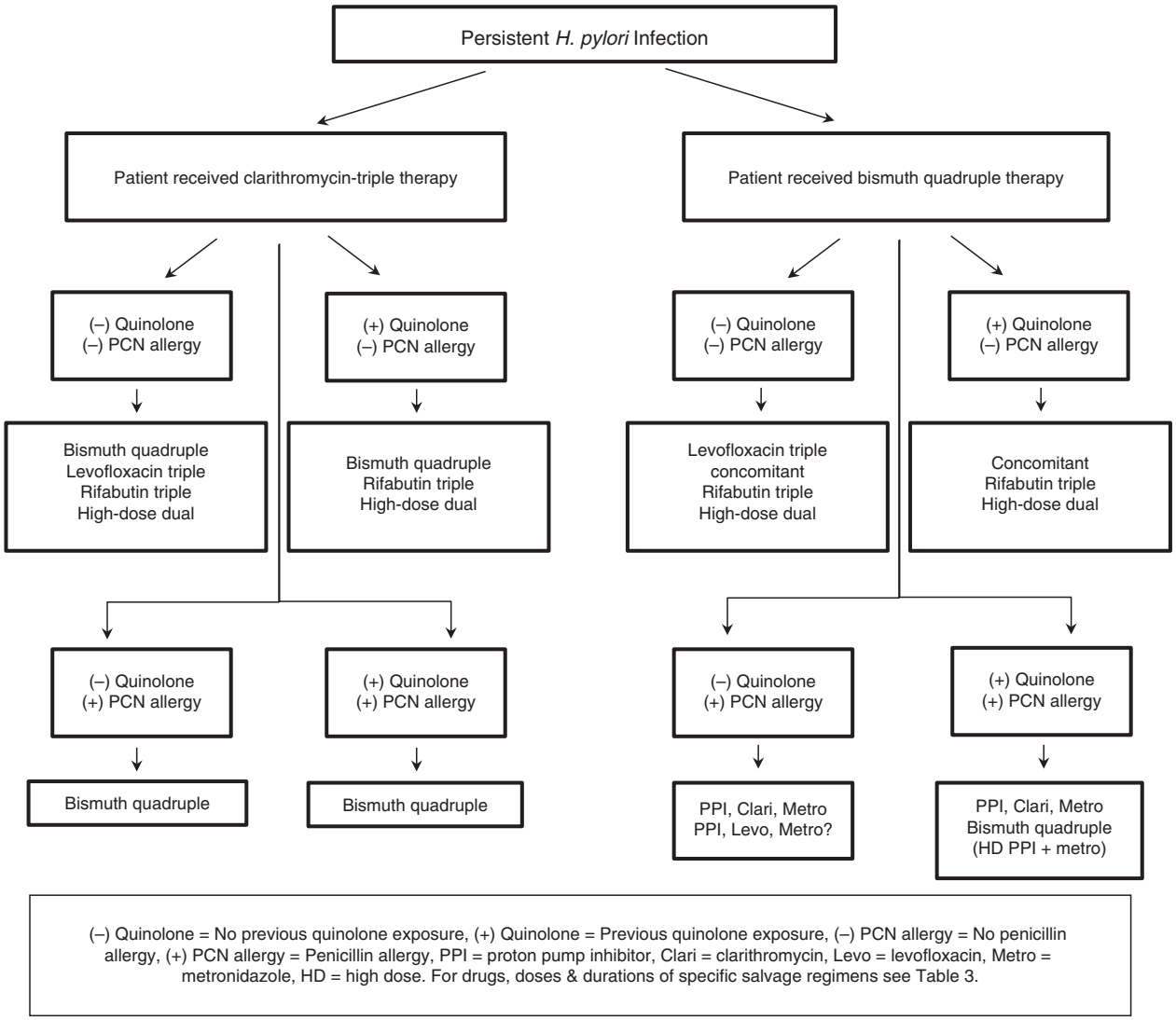

Figure 3. Selection of a salvage treatment regimen for persistent *H. pylori* infection.

and tetracycline). Two studies, one from Europe (178) and one from Asia (179), included patients who had failed one or more eradication attempts with various regimens. The pooled eradication rate for 14-day bismuth quadruple therapy was 80% (95% CI 76–84%), and was significantly higher among Asian studies (82%; 77–86%) compared with European or US studies (74%; 68–81%). in the United States study (177), the overall eradication rate for 14-day bismuth quadruple therapy was 71%, but differed substantially among patients who had previously failed bismuth quadruple treatments for 7–14 days (eradication rate 53%; 28–77%) and the patients who had previously failed triple or dual clarithromycin-based treatments without bismuth (eradication rate 100%; 72–100%).

Levofloxacin triple regimen (PPI, amoxicillin, levofloxacin: PAL)

Fifteen RCTs that compared levofloxacin triple therapy with other regimens as salvage treatment have been published since 2000 (**Supplementary Appendix 4**). Only one of these studies assessed 14-day levofloxacin triple therapy; it was conducted in Taiwan, among 101 patients who had failed treatment with 7 day clarithromycin triple therapy, and found no difference in eradication rates between 14-day levofloxacin triple therapy (86%; 95% CI 77–96%) and 14-day bismuth quadruple (PBMT, 86%; 76–96%)(181). Four RCTs assessed the 10-day levofloxacin triple therapy regimen (176,185–187); all were conducted in Europe and the pooled eradication rate was 84% (73–92%). Ten RCTs, seven from Asia and three from Europe, assessed the 7-day levofloxacin triple therapy regimen; the pooled eradication rate was 66% (95% CI 60–73%) with no difference between Asian and European studies. A meta-analysis of cohort studies and cohort-type data from RCTs which assessed levofloxacin triple therapy showed that the eradication rate was 76% (95% CI 72–81%) after failure of clarithromycin triple therapy among 19 studies, and 81% (95% CI 71–91%) after failure of sequential therapy among five studies (172).

Levofloxacin triple therapy also seems to be efficacious as a third-line treatment. Gisbert *et al.* (188) calculated a pooled eradication rate of 73% for six European cohort studies that assessed 10-day levofloxacin triple therapy in patients who had failed two previous eradication attempts (most patients had clarithromycin triple therapy as first-line and bismuth quadruple therapy as second-line).

Regarding the optimal duration of levofloxacin triple salvage treatment, subgroup analyses (between-study comparisons) from the meta-analysis conducted for this guideline (see above) showed that this regimen given for 10 or 14 days was significantly more effective than when given for 7 days. Only one RCT compared two durations for levofloxacin triple salvage treatment; Di Caro *et al.* (186) compared two types of 10-day and two types of 7-day PAL regimens in Italy and found significantly higher efficacy with longer duration (88% vs. 78%). This finding was confirmed by an RCT from Turkey which reported significantly higher efficacy with longer duration of PAL as first-line treatment (72% with 14-day regimen vs. 34% with 7-day regimen) (189).

The optimal dose of levofloxacin is unclear. Two RCTs that assessed different doses of levofloxacin in salvage treatments found no difference when administering 500 mg of levofloxacin once or twice daily in 7 or 10 day regimens (186,190).

Levofloxacin triple therapy can be adapted for use in patients with persistent *H. pylori* infection despite treatment with an initial course of bismuth quadruple therapy. In 64 penicillin-allergic patients with persistent *H. pylori* infection despite first-line treatment with either bismuth quadruple or metronidazole-clarithromycin triple therapy, 10-day levofloxacin-clarithromycin triple therapy led to a 64% eradication rate (191). This compares with a 37% success rate (9 out of 24 patients) if bismuth quadruple therapy was given after the metronidazole-clarithromycin-based triple therapy had failed in the same study. A remarkable 100% success rate (95% CI: 90–100%) has been reported from Japan in 28 penicillin-allergic patients, (including 17 with prior failed eradication) with a 1 or 2 week PPI, metronidazole and sitofloxacin regimen (192). Sitofloxacin is a quinolone with high activity against *H. pylori*, even in strains resistant to levofloxacin; it is not currently available in North America.

Concomitant therapy

Only two RCTs that compared concomitant therapy with another regimen as salvage treatments have been published since 2000 (193,194). Both studies included patients who had failed first-line treatment with clarithromycin triple therapy. A trial from Japan randomized 104 patients to 7-day triple therapy with a PPI, amoxicillin, and metronidazole or 7-day concomitant regimen; eradication rates were 83% (95% CI 73–93%) and 89% (80–97%), respectively (193). However, these results are not necessarily generalizable to other countries; the efficacy of metronidazole-containing regimens is particularly high in Japan, due to a relatively low resistance of *H. pylori* to this antibiotic, which in turn is probably due to the its restricted use nationally (195). The second trial was conducted in Korea and randomized 124 patients to bismuth quadruple therapy or concomitant therapy for 10 days. The treatments were found to be equally effective (eradication rates 92% vs. 90%) (194).

There is indirect evidence from studies on first-line treatment that concomitant therapy should have acceptable efficacy as a second-line treatment. First, it is one of the most efficacious first-line regimens (129). Second, limited data from Spain and Taiwan suggest that concomitant therapy may even remain effective in patients with dual resistance to clarithromycin and metronidazole (196,197).

There is very little evidence on the optimal duration of salvage concomitant treatment. No RCTs have compared two concomitant regimens of different durations as salvage treatments. A systematic review that assessed the efficacy of 19 cohort studies and cohort-type data from RCTs for first-line treatment found a non-significant trend for increased efficacy with increased durations of treatment: 3 days (85%); 4 days (88%); 5 days (83%); 7 days (91%); and 10 days (90%) (129).

Clarithromycin triple therapy

In current clinical practice in North America, it is uncommon for clarithromycin not to have been used first-line unless the patient had already been judged to have been at high risk for clarithromycin resistance. Theoretically, there is no evidence-based reason to avoid this regimen as a second-line treatment in such situations. That being said, the guideline committee recommends concomitant therapy over clarithromycin triple therapy when a clarithromycin containing salvage regimen is chosen.

The evidence supporting the use of clarithromycin triple therapy as a salvage regimen is limited. After 2000, three RCTs in the United States or Europe assessed triple therapy with a PPI, clarithromycin, and amoxicillin as a second-line treatment (177,198,199), while none assessed triple therapy replacing amoxicillin with metronidazole as a second-line treatment. In a US RCT by Magaret *et al.* (177), patients who had failed one of several first-line treatments for *H. pylori* were randomized to 14-day PAC or 14-day bismuth quadruple therapy. Although not reported in the paper, among the 32 patients who had bismuth quadruple therapy for 10–14 days or ranitidine bismuth citrate-, metronidazole, and tetracycline for 7–10 days as first-line treatment, the eradication rate was 79% (95% CI 49–95%) for clarithromycin triple therapy and 53% (28–77%) for bismuth quadruple therapy (P=NS). In the German RCT (198), all 84 patients had failed PPI, clarithromycin, and metronidazole for 7 days as first-line treatment; not surprisingly, eradication rates were inferior with 7-day clarithromycin triple therapy compared with 7-day bismuth quadruple therapy (43% (28–59%) vs. 68% (51–81%), P=0.03) and the difference was even more pronounced among the 79% of patients who had clarithromycin-resistant strains after first- line treatment. The French RCT (199), showed that among 172 patients in whom first-line clarithromycin triple therapies (clarithromycin triple therapy 87%, PPI, amoxicillin, metronidazole 7%, clarithromycin triple therapy with metronidazole 3%, H_2RA, clarithromycin, and amoxicillin 3%) had failed, empiric second-line treatment with 7- or 14-day triple therapy with a PPI, clarithromycin and amoxicillin had lower eradication rates than 14-day PPI, clarithromycin, and metronidazole (47% vs. 355 vs. 63%, respectively).

As mentioned above, repeating the same triple regimen should be avoided. A meta-analysis of cohort studies and cohort-type data from RCTs showed that, among eight studies that repeated clarithromycin triple therapy as second-line treatment (after failure of the same regimen as first-line treatment), the pooled eradication rate was unacceptably low (46%; 95% CI 34–58%) (172).

Rifabutin-based triple regimen (PPI, amoxicillin, rifabutin: PAR)

The proven efficacy of rifabutin in the treatment of *H. pylori* infection should be balanced against its high cost, the rare risk of myelotoxicity (almost always reversible) and the concerns for inducing resistance among *Mycobacterium tuberculosis* strains (200,201).

Four RCTs have compared rifabutin triple therapy consisting of a PPI, rifabutin and amoxicillin against other regimens as salvage treatments (171,202–204). Ten-day rifabutin triple regimens were assessed in only one RCT by Perri *et al.* in Europe among 135 patients who had failed between one and three previous treatments. Rifabutin triple therapy for 10 days with 300 mg rifabutin once daily (eradication rate 87%; 95% CI 76–96%) was significantly more efficacious than a 10-day regimen with 150 mg rifabutin once daily and 10-day bismuth-based quadruple treatment, both of which had identical eradication rates of 67% (95% CI 53–80%) (204). The other three RCTs, two from Europe (171,203) and one from Asia (202), assessed 7-day rifabutin triple regimens with rifabutin given as 150 mg twice daily; the pooled eradication rate was 66% (45–83%), but with substantial heterogeneity among the studies. In Spain, Navarro *et al.* (174) found lower eradication rates for rifabutin triple therapy than the other RCTs: among 99 patients in whom clarithromycin triple therapy had failed, 7-day rifabutin triple therapy achieved an eradication rate of 44%, which was significantly lower than the eradication rate of 70% with a 7-day bismuth-based quadruple regimen.

In a meta-analysis of cohort studies and cohort-type data from RCTs that used PAR as salvage treatment, pooled eradication rates were 79% (95% CI 67–92%) as second-line, 66% (55–77%) as third-line, and 70% (60–79%) as fourth- or fifth-line (200).

There is little evidence on the optimal duration for the PAR salvage treatment. There have been no RCTs comparing different durations of treatment. Comparisons between subgroups (between-study comparisons) in meta-analyses suggest that, when PAR is used as second-line treatment, 10- to 12-day regimens achieved higher eradication rates than 7-day regimens (95 vs. 69%). It is notable that myelotoxicity which can rarely complicate treatment with rifabutin tends to occur with doses of greater than 600 mg per day or with prolonged use (200). Thus, when rifabutin triple therapy is recommended, a dose of 300 mg once daily and duration of 10 days is appropriate.

High-dose dual regimen with amoxicillin

The reasons for considering high-dose dual therapy as a salvage treatment are that *H. pylori* rarely develops resistance to amoxicillin (122), and that the efficacy of amoxicillin increases with increasing gastric pH (205),

Since 2000, three RCTs have compared 14-day high-dose dual regimens (defined as total daily dose of amoxicillin ≥3 g, and frequency of administration ≥3/day in an attempt to avoid the low trough levels of *b.i.d.* amoxicillin dosing) with other regimens as salvage treatments (178,203,206). Two of these studies have been conducted in Germany, both by Miehlke *et al.* The first study included 84 patients with at least one previous treatment failure (most patients had two or more treatment failures) and compared 14-day high-dose dual therapy (omeprazole 40 mg and amoxicillin 750 mg, both given *q.i.d.*) with 14-day bismuth quadruple treatment. The eradication rates for the two regimens did not differ significantly (dual therapy: 76%, 95% CI: 60–88%, vs. bismuth quadruple therapy: 81%, 67–92%) (178). The second study included 145 patients with at least one previous eradication failure and dual *H. pylori* resistance to metronidazole and clarithromycin who were randomized to high-dose dual therapy for 14 days or rifabutin triple therapy for 7 days. No significant difference between the two regimens was identified (dual therapy: 70%, 95% CI 58–80% vs. rifabutin triple therapy: 74, 62–84%) (203). By proportion meta-analysis, the pooled eradication rate for high-dose dual salvage treatment in the European studies was 71% (63–79%). Finally, in Taiwan, Yang *et al.* (206) included 168 patients with one or more previous eradication failures, and reported that the eradication rate with the 14-day high-dose dual therapy (rabeprazole 20 mg and amoxicillin 750 mg, both given *q.i.d.*) was 89% (81–98%), which was not significantly different than with 7-day levofloxacin triple therapy (79, 67–90%), but was significantly higher than with 10-day sequential therapy (52, 38–65%). The pooled eradication rate for high-dose dual salvage therapy among all three studies was 78% (95% CI 65–89%).

Of note, three other RCTs, all from Japan, assessed a different 10- to 14-day dual salvage regimen that contained high-dose PPI (a standard dose but given *q.i.d.*) with standard dose amoxicillin (i.e., 500 mg *q.i.d.*) (207–209). The results were highly heterogeneous among these studies, with eradication rates of 0, 54, and 91%.

Other salvage treatments: sequential therapy, hybrid therapy, and furazolidone-containing regimens

Sequential therapy has mainly been tested as a first-line treatment. Only two RCTs have assessed its efficacy as a salvage treatment, and the results are discouraging. One RCT, conducted in Taiwan, included 168 patients who had failed one or more previous eradication treatments; the eradication rate with 10-day sequential therapy (52%, 95% CI 38–65%) was significantly lower than with 14-day high-dose dual amoxicillin therapy (89%, 81–98%) or 7-day levofloxacin triple therapy (79, 67–90%) (206). The other RCT was conducted in Korea and included 158 patients who had failed clarithromycin triple therapy; 10-day sequential therapy was significantly inferior to 10-day bismuth-based quadruple therapy (eradication rates 57 vs. 84%) (210). Based upon the lack of North American data and discouraging data from Asia, we do not recommend sequential therapy as a salvage treatment.

We were unable to identify any RCTs that compared hybrid therapy with other regimens as salvage treatment. Therefore, there is insufficient evidence to support a recommendation for hybrid therapy as a salvage treatment.

The nitrofuran-based antimicrobial furazolidone is not currently available in the United States. There are no published studies of its use as a salvage therapy in North America. Non-randomized studies from Russia, Ireland and Australia utilizing three- and four-drug regimens, have reported ITT eradication rates ranging from 60 to 86% for furazolidone salvage regimens (211–213). The lack of RCTs reporting the comparative efficacy of furazolidone salvage therapy and its potential for harms including hypotension, urticaria, gastrointestinal symptoms, and reversible hemolysis make it impossible to recommend its use as a salvage treatment.

QUESTION 9: WHEN SHOULD PENICILLIN ALLERGY TESTING BE CONSIDERED IN PATIENTS WITH *H. PYLORI* INFECTION?

Recommendation

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).

Amoxicillin is an important component of first-line and salvage regimens used to treat *H. pylori* infection. Fortunately, there are a number of evidence-based regimens that do not include amoxicillin and that can be used in patients with true allergy—most notably bismuth quadruple therapy. If a "penicillin-allergic" patient has failed 1 or 2 eradication attempts, it is then advisable to consider investigating whether or not the patient has a true penicillin allergy. Numerous studies have demonstrated that, although 5–10% of the US population state that they are "allergic" to penicillin, ~90% of such patients have negative skin testing and can tolerate penicillin without hypersensitivity (214). Furthermore, penicillin avoidance without confirming true allergy is recognized in the United States as a public health issue, as it contributes to the overuse of non-beta-lactam containing antibiotics (http://www.choosingwisely.org/clinician-lists/american-academy-allergy-asthma-immunlogy-non-beta-lactam-antibiotics-penicillin-allergy/). Referral of these "penicillin-allergic" patients for skin testing will, therefore, result in most being found to be not truly allergic. After excluding true allergy, they can safely be prescribed amoxicillin-containing salvage regimens, as recommended for the non-allergic population.

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

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.

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.

This guideline is in overall agreement with the recently published Toronto Consensus for the treatment of *H pylori* infection in adults, which had a narrower focus and was restricted only to treatment options (215). Both guidelines attempt to restrict the use of clarithromycin triple therapy and strengthen the role of bismuth quadruple therapy and concomitant therapy. Both guidelines advocate for a longer duration of treatment (14 days for almost all regimens in the Toronto Consensus; 10–14 for almost all regimens in the ACG guideline). There are only a few differences between the two guidelines, occurring in areas with limited, low-quality evidence. The Toronto Consensus recommends against the use of sequential treatment (neither as a first-line therapy nor as a rescue treatment), while the ACG guideline conditionally recommends it as first-line therapy. Hybrid therapy and high-dose dual therapy are not officially endorsed by the Toronto Consensus, whereas the ACG guideline conditionally recommends them as first-line and rescue therapy respectively.

Given the rising rates of antimicrobial resistance and growing complexity of *H. pylori* therapy (216), a preventive or therapeutic vaccine remains an attractive long-term solution for managing this infection. Although progress has been slow, recent results from a large phase 3 trial conducted in China provide proof of principle for *H. pylori* vaccination (Zeng *et al.* (217)). In that report, an oral *H. pylori* vaccine based upon recombinant urease B provided about 70% protection against *H. pylori* acquisition in children. Although the efficacy of the vaccine started to wane after a year, this landmark study will likely prompt further efforts to develop a clinically useful and much needed alternative to antibiotic regimens for the prevention of *H. pylori*-associated diseases rather for than the treatment of established *H. pylori* infection.

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CONFLICT OF INTEREST

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