Helicobacter pylori

By Adam Jackson, Pharm.D., BCACP

Reviewed by: Pramodini B. Kale-Pradhan, Pharm.D., FCCP; Dareen Bleibel, Pharm.D., BCACP; and Martin Ziska, Pharm.D.

LEARNING OBJECTIVES

1. Assess the need to test a patient and offer treatment for a *Helicobacter pylori* infection.
2. Evaluate potential goals of, and key factors that affect, *H. pylori* therapy selection and success.
3. Design an *H. pylori* eradication regimen for a patient who has not previously received *H. pylori* eradication therapy.
4. Design a testing strategy after use of *H. pylori* therapy.
5. Design an *H. pylori* eradication regimen for a patient who has previously received one or more *H. pylori* eradication regimens.

ABBREVIATIONS IN THIS CHAPTER

ACG	American College of Gastroenterology
GERD	Gastroesophageal reflux disease
ITP	Idiopathic thrombocytopenic purpura
LOAD	Proton pump inhibitor, levofloxacin, amoxicillin, and nitazoxanide (regimen)
MALT	Mucosa-associated lymphoid tissue
PPI	Proton pump inhibitor
PUD	Peptic ulcer disease

Table of other common abbreviations.

INTRODUCTION

Although the idea that stress is a major cause of peptic ulcer disease (PUD) may seem quaint to younger clinicians, it used to be considered established medicine. *Helicobacter pylori* was first isolated almost 40 years ago, but standardized testing and treatment regimens were not common for another 20 years or more (Cover 2020). As with most topics that evolve over a long period, there is a great deal of information that both helps and hinders patient care.

A common microorganism of the human GI tract, *H. pylori* is inherently pathogenic because it increases the risk of several diseases. The presence of *H. pylori* does not guarantee such disease states, however, and many patients with this infection remain asymptomatic or never have symptoms sufficiently severe (e.g., vague GI concerns like dyspepsia) to cause them to seek medical care. Several disease states associated with *H. pylori* may improve only marginally with *H. pylori* eradication. In addition, *H. pylori* appears to have a protective effect against gastroesophageal reflux disease (GERD) (Crowe 2019). Clinicians need to understand the context of *H. pylori* to determine the need for testing and treatment (Chey 2017). This chapter's goals are to provide the information necessary to (1) make clinical decisions for individual patients and (2) understand the multifaceted nature of *H. pylori* to help create realistic expectations of diagnosis and treatment.

TESTING FOR *H. PYLORI*

This chapter will not discuss intricate details of *H. pylori* testing, such as how each test is performed. All commonly used tests for *H. pylori* are 95% accurate or greater in confirming the diagnosis (Crowe 2019). Instead, the discussion will focus on which tests should be used in which setting. The most practical way to divide *H. pylori* testing is by tests that are invasive (i.e. those that require endoscopy)

versus those that are noninvasive, their availability in common health care settings, and their ability to be used to test for eradication (Table 1).

WHOM TO TEST, WHOM TO TREAT

Management of most infectious diseases follows a relatively straightforward algorithm of diagnosis leading to treatment, eradication, and ultimately clinical improvement. Although *H. pylori* is viewed in this paradigm, the situation is often not as clear.

Treat if Positive Does Not Necessarily Mean Testing Is Needed

The primary principle behind *H. pylori* therapy must be recognized before venturing into the specific disease states caused by and the potential eradication therapies for *H. pylori*. A decision to test is a decision to treat (i.e., because *H. pylori* is a known carcinogen and a potential pathogen, all patients with active infection should be offered eradication therapy) (Chey 2017). This does not necessarily mean, however, that eradication of infection will be easy or even possible. Nor does it mean that if *H. pylori* is successfully eradicated, the patient's symptoms will improve. Rather, eradication of *H. pylori* may improve clinical symptoms and reduce the risk of future clinical disease. But the likelihood and degree of benefit, and whether such benefits exceed the risks of therapy, depend on the specific disease state and the patient. These factors should be considered before testing for *H. pylori* infection (i.e., do not ask the question if you do not want the answer).

H. pylori should only be tested for if (1) the clinical diagnosis is likely to be caused or at least worsened by *H. pylori*, (2) the patient is likely to experience clinical or symptomatic improvement with eradication of the infection, (3) treatment is likely to eradicate *H. pylori*, and (4) the risks of treatment (adverse drug reactions, subsequent *Clostridioides difficile* infection) are outweighed by the benefits associated with eradication of *H. pylori* (Table 2).

Patients who are not tested for *H. pylori* should still receive a standard diagnostic workup and clinical management of their syndrome. For example, patients with GERD who are not tested for *H. pylori* should still undergo endoscopy in the presence of warning signs and symptomatic therapy with a proton pump inhibitor (PPI), if necessary.

Should Test for *H. pylori*, According to Generally High-Quality Evidence

Although evidence is inconclusive that *H. pylori* causes any disease state, there is ample evidence of its association with several disease states. The quantity and quality of evidence for each of these associations, together with the severity of the disease, determine the need to test for *H. pylori* infection.

In only three disease states (PUD, gastric cancer, and gastric mucosa-associated lymphoid tissue [MALT] lymphoma) is there substantial evidence that *H. pylori* plays a substantive role in the disease process and that eradication of the organism provides clear and substantial clinical benefits. Testing in these disease states is necessary and agreed on by practice guidelines and should be done both in patients with active disease and those with a history of disease who have not received *H. pylori* treatment (Chey 2017).

Peptic Ulcer Disease

H. pylori infection occurs in 90% or more of patients with duodenal ulcers and up to 80% of patients with gastric ulcers. Eradication of *H. pylori* heals PUD and lowers recurrence rates (Chey 2017). The sequela caused by PUD (e.g., GI bleeding) are severe and, combined with the strong association of *H. pylori*, make a compelling case for testing and treating *H. pylori* infection in patients with PUD.

BASELINE KNOWLEDGE STATEMENTS

Readers of this chapter are presumed to be familiar with the following:

- General knowledge of the microbiology of *H. pylori*
- Understanding of the disease states, including common presentation and diagnostic workup, for which testing for and possible treatment of *H. pylori* are recommended
- Knowledge of the most common tests for *H. pylori*
- Drug knowledge of the antimicrobial agents used to treat *H. pylori* (e.g., common adverse reactions, drug interaction potential)

Table of common laboratory reference values.

ADDITIONAL READINGS

The following free resources have additional background information on this topic:

- Correa P, Piazuelo MB. Natural history of *Helicobacter pylori* infection. Dig Liver Dis 2008;40:490-6.
- Graham DY. History of *Helicobacter pylori*, duodenal ulcer, gastric ulcer and gastric cancer. World J Gastroenterol 2014;20:5191-204.
- American College of Gastroenterology *Helicobacter pylori* video presentation. ACG management approaches to H. pylori management.
- American College of Gastroenterology *Helicobacter pylori* video presentation ACG management of resistant *H. pylori*.

Table 1. Characteristics of Tests for *H. pylori* Infection

Test	Invasive (endoscopy required)?	Can Test for Eradication	Comments
Urea breath	No	Yes, if at least 1–2 wk since PPI completion and 4 wk since bismuth and antibiotic completion	Commonly used and usually with rapid results
Serology	No	No	Very easy and quick. Does not detect active infection vs. infection that has been eradicated. Only viable for first-time testing because it will detect antibodies even after bacterial eradication
Stool antigen	No	Yes, if at least 1–2 wk since PPI completion and 4 wk since bismuth and antibiotic completion	Easy and quick, but some patients would rather not provide a stool specimen. Less expensive than urea breath testing
Urease detection	No	Yes	Rapid results
Culture by endoscopy	Yes	Yes	Not used in most community settings. Can be used for susceptibility testing. Results take weeks
Histology by endoscopy	Yes	Yes	Although endoscopy is common, histology is not commonly performed
Biopsy by endoscopy	Yes	Yes	Most common invasive test

PPI = proton pump inhibitor.

Information from: Crowe SE. *Helicobacter pylori* infection. N Engl J Med 2019;380:1158-65.

Gastric Cancer

H. pylori infection does not cause gastric cancer on its own – many other mostly undefined oncogenic factors likely also play a role in the development of gastric cancer. However, the risk of gastric cancer is increased by *H. pylori* infection and is particularly high in East Asian countries. The antrum and body of the stomach appear to be the most affected by *H. pylori*. As *H. pylori* infection has declined and therapy for *H. pylori* has become more common, cancer of the upper and lower stomach has become more common (Choi 2020; Crowe 2019). Eradication of *H. pylori* can reduce the risk of gastric cancer by 50% or more (Chey 2017). In addition, patients with a history of gastric cancer resected by endoscopy have a 50% reduction (13.4% vs. 7.2%) in metachronous gastric cancer (cancer isolated more than a year after previous gastric cancer resection) after *H. pylori* treatment. However, no reduction in all-cause mortality has been identified (Choi 2018).

Gastric MALT Lymphoma

The nomenclature "marginal zone B-cell lymphoma of MALT type" is replacing "gastric MALT lymphoma." The term *gastric MALT lymphoma* is still commonly used, however, and is especially prevalent in the older literature; it will therefore be used in this chapter.

Although *H. pylori* and gastric MALT lymphoma are strongly associated, *H. pylori* eradication does not appear to be as effective in this disease state as in PUD and gastric cancer. Treatment causes histologic improvement in most patients, but recurrence occurs in 3% of patients within 2 years and up to 20% of patients within 4 years of eradication (Chey 2017).

Should Test for *H. pylori*, According to Generally Low-Quality Evidence

The quantity and quality of evidence supporting an association between *H. pylori* and disease are not as strong for the diseases in this section as for PUD, gastric MALT lymphoma, and gastric cancer.

Patients Starting Chronic NSAID Therapy

H. pylori infection is a strong risk factor for PUD in patients who are taking chronic NSAIDs. However, the effect of *H. pylori* treatment on preventing ulcers in patients taking chronic NSAIDs is less clear. The risk of PUD is reduced in patients treated for *H. pylori* before starting chronic NSAIDs, but patients who are already taking NSAIDs do not benefit from *H. pylori* treatment (Chey 2017). Therefore, it appears that whatever risk *H. pylori* infection imparts to patients taking NSAIDs can partly be prevented but not effectively treated.

Table 2. Possible Indications and Considerations for *H. pylori* Testing[a]

General Recommendation	Summary of Evidence	Indication	Comments
Testing for *H. pylori* is routinely recommended	ACG guidelines state this is a strong recommendation with generally high-quality evidence	PUD	These disease states have the best and most consistent evidence for improved outcomes with testing and subsequent treatment for *H. pylori*
		Gastric cancer	
		Gastric MALT lymphoma	
Testing for *H. pylori* is recommended	ACG guidelines state this is a conditional recommendation according to generally low-quality evidence	Patients starting chronic NSAID therapy	Although the evidence supporting testing and treating these disease states is not as strong as that for PUD and gastric cancer, patients are still likely to benefit from testing and treatment
		Patients with unexplained iron-deficiency anemia despite standard diagnostic workup	
		ITP	
Testing may be considered	ACG guidelines state this is a conditional recommendation according to moderate-quality evidence	Patients taking chronic low-dose aspirin	Patients taking chronic low-dose aspirin therapy may have a reduced risk of ulcer bleeding after *H. pylori* eradication
	ACG guidelines published in 2017 stated no recommendation could be made	Family history of gastric cancer	Since publication of the ACG guidelines, high-quality evidence from South Korea shows a reduction in gastric cancer by screening and treating these patients for *H. pylori*. It is unclear whether this evidence can be applied to other populations (e.g., those in North America) with a lower risk of gastric cancer
Noninvasive testing may be considered for adults < 60 with dyspepsia but without alarm symptoms	Conditional/generally high-quality evidence	Dyspepsia	See text for full discussion
Testing is not recommended	No evidence that testing for or eradication of *H. pylori* improves outcomes	GERD	Testing patients with GERD symptoms who do not have PUD for *H. pylori* is unlikely to be beneficial

[a]Patients who test positive for *H. pylori* should be offered eradication therapy. Therefore, the most important decision in *H. pylori* management is whether to test.

ACG = American College of Gastroenterology; GERD = gastroesophageal reflux disease; ITP = idiopathic thrombocytopenic purpura; MALT = mucosa-associated lymphoid tissue; PUD = peptic ulcer disease.

Information from: Crowe SE. *Helicobacter pylori* infection. N Engl J Med 2019;380:1158-65.

Patients with Unexplained Iron-Deficiency Anemia Despite Standard Diagnostic Workup

Iron deficiency and iron-deficiency anemia are more common in patients with *H. pylori* infection than in those without the infection (Crowe 2019). *H. pylori* treatment does not cure iron-deficiency anemia, and iron supplementation is still necessary in such patients.

Idiopathic Thrombocytopenic Purpura

Current American College of Gastroenterology (ACG) guidelines recommend *H. pylori* testing in adults with idiopathic thrombocytopenic purpura (ITP), whereas the most recent guidelines from the American Society of Hematology simply state that testing can be considered (Chey 2017; Neunert 2011). The combined number of patients in studies of the effect of *H. pylori* treatment on ITP is relatively low compared with that in diseases such as PUD. No definitive evidence exists to predict

which patients with ITP are most likely to benefit from testing and treatment of *H. pylori*, but there may be a greater likelihood of benefit in areas with higher *H. pylori* prevalence.

Testing May Be Considered

Patients Taking Chronic Low-Dose Aspirin Therapy

H. pylori infection is a risk factor for PUD in addition to the risk of PUD already present in patients taking chronic low-dose aspirin. However, no prospective controlled trials have shown that *H. pylori* treatment reduces the PUD risk in such patients. Current ACG guidelines suggest that testing for *H. pylori* should be done in patients taking low-dose aspirin, but the evidence base is not strong enough to recommend testing on a routine basis (Chey 2017).

Family History of Gastric Cancer

When the 2017 ACG guidelines were published, evidence was insufficient to justify screening patients with a family history of gastric cancer for *H. pylori* infection. However, a randomized controlled trial published since the 2017 guidelines showed a 55% reduction in gastric cancer in patients treated for *H. pylori* infection who had a first-degree relative with a history of gastric cancer. Patients who had successful eradication of *H. pylori* had a 73% reduction in the risk of gastric cancer (Choi 2020). This study was conducted in South Korea, which has higher rates of gastric cancer than the United States; therefore, it is unknown whether the results would be similar in a less homogeneous ethnic group. Therefore, screening for *H. pylori* in patients with a family history of gastric cancer is not yet routinely recommended but should be considered on an individual basis.

Dyspepsia – Reasonable to Test but with Caveats

Dyspepsia is the most common disease state associated with *H. pylori*. Dyspepsia is defined as pain or discomfort predominantly in the upper abdominal area (Chey 2017). Uninvestigated dyspepsia refers to dyspepsia not investigated by endoscopy. Most patients with dyspepsia have negative findings on endoscopy or otherwise do not have a confirmed disease state causing dyspepsia (e.g., PUD, gastric cancer) leading to the diagnosis of functional dyspepsia (also called non-ulcer dyspepsia). Patients who have a specific cause for dyspepsia represent a small portion of all patients with dyspepsia.

According to guideline statements, noninvasive testing for *H. pylori* in patients younger than 60 is recommended. However, clinicians should be aware that although most evidence shows benefit, the degree of benefit is relatively low and occurs in only a few patients. The primary studies compared "test and treat" for *H. pylori* with endoscopy or PPI therapy and showed only a 14.2% absolute reduction in the risk of dyspepsia (Moayyedi 2017).

Studies of *H. pylori* treatment in patients with functional dyspepsia are even less impressive. A Cochrane collaboration analysis concluded that 14 patients with functional dyspepsia would need to be treated for *H. pylori* in order to cure one case of dyspepsia (an absolute risk reduction of only 7%) (Moayyedi 2006). One trial showed a lower number needed to treat of 8, but this was to achieve a 50% reduction in symptoms. Even in this case, only 49% of patients achieved the primary outcome of a 50% reduction in symptoms. This means that one-half of patients with functional dyspepsia treated for *H. pylori* have less than a 50% reduction in symptoms (Mazzoleni 2011).

This information should not be used to decide against testing patients with dyspepsia (uninvestigated or functional) for *H. pylori* because evidence shows that some patients will benefit. Rather, clinicians and patients must have realistic expectations, both with respect to the likelihood of benefit (only a small fraction of patients will benefit) and the degree of benefit (cure of dyspepsia is uncommon).

Testing Should Not Be Performed – GERD

There is a lack of association between *H. pylori* and GERD. Although far from definitive because of several confounding factors, a temporal relationship exists between reduced *H. pylori* infection and increased *H. pylori* treatment on a population basis and an increase in esophageal disease. In addition, no compelling evidence indicates that *H. pylori* treatment benefits patients with GERD (Chey 2017). Because *H. pylori* treatment needs to be offered to all patients who test positive, the key step is not testing patients with GERD but instead pursuing other diagnostic examinations (e.g., endoscopy if warranted) and treatments (e.g., PPIs).

CONSIDERATIONS OF *H. PYLORI* THERAPY

Barriers to Choosing *H. pylori* Therapy

Treatment of most bacterial diseases has at its core matching bacteria with antibiotics with activity against the bacteria. Many treatments of infectious disease are decided not by specific clinical trials, but by selecting an antibiotic with activity against the pathogen. Treatment regimens for *H. pylori*, however, differ and should be supported with randomized controlled trial evidence. *H. pylori* is difficult to isolate and culture, making susceptibility testing rare. Clinicians cannot rely on large sets of susceptibility data, or even availability of local data, to help choose empiric therapy. In addition, the likelihood of obtaining susceptibility data in a patient either before or after therapy is essentially zero. Without isolate-specific data, clinicians must rely on the best available susceptibility data, clinical trial data, and patient-specific information to make an educated guess. After therapy, clinicians hope that follow-up testing shows eradication, without ever knowing for certain why therapy did not work (e.g., antimicrobial resistance, patient nonadherence) in patients with continued infection.

Factors That Affect Success

The antibiotic regimen selected is the first factor in determining whether *H. pylori* therapy is likely to be successful. The ACG guidelines list only 10 regimens that use a total of four possible antibiotics. Each regimen usually must contain two or three antibiotics plus a PPI and be used for at least 7 days and no more than 14 days, with the duration determined by the specific regimen. Several bacterial, drug, and patient factors combine to make *H. pylori* treatment selection difficult.

H. pylori *Drug Resistance*

H. pylori drug resistance is a key determinant of successful therapy. Four alarming details should be considered: (1) rates of resistance are rather high, (2) the number of isolates tested is very low, (3) much of the data are old, and (4) the most recent substantial data for the United States are almost 10 years old and include fewer than 200 isolates (Chey 2017). Whether and how much of these data can be extrapolated to the United States as a whole, much less to an individual patient, are debatable. Regardless, the available data show cause for concern.

Few susceptibility data are specific to the United States. The available data approximate levofloxacin, metronidazole, and clarithromycin resistance rates of 30%, 20%, and 20%, respectively. Resistance rates in many other nations are even higher for these antibiotics. Amoxicillin, tetracycline, and rifabutin still have good activity against *H. pylori* in both the United States and many other countries, with resistance rates generally less than 5%. However, antibiotic resistance of *H. pylori* has generally increased over time, and some data analyses link increased rates of community antibiotic use with an increased likelihood of *H. pylori* antibiotic resistance (Shiota 2015; Duck 2004).

There is also a clear, direct link between antibiotic resistance and treatment failure with *H. pylori.* Although the effect of antibiotic resistance on *H. pylori* treatment success depends on the specific antibiotic, eradication is reduced by 25%–50% (Table 3).

Patient Factors

The four most important patient parameters that help guide selection of *H. pylori* therapy are past antibiotic use (no matter how distant in the past), history of allergies or adverse drug reactions, presence of potential drug-drug interactions, and adherence.

As with most bacteria, *H. pylori* has a strong relationship between past antibiotic use and resistance. What sets *H. pylori* apart from other bacteria is that any previous use in a patient's life increases the risk of resistance. The generally low resistance rates of *H. pylori* to amoxicillin, tetracycline, and rifabutin make past use of these agents less important. The primary antibiotics of concern are metronidazole, clarithromycin, and levofloxacin. However, resistance risk is not predicated on use of these specific agents. Rather, use of any antibiotic from within the same class increases the risk of resistance. In addition, there is a positive correlation between the number of these previous antibiotic courses and increased resistance rates (Chey 2017). Therefore, classes of antibiotics that have previously been used by the patient are generally avoided.

Careful review of a patient's history of allergic and nonallergic adverse drug reactions can help reveal potential antibiotic options. Adverse reactions, especially those involving the GI tract, are common with both metronidazole and

Table 3. *H. pylori* Resistance to Antibiotics

Antibiotic	Resistance Rate in North America	Resistance Rates Outside North America	Effect of Resistance on Eradication Rates
Clarithromycin	13%–30%	18%–50%	Reduces eradication by ~50%
Metronidazole	20%–42%	30%–65%	Varies depending on regimen, dose, duration, and use of PPIs: < 25%
Levofloxacin	19%–30%	14%–50%	Reduces eradication by 20%–40%
Amoxicillin Rifabutin Tetracycline	< 2%	< 5%	Slight because of low resistance rates

Information from: Chey WD, Leontiadis GI, Howden CW, et al. ACG guideline: treatment of *Helicobacter pylori* infection. Am J Gastroenterol 2017;112:212-38; Shiota S, Reddy R, Alsarraj A, et al. Antibiotic resistance of *Helicobacter pylori* among male United States veterans. Clin Gastroenterol Hepatol 2015;13:1616-24; Megraud F, Coenen S, Versporten A, et al. *Helicobacter pylori* resistance to antibiotics in Europe and its relationship to antibiotic consumption. Gut 2013;62:34-42; Thung I, Aramin H, Vavinskaya V, et al. Review article: the global emergence of *Helicobacter pylori* antibiotic resistance. Aliment Pharmacol Ther 2016;34:514-33; Duck WM, Sobel J, Prukler JM, et al. Antimicrobial resistance incidence and risk factors among *Helicobacter pylori*-infected persons, United States. Emerg Infect Dis 2004;10:1088-94; Dore MP, Leandro G, Realdi G, et al. Effect of pretreatment antibiotic resistance to metronidazole and clarithromycin on outcome of *Helicobacter pylori* therapy; a meta-analytical approach. Dig Dis Sci 2000;45:68-76; Fischbach L, Evans EL. Meta-analysis: the effect of antibiotic resistance status on the efficacy of triple and quadruple first-line therapies for *Helicobacter pylori*. Aliment Pharmacol Ther 2007;26:343-57; Kuo H, Hu HM, Kuo FC, et al. Efficacy of levofloxacin-based rescue therapy for *Helicobacter pylori* infection after standard triple therapy: a randomized controlled trial J Antimicrob Chemother 2009;63:1017-24; Perna F, Zullo A, Ricci C, et al. Levofloxacin-based triple therapy for *Helicobacter pylori* re-treatment: role of bacterial resistance. Dig Liver Dis 2007;39:1001-5.

clarithromycin. True penicillin allergies are common and necessitate avoidance of amoxicillin. A nonallergic reaction such as GI intolerance does not require avoiding amoxicillin.

Presence of a potential drug-drug interaction requires the pharmacist to investigate the likelihood as well as the potential severity of the interaction. Rifabutin may lower the serum concentrations of some antidepressants, but if the patient has well-controlled, uncomplicated depression, a 10- to 14-day course of an enzyme inducer may not be clinically significant. Enzyme induction is of greater concern in a patient taking warfarin with a history of labile INR results.

Treatment regimens for *H. pylori* include factors that complicate medication adherence such as multiple-times-daily dosing, longer courses of multiple drugs, and a high likelihood of adverse reactions. In some instances, choice of a regimen may depend on using a specific factor as a tiebreaker. Often, however, the clinician can do little to change these factors. Counseling patients on the importance of adherence is vital to ensuring therapy is as successful as possible. Preparing patients for a potentially challenging course of therapy may make them more willing to finish a course of therapy. In addition, providing patients with tools to help with their primary concern can be effective. Coaching patients on how to minimize nausea with medications (e.g., taking with food) or identifying reminders to take their medications may also help. Patients may also be more willing to accept the adverse reactions of medications if the reason for taking the medication is sufficiently compelling. Patients who are prescribed *H. pylori* regimens to heal an ulcer may feel more inclined to finish therapy than those with uncomplicated dyspepsia. Alternatively, patients' perception of their disease may provide an incentive to start and finish therapy.

PRINCIPLES AND GOALS OF THERAPY

Goals of Therapy

Eradication of *H. pylori* is the direct goal of therapy, but the ultimate goal of therapy depends on the specific reason for testing and involves eliminating or improving the clinical disease. Eradication is necessary for clinical improvement in conditions with the strongest association with *H. pylori* (e.g., PUD) but may not be enough for those with weaker associations (e.g., functional dyspepsia) (Table 4).

Structure and Duration of Therapy

Treatment of *H. pylori* requires several drugs from different classes used concurrently. The regimens used most contain at least two antibiotics, and all regimens contain a PPI. Before the widespread availability of PPIs, histamine-2 receptor antagonists were used (Table 5).

Some regimens contain bismuth subsalicylate, which has activity against *H. pylori* even though it is not an antibiotic (Chey 2017). Several *H. pylori* regimens have been studied with tetracycline. Even though doxycycline does not have the same activity as tetracycline against *H. pylori*, it may need to

Table 4. Conditions Associated with *H. pylori* and Effect of Eradication on Condition

Condition	Degree of Association	Should Patients with Disease Be Tested for H. pylori?
PUD	Strong	Yes
Gastric cancer	Strong	Yes
Gastric MALT lymphoma	Strong	Yes
ITP	Moderate	ACG *H. pylori* guideline – Yes ASH ITP guideline – Consider testing
Unexplained iron-deficiency anemia despite standard diagnostic workup	Weak to moderate	Yes
Patients starting chronic NSAID therapy	Weak to none	Yes – before starting
Patients taking chronic aspirin therapy	Weak to none	Consider
Family history of gastric cancer	Moderate to strong	Consider
Dyspepsia in adults < 60 yr	Weak to none	ACG *H. pylori* guideline – Consider testing ACG dyspepsia guideline – Yes
GERD	No, possibly negative association	Do not test
Family history of gastric disease	None	Do not test

ASH = American Society of Hematology.

Information from: Chey WD, Leontiadis GI, Howden CW, et al. ACG guideline: treatment of *Helicobacter pylori* infection. Am J Gastroenterol 2017;112:212-38; Neunert C, Lim W, Crowther M, et al. The American Society of Hematology 2011 evidence-based practice guideline for immune thrombocytopenia. Blood 2011;117:4190-207; Moayyedi PM, Lacy BE, Andrews CN, et al. ACG and CAG clinical guideline; management of dyspepsia. Am J Gastroenterol 2017;112:988-1013.

Table 5. PPI Dosing in *H. pylori* Therapy

Proton Pump Inhibitor	Regular Dose (mg)	High Dose (mg)
Dexlansoprazole	60	120
Esomeprazole	20	40
Lansoprazole	30	60
Omeprazole	20	40
Pantoprazole	40	80
Rabeprazole	20	40

Information from: Graham DY, Lu H, Dore MP. Relative potency of proton-pump inhibitors, *Helicobacter pylori* therapy cure rates, and meaning of double-dose PPI. Helicobacter 2019;24:312554.

be used in place of tetracycline because of the periodic shortages of tetracycline.

Therapy for at least 10–14 days is required. When the option of 10 or 14 days is available, some clinicians may choose the longer therapy to potentially maximize the chances of eradication. Other clinicians may prefer the shorter course of therapy, especially in patients with adherence concerns, believing the chances of finishing a 10-day course are higher than for a 14-day course. Two regimens consist of two 7-day segments, but a total of 14 days is still required (Table 6).

Even the most reliable *H. pylori* regimens do not achieve 90% eradication rates in clinical trials, which typically have higher efficacy rates than in clinical practice (Chey 2017). Educating patients requires acknowledging the following steps: finishing therapy is required but does not guarantee eradication, and eradication may not have as much effect as the patient hopes.

Table 6. Characteristics, Including Eradication Rates, of First-line *H. pylori* Regimens

Regimen Name	Drugs	Dose[a]	Frequency	Duration (days)	Eradication Rates
Clarithromycin triple	PPI	Regular or high dose	BID	14	~70%–80%
	Clarithromycin	500 mg			
	Amoxicillin or	1000 mg			
	Metronidazole	500 mg	TID		
Bismuth quadruple	PPI	Regular dose	BID	10–14	~80%–90%
	Bismuth subcitrate or	120–300 mg	QID		
	Bismuth subsalicylate	300 mg			
	Metronidazole	250 mg or	QID		
		500 mg	TID or QID		
	Tetracycline or	500 mg	QID		
	Doxycycline (if tetracycline unavailable)	100 mg	BID		
Concomitant	PPI	Regular dose	BID	10–14	~80%–90%
	Clarithromycin	500 mg			
	Amoxicillin	1000 mg			
	Metronidazole or	500 mg			
	Tinidazole				

(*Continued*)

Table 6. Characteristics, Including Eradication Rates, of First-line *H. pylori* Regimens (*Continued*)

Regimen Name	Drugs	Dose[a]	Frequency	Duration (days)	Eradication Rates
Sequential phase 1 followed by	PPI	Regular dose	BID	5–7 for each phase (10–14 days total)	~82%–84%
	Amoxicillin	1000 mg			
Phase 2:	PPI	Regular dose			
	Clarithromycin	500 mg			
	Metronidazole or	500 mg			
	Tinidazole				
Hybrid phase 1 followed by	PPI	Regular dose	BID	7 days for each phase (14 days total)	~87%–89%
	Amoxicillin	1000 mg			
Phase 2:	PPI	Regular dose			
	Amoxicillin	1000 mg			
	Clarithromycin	500 mg			
	Metronidazole or	500 mg			
	Tinidazole				
Levofloxacin triple	PPI	Regular dose	BID	10–14	~80%–90%
	Amoxicillin	1000 mg	BID		
	Levofloxacin	500 mg	QD		
Levofloxacin sequential phase 1 followed by	PPI	Regular or high dose	BID	5–7 for each phase (10–14 days total)	~83%–88%
	Amoxicillin	1000 mg			
Phase 2:	PPI	Regular or high dose	BID		
	Amoxicillin	1000 mg	BID		
	Levofloxacin	500 mg	QD		
	Metronidazole or	500 mg	BID		
	Tinidazole				
LOAD	Levofloxacin	250 mg	QD	7–10	~89%
	PPI	High dose	QD		
	Nitazoxanide	500 mg	BID		
	Doxycycline	100 mg	QD		

[a]See Table 5 for definitions of regular and high-dose PPIs.

BID = twice daily; LOAD = PPI, levofloxacin, amoxicillin, and nitazoxanide; QD = once daily; QID = four times daily; TID = three times daily.

Information from: Chey WD, Leontiadis GI, Howden CW, et al. ACG guideline: treatment of *Helicobacter pylori* infection. Am J Gastroenterol 2017;112:212-38.

FIRST-LINE THERAPY

How to Select Therapy

The two main criteria that determine regimen selection are previous use of macrolides, nitroimidazoles, or fluoroquinolones and any allergies or adverse reactions to the drugs used in *H. pylori* therapy. A regimen to which the patient has had no previous antibiotic exposure (especially to macrolides, nitroimidazole, and fluoroquinolones) is ideal. Other factors that may help guide therapy include patient or clinician preferences on length of therapy, dosing frequency, and cost (Figure 1 and Figure 2).

Understanding the ACG Choices

All *H. pylori* regimens in the ACG guidelines have clinical trial data to support their use. However, few trials have directly compared these regimens, and most information comes from clinical trials conducted outside the United States. The available data cannot be related to many patients and choosing one regimen over another cannot be based on the highest-quality evidence. These quandaries led the ACG guideline panel to use the terms *recommended* and *suggested* to indicate which regimens are preferred. Clarithromycin triple, bismuth quadruple, and concomitant regimens were "recommended" by the ACG panel, whereas five regimens (sequential, hybrid,

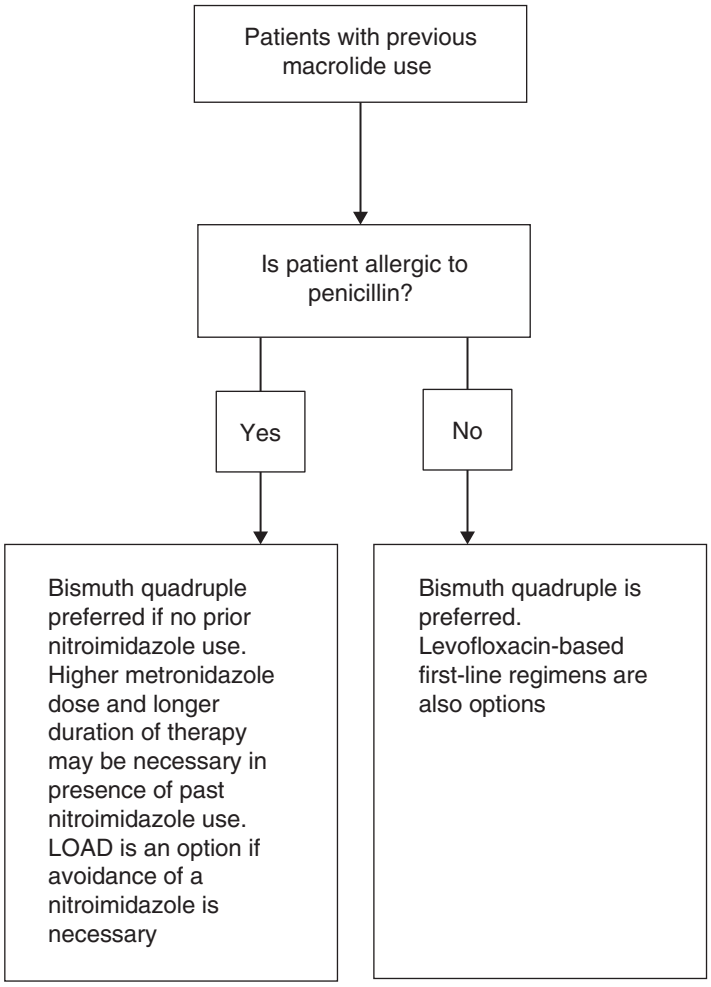

Figure 1. General approach to selecting therapy for *H. pylori* infection in patients with previous macrolide use.

LOAD = proton pump inhibitor, levofloxacin, amoxicillin, and nitazoxanide.

Information from: Chey WD, Leontiadis GI, Howden CW, et al. ACG guideline: treatment of *Helicobacter pylori* infection. Am J Gastroenterol 2017;112:212-38; Crowe SE. *Helicobacter pylori* infection. N Engl J Med 2019;380:1158-65.

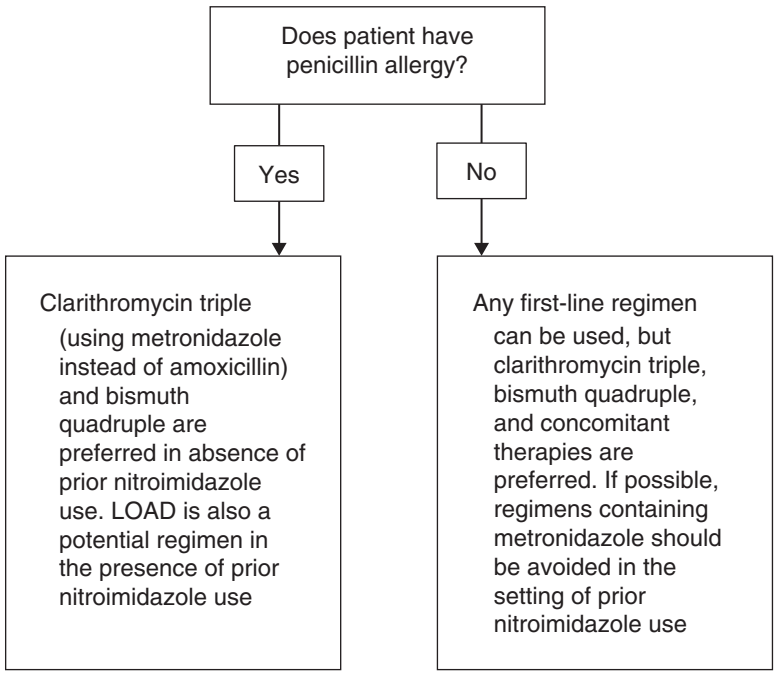

Figure 2. General approach to selecting therapy for *H. pylori* infection in patients without previous macrolide use.

Information from: Chey WD, Leontiadis GI, Howden CW, et al. ACG guideline: treatment of *Helicobacter pylori* infection. Am J Gastroenterol 2017;112:212-38; Crowe SE. *Helicobacter pylori* infection. N Engl J Med 2019;380:1158-65.

levofloxacin triple, levofloxacin sequential, and LOAD [PPI, levofloxacin, amoxicillin, and nitazoxanide]) were "suggested" (Chey 2017). This terminology does not necessarily indicate which regimen should be used in individual patients because patient-specific considerations may take priority.

Commentary on First-line Regimens

Clarithromycin Triple

The regimen of a PPI plus clarithromycin plus amoxicillin (or metronidazole) has the most clinical experience with its use but is adversely affected by increased rates of clarithromycin-resistant *H. pylori*. The ACG guidelines caution against its use in areas with clarithromycin resistance greater than 15%. Available data analyses indicate such resistance rates are likely in most areas of the United States. In addition, data analyses from primarily outside the United States show that eradication rates may now be less than 80% (Chey 2017). The clarithromycin triple regimen remains a reasonable choice but should be limited to patients without a history of macrolide use (which is probably very few individuals). Metronidazole can be substituted for amoxicillin in this regimen, but the combination of metronidazole and clarithromycin may be difficult for many patients to tolerate because of GI adverse reactions.

Bismuth Quadruple

Increasing rates of clarithromycin resistance together with the substantial impact of such resistance on eradication rates have made the quadruple regimen of a PPI plus bismuth plus metronidazole plus tetracycline a primary workhorse of *H. pylori* therapy. Limited data analyses comparing bismuth quadruple with clarithromycin triple generally indicate that the quadruple regimen has better eradication rates (Chey 2017). Four-times-daily dosing weighs against the use of bismuth quadruple in patients for whom adherence is a concern. Assuming that frequent dosing is not a substantial burden, bismuth quadruple is an important regimen, especially for patients with past macrolide use.

Concomitant

Concomitant therapy can be considered the "kitchen-sink approach," in which all three antibiotics (amoxicillin, either tinidazole or metronidazole, clarithromycin) are used. This regimen appears to have higher eradication rates than clarithromycin triple, but comparative trials in the United States are lacking. The optimal therapy duration is not known, though eradication rates appear to be increased with longer durations (Chey 2017). A therapy duration of 10–14 days is recommended, but the recommendation for a specific patient

is determined by weighing the potential benefit of increased eradication against the potential difficulty of completing 4 additional days of therapy.

Sequential

Sequential *H. pylori* therapy is an attempt to "split the difference" by dividing concomitant therapy into two equal 5- to 7-day blocks, with the first block consisting of a PPI and amoxicillin and the second block consisting of a PPI plus clarithromycin plus a nitroimidazole. However, available data analyses do not show superiority compared with clarithromycin triple. In addition, sequential therapy has not yielded eradication rates similar to concomitant therapy (Chey 2017). Sequential therapy is not often recommended because the complexity of taking two separate regimens and timing the two regimens correctly is not justified by higher eradication rates.

Hybrid

Hybrid *H. pylori* therapy is an attempt, like sequential therapy, to obtain higher eradication rates by dividing the regimen into two segments. The first segment consists of a 7-day course of a PPI and amoxicillin-like sequential therapy, but it then continues the amoxicillin therapy as a component of the second segment of therapy together with the PPI, clarithromycin, and a nitroimidazole. This regimen may be more attractive than the sequential regimen because its eradication rates appear higher, but no direct comparative evidence exists, and there are no North American trials (Chey 2017). If therapy broken into two segments is desired, hybrid therapy is likely preferred to sequential therapy, with the recognition that this is based on noncomparative data.

Levofloxacin First-line Regimens

Levofloxacin Triple

Levofloxacin triple therapy consists of a PPI, levofloxacin, and amoxicillin. This regimen is attractive for individuals who cannot take either metronidazole or clarithromycin, whether because of allergies, adverse reactions, or drug-drug interactions. Evidence is conflicting, with some comparative data showing levofloxacin triple to have eradication rates similar to clarithromycin triple and others showing higher eradication rates (Chey 2017). This regimen is expected to be better tolerated than regimens containing both metronidazole and clarithromycin. One safety concern is the small absolute risk but increased relative risk of QTc prolongation and resulting ventricular arrhythmias when combined with other drugs known to prolong the QTc interval.

Levofloxacin Sequential

Levofloxacin sequential therapy replaces the clarithromycin in sequential therapy with levofloxacin. This change creates a 5- to 7-day course of a PPI plus amoxicillin, followed by 5–7 days of a PPI plus amoxicillin plus levofloxacin plus a nitroimidazole. Pooled evidence (not from the United States) suggests that levofloxacin sequential therapy has higher eradication rates than both clarithromycin triple and sequential therapies (Chey 2017).

Patient Care Scenario

A 45-year-old man is given a diagnosis of PUD of the gastric antrum after an endoscopy. Biopsy results confirm *H. pylori* infection. The patient has an extensive history of macrolide use for past sinus infections. He has also used penicillin in the distant past but cannot remember the names of any other antibiotics he has taken. He has no known drug allergies, and his only medication is pravastatin for hyperlipidemia. What would be the best regimen to attempt eradication of *H. pylori*?

ANSWER:

Before determining a treatment regimen, it is best to investigate the reason for testing. In this case, the patient has a clear indication for testing because of the diagnosis of PUD on endoscopy. The next step is to determine what degree of clinical benefit can be expected if eradication is successful. Eradication of *H. pylori* accelerates healing of PUD and reduces risk of recurrence. Treatment should be offered to all patients with *H. pylori* infection, and an appraisal of the risk-benefit should be made available to the patient.

Avoiding antibiotic classes previously used is the first determinant of successful therapy. Past allergic reactions and potential drug interactions are also necessary considerations. Given that this patient has been known to use only macrolides in the past, without use of the two other antibiotics most susceptible to resistance from past use (i.e., fluoroquinolones and metronidazole), the chances of successful therapy are good – likely 80% or greater with most of the common first-line regimens, assuming full adherence. The necessity for complete adherence and information on the hopeful, but not guaranteed, eradication rates are both essential to teach the patient.

None of the clarithromycin-containing first-line regimens are adequate because of the high probability of clarithromycin-resistant *H. pylori*. This leaves bismuth quadruple or any of the three levofloxacin-containing regimens. Bismuth quadruple is preferred because of more evidence supporting its use and the desire to reserve levofloxacin-containing regimens for therapy if bismuth quadruple fails.

A levofloxacin-containing regimen should be chosen instead of bismuth quadruple if there are adherence concerns or the patient has a history of treatment with metronidazole.

1. Chey WD, Leontiadis GI, Howden CW, et al. ACG guideline: treatment of *Helicobacter pylori* infection. Am J Gastroenterol 2017;112:212-38.
2. Venerito M, Krieger T, Ecker T, et al. Meta-analysis of bismuth quadruple therapy versus clarithromycin triple therapy for empiric primary treatment of *Helicobacter pylori* infection. Digestion 2013;88:33-45.

LOAD Regimen

The LOAD regimen is a complex combination of a PPI, levofloxacin, amoxicillin, and nitazoxanide. The primary evidence supporting its use is from an open-label trial. The other first-line regimens have stronger evidence supporting their use. In addition to the complexity of four medications, LOAD is the most expensive regimen listed because it includes nitazoxanide, a drug not yet available in a generic formulation. This extra cost does not come with evidence of improved eradication rates or other advantages (Chey 2017).

TESTING AFTER THERAPY

Testing for eradication after completion of *H. pylori* therapy is both recommended by the ACG guidelines and routinely done in most settings (Chey 2017). Wanting to confirm eradication of *H. pylori* is logical and even more desirable when the indication for treatment is particularly compelling (e.g., PUD, early gastric cancer). However, evidence is not conclusive that routine testing after therapy leads to better outcomes or to benefits that outweigh the additional costs and complexity of care. Testing after therapy poses the same problem as testing before therapy – namely, a problem may be uncovered that is difficult or impossible to solve. Anecdotally, patients can develop an obsession to eradicate *H. pylori* when the infection may not objectively affect their life. This can be particularly damaging when the reason for therapy is unlikely to be eliminated, even with successful therapy (i.e., functional dyspepsia). Clinicians should have straightforward conversations when eradication appears unlikely (e.g., after several courses of therapy) or not beneficial.

If testing after treatment is elected, a noninvasive test (i.e., urea breath or stool antigen) is usually best unless an endoscopy is otherwise indicated, in which case an endoscopy-based test can be performed. Endoscopy or other invasive testing is unnecessary when testing for eradication success is the only clinical information needed. Clinically, the most important criteria are to wait at least 4 weeks after therapy has been completed and 2 weeks after PPI therapy has been discontinued before testing for eradication.

SALVAGE THERAPY

How to Select Salvage Therapy

Salvage therapy is treatment of *H. pylori* after the failure of previous *H. pylori* regimens. Avoiding the antibiotics (especially clarithromycin and levofloxacin) previously used by a patient who has tried one or more *H. pylori* regimens is paramount. Previous rifamycin use is less likely than use of either macrolides or fluoroquinolones. In general, metronidazole should also be avoided if used previously, but some data analyses show that it may retain effectiveness if used at higher doses (defined as 500 mg either three or four times daily) and for longer durations (14 days). Amoxicillin and doxycycline have relatively low resistance rates and can still be used in salvage therapy, if necessary (Chey 2017) (Figures 3–8).

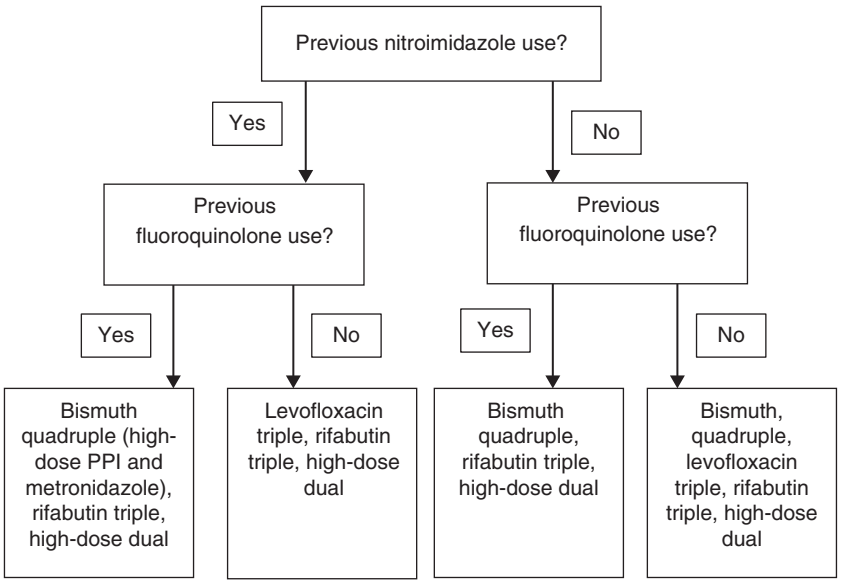

Figure 3. General approach to selecting salvage therapy for patients after unsuccessful therapy with clarithromycin triple (using amoxicillin, not metronidazole).

Information from: Chey WD, Leontiadis GI, Howden CW, et al. ACG guideline: treatment of *Helicobacter pylori* infection. Am J Gastroenterol 2017;112:212-38; Crowe SE. *Helicobacter pylori* infection. N Engl J Med 2019;380:1158-65.

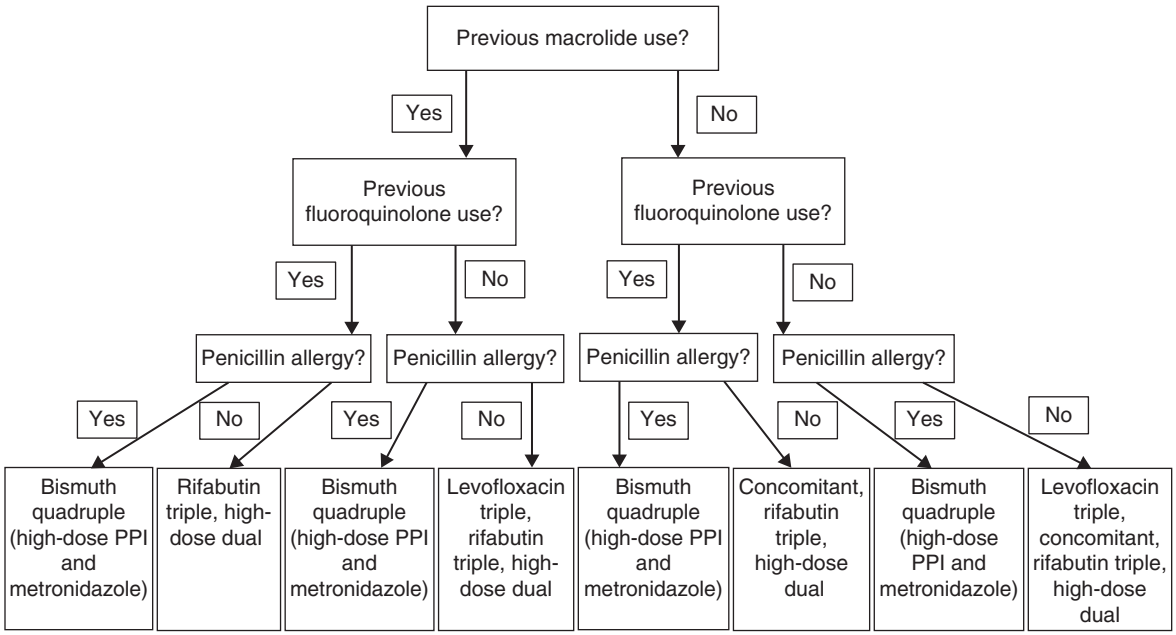

Figure 4. General approach to selecting salvage therapy in patients after unsuccessful therapy with bismuth quadruple.

Information from Chey WD, Leontiadis GI, Howden CW, et al. ACG Guideline: Treatment of *Helicobacter pylori* infection. Am J Gastroenterol 2017;112:212-38; Crowe SE. *Helicobacter pylori* infection. N Engl J Med 2019;380:1158-65.

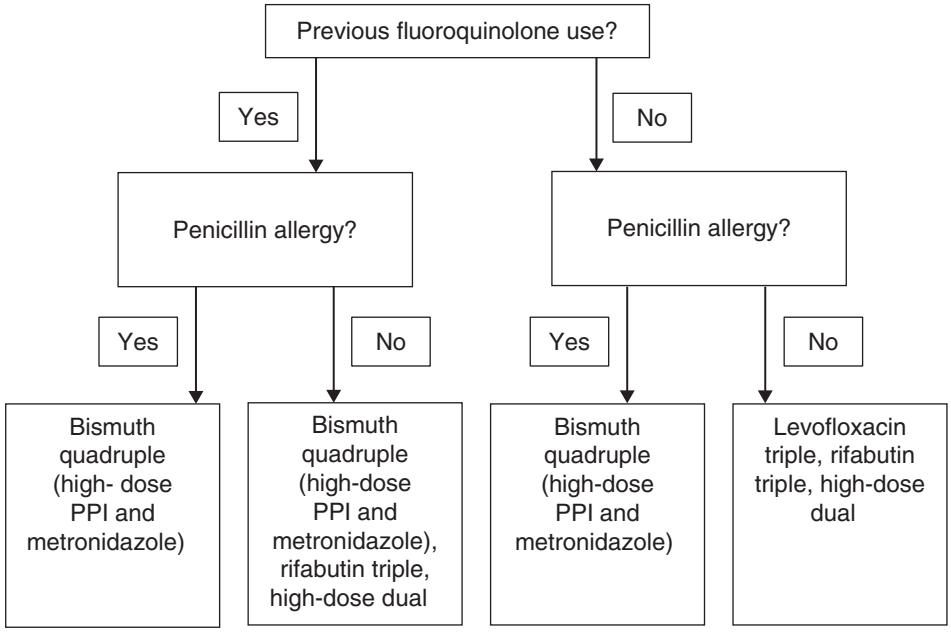

Figure 5. General approach to selecting salvage therapy in patients after unsuccessful therapy with concomitant, sequential or hybrid regimens.

Information from Chey WD, Leontiadis GI, Howden CW, et al. ACG Guideline: Treatment of *Helicobacter pylori* infection. Am J Gastroenterol 2017;112:212-38; Crowe SE. *Helicobacter pylori* infection. N Engl J Med 2019;380:1158-65.

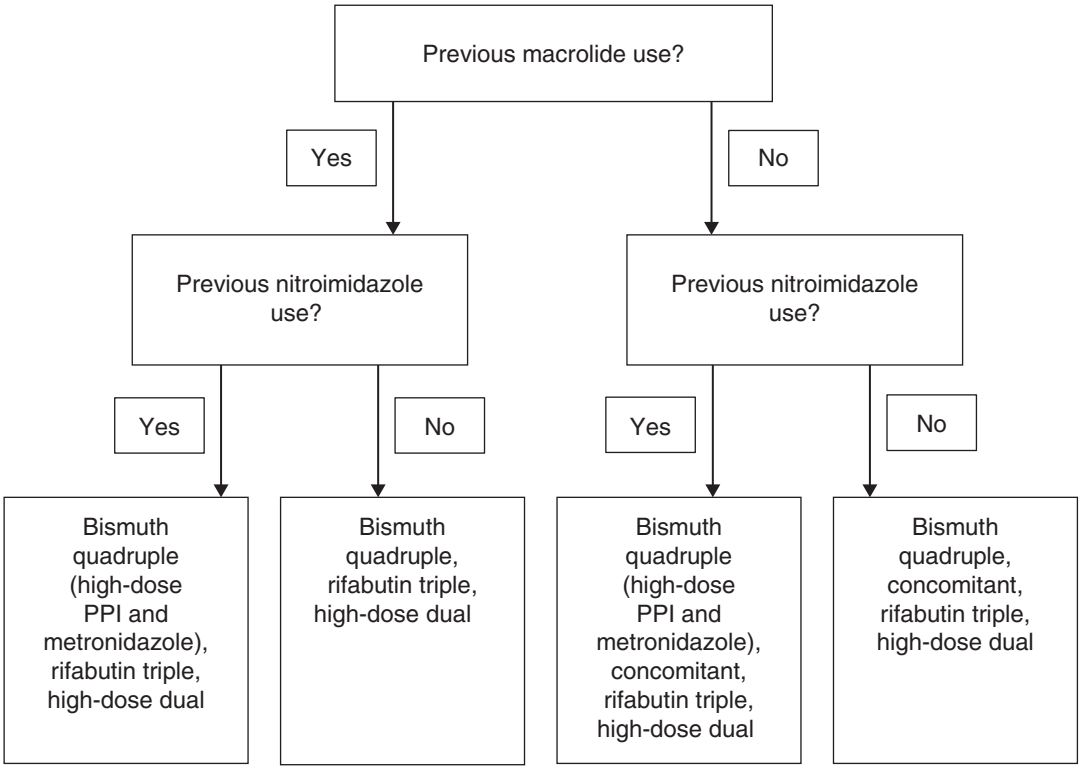

Figure 6. General approach to selecting salvage therapy in patients after unsuccessful therapy with levofloxacin triple.

Information from Chey WD, Leontiadis GI, Howden CW, et al. ACG Guideline: Treatment of *Helicobacter pylori* infection. Am J Gastroenterol 2017;112:212-38; Crowe SE. *Helicobacter pylor*i infection. N Engl J Med 2019;380:1158-65.

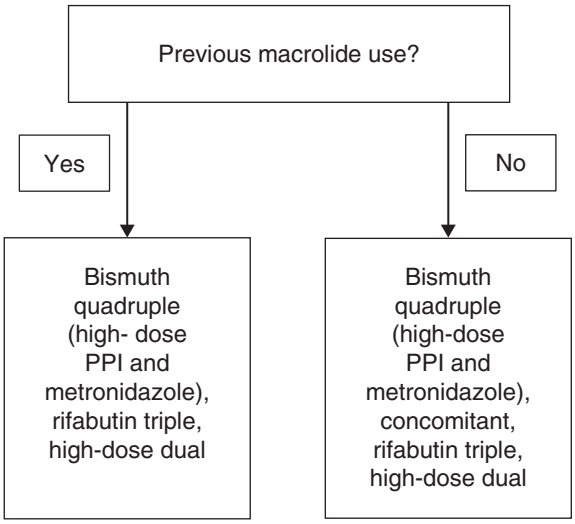

Figure 7. General approach to selecting salvage therapy in patients after unsuccessful therapy with levofloxacin sequential.

Information from Chey WD, Leontiadis GI, Howden CW, et al. ACG Guideline: Treatment of *Helicobacter pylori* infection. Am J Gastroenterol 2017;112:212-38; Crowe SE. *Helicobacter pylori* infection. N Engl J Med 2019;380:1158-65.

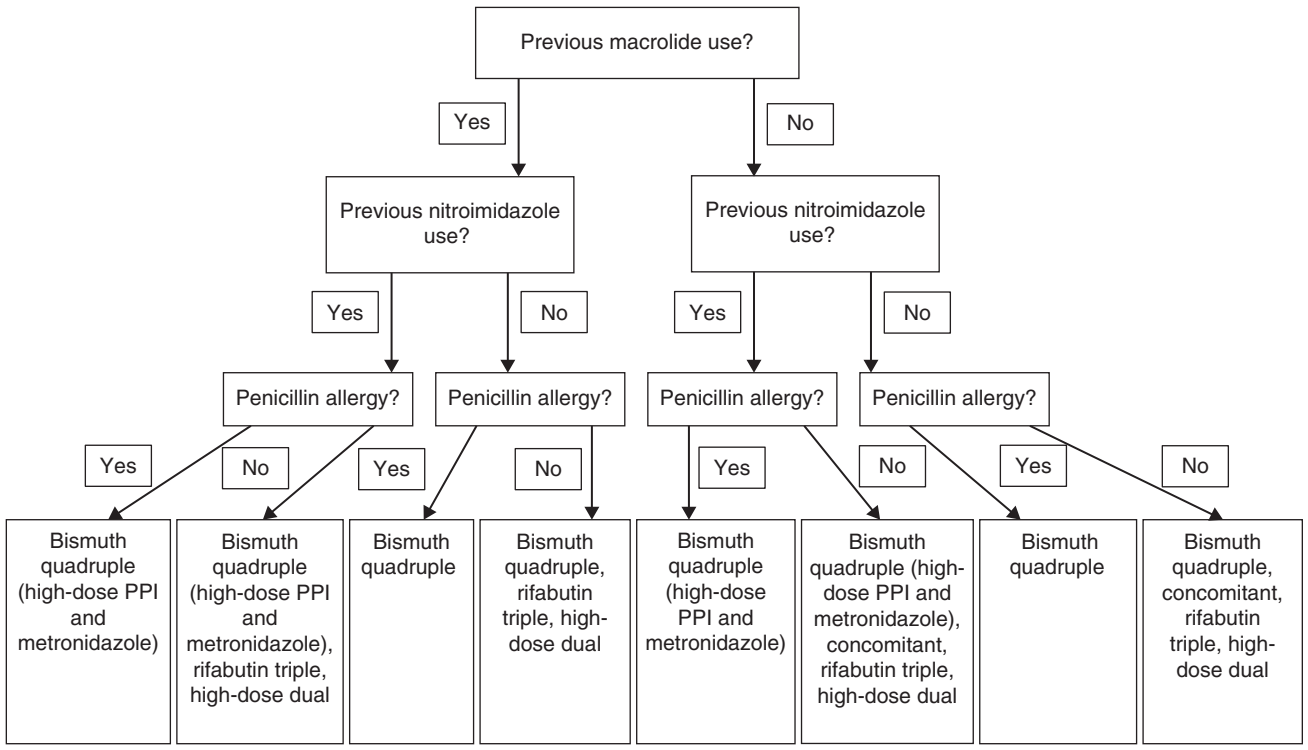

Figure 8. General approach to selecting salvage therapy in patients after unsuccessful therapy with LOAD.

Information from Chey WD, Leontiadis GI, Howden CW, et al. ACG Guideline: Treatment of *Helicobacter pylori* infection. Am J Gastroenterol 2017;112:212-38; Crowe SE. *Helicobacter pylori infection.* N Engl J Med 2019;380:1158-65.

Commentary on Salvage Therapy Regimens

Only two of the regimens listed for salvage therapy (bismuth quadruple and levofloxacin triple) are "recommended" by the ACG guidelines. The other three regimens (concomitant, rifabutin triple, and high-dose dual) are "suggested" (Chey 2017). All salvage therapies listed by the ACG are preferred for salvage therapy because clinical trials have shown their usefulness in the salvage setting. Depending on individual patient factors, it may be necessary to choose an alternative regimen from those listed as first line if the regimen meets the general criteria of choosing a regimen without previously used antibiotics. This strategy may be useful when repeat treatment is required, but standard salvage regimens are unlikely to be successful given the patient's past antibiotic use or when a history of allergic reactions eliminates options. The clarithromycin triple regimen should specifically be avoided after treatment failure of one or more first-line regimens. The lower eradication rates even in the first line setting and unacceptably high risk of clarithromycin resistance in most patients whose treatment has failed with one or more first-line regimens make clarithromycin triple a poor choice (Table 7).

Bismuth Quadruple

Bismuth quadruple is more aggressive in the salvage setting than in the first-line setting because of the listing of a longer duration (14 days vs. 10–14 days) and higher dose of a nitroimidazole (500 mg given by mouth three or four times daily) (Chey 2017). Bismuth quadruple is sometimes necessary even in the presence of past nitroimidazole use, in which case using a high-dose PPI (see Table 5) and higher-dose metronidazole (defined as 500 mg either three or four times daily) is reasonable, even if specific evidence for this strategy is lacking. The primary advantages of bismuth quadruple are the clinical trial data and extensive experience supporting its use. However, many patients have previously used either metronidazole on its own or bismuth quadruple therapy, limiting the regimen's effectiveness.

Levofloxacin Triple

Levofloxacin triple therapy should be given as a 14-day regimen (Chey 2017). Although some evidence exists for using levofloxacin at a dose of 500 mg orally twice daily, most evidence is at the standard dose of 500 mg once daily. This regimen is relatively simple and avoids the two most common antibiotics in first-line regimens: metronidazole and clarithromycin.

Concomitant

Concomitant therapy has the option of a higher dose of metronidazole (500 mg orally four times daily) but is otherwise

Table 7. Characteristics of Salvage Therapy *H. pylori* Regimens

Regimen Name	Drugs	Dose[a]	Frequency	Duration (in days)
Bismuth quadruple	PPI	Regular dose	BID	14
	Bismuth subcitrate or	120–300 mg	QID	
	Bismuth subsalicylate	300 mg		
	Metronidazole	500 mg	TID or QID	
	Tetracycline or	500 mg	QID	
	Doxycycline (if tetracycline unavailable)	100 mg	BID	
Levofloxacin triple	PPI	Regular dose	BID	14
	Amoxicillin	1000 mg	BID	
	Levofloxacin	500 mg	QD	
Concomitant	PPI	Regular dose	BID	10–14
	Clarithromycin	500 mg	BID	
	Amoxicillin	1000 mg	BID	
	Metronidazole or	500 mg	BID or TID	
	Tinidazole			
Rifabutin triple	PPI	Regular dose	BID	10
	Amoxicillin	1000 mg	BID	
	Rifabutin	300 mg	QD	
High-dose dual	PPI	Regular or high dose	TID or QID	14
	Amoxicillin	1000 mg	TID	
		750 mg	QID	

[a]See Table 5 for definitions of regular and high-dose PPIs.

Information from: Chey WD, Leontiadis GI, Howden CW, et al. ACG guideline: treatment of *Helicobacter pylori* infection. Am J Gastroenterol 2017;112:212-38.

identical to first-line concomitant therapy (Chey 2017). However, concomitant therapy is often the least likely salvage regimen to be chosen because of the high rates of previous use of clarithromycin and metronidazole in the salvage setting.

Rifabutin Triple

Rifabutin-based salvage therapy has the advantage of containing a drug class unlikely to have been used previously by patients. The primary disadvantages of rifabutin triple therapy are the potent induction of several CYP isoenzymes and the high cost of rifabutin (Chey 2017). The ACG guidelines also discuss the risk of myelosuppression and increased selective pressure for rifamycin-resistant *Mycobacterium tuberculosis*, but these two risks are slight and rarely enter decision-making.

High-Dose Dual

Evidence supporting the use of high-dose dual regimens in salvage therapy is not as compelling as for most of the other therapies listed (Chey 2017). Considering the relative lack of available options and the relative simplicity of the regimen, high-dose dual is attractive for some patients, especially those for whom cost is a primary consideration.

CONCLUSION

Effective management of *H. pylori* requires a full understanding of the complexity of the disease states caused by, and the testing and treatment for, *H. pylori*. Patients must be given realistic expectations regarding the role of *H. pylori* in their disease state. In addition, the complexity of therapy and difficulty of adherence needs to be explained. Although most

Practice Points

Appropriate management of *H. pylori* requires an understanding of the nature of the infection as well as key inflection points:

- ***H. pylori* is a common infection that may cause serious disease but is not overtly harmful in most patients.**
- ***H. pylori* is a known carcinogen and therefore requires offering therapy to anyone with *H. pylori* infection.**
- **Whether to test for infection is the single most important decision in *H. pylori* management.**
- **PUD, gastric cancer, and early gastric MALT lymphoma are the three disease states most clearly linked to *H. pylori* infection and the three most likely to benefit from treatment.**
- **Testing for *H. pylori* in patients with functional dyspepsia is reasonable but should only be done with awareness that relatively few people will clinically benefit from treatment. The available treatment options, potential eradication rates, and risks of therapy should be considered when selecting *H. pylori* testing.**
- **Past use of antibiotics for *H. pylori*, especially clarithromycin, levofloxacin, and metronidazole, is the key factor in choosing a regimen.**
- **In general, patients with previous use of macrolides or fluoroquinolones should not receive regimens containing these antibiotics. If these regimens are chosen, the patient should be made aware of the low chances of successful eradication.**
- **Metronidazole at higher doses may be effective in some patients with previous use of nitroimidazoles.**
- **Educate patients on the adverse effects of *H. pylori* treatment and the need for complete adherence.**
- **Posttreatment testing is recommended for all patients who complete a course of therapy.**
- **Eradication of infection may not be feasible after several unsuccessful *H. pylori* regimens.**
- **Patients should be informed of realistic expectations at each stage of treatment.**

patients will experience eradication, such success can never fully be predicted. This may present a very pessimistic impression to patients, but it is necessary, especially considering the temptation to think of *H. pylori* as an easily treated infection with readily apparent clinical improvement upon eradication.

REFERENCES

Chey WD, Leontiadis GI, Howden CW, et al. ACG guideline: treatment of *Helicobacter pylori* infection. Am J Gastroenterol 2017;112:212-38.

Choi IJ, Kim CG, Lee JY, et al. Family history of gastric cancer and *Helicobacter pylori* treatment. N Engl J Med 2020;382:427-36.

Choi IJ, Kook MC, Kim YI, et al. *Helicobacter pylori* therapy for the prevention of metachronous gastric cancer. N Engl J Med 2018;378:1085-95.

Cover TL, Blaser MJ. *Helicobacter pylori* and other gastric *Helicobacter* species. In Bennett JE, Dolin R, Blaser MJ, eds. Mandell, Douglas, and Bennett's principles and practice of infectious diseases. Philadelphia: Elsevier; 2020:2660-8.

Crowe SE. *Helicobacter pylori* infection. N Engl J Med 2019;380:1158-65.

Duck WM, Sobel J, Prukler JM, et al. Antimicrobial resistance incidence and risk factors among *Helicobacter pylori*-infected persons, United States. Emerg Infect Dis 2004;10:1088-94.

Mazzoleni LE, Sander GB, Francesconi CFdM, et al. *Helicobacter pylori* eradication in functional dyspepsia. Arch Intern Med 2011;171:1929-36.

Moayyedi P, Soo S, Deeks J, et al. Eradication of *Helicobacter pylori* for non-ulcer dyspepsia. Cochrane Database Syst Rev 2006;2:CD002096.

Moayyedi PM, Lacy BE, Andrews CN, et al. ACG and CAG clinical guideline; management of dyspepsia. Am J Gastroenterol 2017;112:988-1013.

Neunert C, Lim W, Crowther M, et al. The American Society of Hematology 2011 evidence-based practice guideline for immune thrombocytopenia. Blood 2011;117:4190-207.

Perna F, Zullo A, Ricci C, et al. Levofloxacin-based triple therapy for *Helicobacter pylori* re-treatment: role of bacterial resistance. Dig Liver Dis 2007;39:1001-5.

Shiota S, Reddy R, Alsarraj A, et al. Antibiotic resistance of *Helicobacter pylori* among male United States veterans. Clin Gastroenterol Hepatol 2015;13:1616-24.

Self-Assessment Questions

Questions 1 and 2 pertain to the following case.

R.S., a 22-year-old man, is given a diagnosis of functional dyspepsia after findings of gastritis on endoscopy. Biopsy results were positive for *H. pylori* infection. R.S. states that he has taken azithromycin a few times for sinus infections. He denies any other medication use but states that he needs a regimen that is generic and inexpensive because he has no health insurance.

1. Which one of the following is the best antibiotic regimen to recommend for R.S.?

   A. Clarithromycin triple
   B. Levofloxacin triple
   C. Proton pump inhibitor (PPI), levofloxacin, amoxicillin, and nitazoxanide (LOAD)
   D. Hybrid

2. Two months after R.S. completes therapy, his physician asks for a recommendation on which test should be used to test for treatment success. Which one of the following tests is best to recommend for R.S.?

   A. Culture
   B. Serology
   C. Urea breath test
   D. Histology

3. A patient is prescribed clarithromycin triple for *H. pylori* infection. The patient states he was tested for *H. pylori* because of a gastric ulcer. The patient asks what will happen if the treatment is successful. Which one of the following is the best response to this patient's question?

   A. Healing of his ulcer
   B. Prevention of gastric cancer
   C. Possible onset of heartburn
   D. Slight decrease in ulcer symptoms

4. A patient has been treated with both bismuth quadruple and levofloxacin triple for *H. pylori* infection. The patient has an extensive history of macrolide use and states he just lost his job and needs a low-cost option. The gastroenterologist asks for your recommendation for salvage therapy. Which one of the following is the best regimen to recommend for this patient?

   A. LOAD
   B. Concomitant
   C. Rifabutin triple
   D. High-dose dual

5. Which one of the following patients is most likely to benefit from *H. pylori* testing?

   A. 25-year-old woman with functional dyspepsia
   B. 35-year-old man with gastroesophageal reflux disease (GERD)
   C. 45-year-old man starting chronic naproxen for gout
   D. 75-year-old man who has been taking daily aspirin for 2 years

6. A 54-year-old woman with a history of gastric cancer has *H. pylori* infection. She denies previous use of macrolides but describes an itchy rash to tetracycline and vomiting with metronidazole. Which one of the following is the best initial treatment to recommend for this patient?

   A. High-dose dual
   B. Levofloxacin triple
   C. Levofloxacin sequential
   D. LOAD

7. Which one of the following patients would most benefit from *H. pylori* testing?

   A. 55-year-old man with heartburn
   B. 25-year-old woman with dyspepsia
   C. 45-year-old man with a duodenal ulcer found on endoscopy
   D. 65-year-old woman with a family history of colorectal cancer

8. Eight days ago, a patient began a 14-day course of bismuth quadruple (omeprazole 20 mg orally twice daily, bismuth subsalicylate 300 mg orally four times daily, metronidazole 250 mg orally four times daily, tetracycline 500 mg orally four times daily) for first-line therapy. Today, the patient calls his physician with concerns of nausea. The physician asks for your recommendation. Which one of the following is best to recommend for this patient?

   A. Change bismuth quadruple to clarithromycin triple.
   B. Continue current regimen for 2 more days.
   C. Continue current regimen for 6 more days.
   D. Decrease the metronidazole dose to 250 mg three times daily.

9. A 60-year-old man recently tested positive for *H. pylori*, and his physician wants to treat him with clarithromycin triple therapy. Which one of the following factors is the most likely to determine *H. pylori* treatment success?

   A. Therapy duration
   B. Antibiotic dose
   C. Dose of PPI
   D. Local *H. pylori* resistance rates

10. Six months ago, a patient was initiated on LOAD for treatment of an *H. pylori* infection. She was tested for *H. pylori* because of persistent functional dyspepsia. Follow-up testing after completion of therapy showed eradication of *H. pylori*. Today, the patient calls the clinic, stating that her dyspepsia symptoms have improved over the past 6 months but are still bothersome. Which one of the following is the most appropriate response to the patient?

    A. You should be tested for *H. pylori* infection because you may have been reinfected.
    B. Eradication of *H. pylori* does not usually eliminate dyspepsia.
    C. Previous testing may have been incorrect and retreatment is warranted.
    D. Persistent dyspepsia is of concern and an endoscopy is warranted.

11. A patient is prescribed levofloxacin triple (containing omeprazole as the PPI) for 14 days to treat *H. pylori* infection. Which one of the following is the most appropriate counseling point to provide this patient?

    A. Levofloxacin often causes severe nausea, so take the antibiotic with food.
    B. No regimen is 100% successful, so retreatment may be necessary.
    C. Omeprazole is not as important as the antibiotics in treating the infection.
    D. Taking each dose of the regimen is important to successfully treat the infection.

12. A patient with active peptic ulcer disease (PUD) was found to have an *H. pylori* infection. He subsequently received bismuth quadruple for 14 days as a first-line regimen but had a positive *H. pylori* test a few months after completing therapy. He then received concomitant therapy for 10 days as salvage therapy about 4 months ago and today had another positive *H. pylori* test. Which one of the following is the best salvage therapy to recommend for this patient?

    A. Concomitant therapy for 14 days
    B. Levofloxacin triple for 14 days
    C. Clarithromycin triple for 14 days
    D. LOAD for 10 days

13. A physician is seeing a patient for nausea and abdominal pain, especially after eating. Given these symptoms, the physician has referred the patient for an endoscopy to investigate for PUD, which is scheduled for tomorrow. The physician states the patient received *H. pylori* therapy 10 years ago. Which one of the following is the best testing strategy to confirm eradication in this patient?

    A. Biopsy
    B. Serology
    C. Urea breath test
    D. Stool antigen

14. A patient tests positive for *H. pylori* after a 14-day regimen of a PPI, clarithromycin, and amoxicillin. Which one of the following is the best salvage regimen to recommend for this patient?

    A. Concomitant
    B. Hybrid
    C. Sequential
    D. Bismuth quadruple

15. Which one of the following is the most reasonable goal of *H. pylori* therapy in a patient with a history of gastric cancer?

    A. Prevention of metastatic disease
    B. Reduction in cancer mortality
    C. Reduction in risk of gastric cancer
    D. Reduction in symptoms