REVIEW

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A clinician's guide to managing *Helicobacter pylori* infection

ABSTRACT

Helicobacter pylori infection is chronic and very common. Its clinical consequences vary widely, ranging from being asymptomatic and clinically insignificant in many cases to causing dyspepsia, peptic ulcer disease, and gastric malignancy in others. Care must be used in deciding whom to test for *H pylori* infection, as a positive result mandates treatment, making broad-based screening impractical.

KEY POINTS

Available diagnostic studies include invasive and noninvasive tests. The best test must be chosen for the specific clinical setting.

Many drugs in multiple combinations have been used, with varying degrees of success. The first-line regimens are clarithromycin-based triple-drug therapy (used in patients who are not allergic to penicillin) and bismuth-based quadruple therapy (used in penicillin-allergic patients).

All patients with an *H pylori*-associated ulcer should undergo testing to prove eradication after a course of therapy; the urea breath test and fecal antigen test are the most appropriate noninvasive options.

Salvage therapy for persistent *H pylori* infection should be given for 10 to 14 days and should not include antibiotics used previously.

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HELICOBACTER PYLORI INFECTION is extremely common but does not always cause clinical disease. One must choose carefully which patients to test because widespread treatment is neither justified clinically nor cost-effective.

This article will help the clinician determine which patients should be tested for *H pylori* and choose the most appropriate diagnostic test. We also discuss treatment strategies, including methods for ensuring that *H pylori* has been eradicated.

IMPACT OF *H PYLORI* INFECTION

H pylori is the most common bacterial infection in humans: an estimated half of the world's population is infected.[1] It is also the most common cause of chronic gastritis.[2]

The prevalence of *H pylori* infection is closely tied to socioeconomic conditions. Although this infection is more common in third-world countries than in developed countries such as the United States, 30% to 40% of the US population may be infected.[3]

The vast majority of infected people acquire the organism during childhood. On the basis of this observation and that *H pylori* infection rates in children are falling, the population-based prevalence of *H pylori* in the United States will likely continue to fall in coming years.

INDICATIONS FOR *H PYLORI* TESTING

Although *H pylori* infection is usually clinically silent, a number of medical conditions are known to be associated with it. The indications for testing for *H pylori* infection (and treating it if it is present) are listed in **TABLE 1**.

TABLE 1

Indications for testing for *H pylori*

Established indications
- Active peptic ulcer disease (gastric or duodenal)
- Confirmed history of peptic ulcer disease (not previously treated for *H pylori*)
- Use of maintenance antisecretory therapy for a history of peptic ulcer disease
- Gastric mucosa-associated lymphoid tissue lymphoma (low grade)
- Following endoscopic resection of early gastric cancer
- Uninvestigated dyspepsia (depending on *H pylori* prevalence in community)

Controversial indications
- Nonulcer dyspepsia
- Long-term use of nonsteroidal anti-inflammatory drugs
- Gastroesophageal reflux disease
- Long-term proton pump inhibitor use
- Family history of gastric malignancy
- Populations with a high risk for gastric cancer

***H pylori* is the most common bacterial infection worldwide**

Established indications

Peptic ulcer disease. There is a clear link between *H pylori* infection and the pathogenesis of peptic ulcer disease. In view of the overwhelming evidence,[4–6] few would question the clinical and economic merits of *H pylori* eradication in this population.

Gastric tumors. The prevalence of *H pylori* infection in patients with gastric adenocarcinoma and mucosa-associated lymphoid tissue lymphoma (MALToma) is significantly higher than in controls.[7–9] Because up to two thirds of patients with low-grade gastric MALToma will experience tumor regression following *H pylori* eradication, all patients with MALToma should be tested for *H pylori*.[10–12]

In addition, a study from Japan reported that eradication of *H pylori* reduces the likelihood of recurrence following endoscopic resection of early gastric adenocarcinoma.[13]

Uninvestigated ulcer-like dyspepsia. A number of organizations have recommended that patients with uninvestigated ulcer-like dyspepsia who are younger than 50 years and have no "alarm features" (weight loss, evidence of bleeding, vomiting, dysphagia, anemia, or family history of gastric malignancy) undergo testing and treatment for *H pylori*.[14]

This "test-and-treat" strategy may reduce upper endoscopy utilization and expenditures associated with the care of dyspeptic patients. However, the benefits of this strategy are largely derived from patients with undiagnosed ulcers, in whom *H pylori* eradication is potentially curative.[15]

Controversial indications

A number of controversial indications for the diagnosis and treatment of *H pylori* deserve mention.

Nonulcer dyspepsia. Two recent meta-analyses highlight that the benefits of treating *H pylori* in patients with functional or nonulcer dyspepsia are less clear.[16,17]

Though the conclusions of the available studies on the treatment of *H pylori* in nonulcer dyspepsia have conflicted, the reported likelihood of symptom response has been remarkably consistent, ranging from 21% to 46%. The most recent update of the Cochrane database on this issue[18] reported a small but statistically significant symptomatic benefit to curing *H pylori* in patients with nonulcer dyspepsia: 37% with *H pylori* cure vs 29% with placebo, relative risk 0.91.

Therefore, although there appears to be a statistically significant benefit to curing *H pylori* in patients with nonulcer dyspepsia, the incremental benefit of this strategy on a population basis is likely to be modest.[19] As such, the cost-effectiveness of the test-and-treat strategy will require periodic re-evaluation, given the changing costs of specific diagnostic tests and therapies and the falling prevalence of *H pylori* in general, and more specifically of *H pylori*-associated ulcers in the western world.[20]

NSAID use. *H pylori* and nonsteroidal anti-inflammatory drugs (NSAIDs) are independent risk factors for the development of peptic ulcer disease, and recent work suggests that these independent risk factors additively increase the risk of peptic ulcer disease.[21] With this thought in mind, all patients with an ulcer, regardless of whether they are taking an NSAID, should be tested for *H pylori*. Whether asymptomatic individuals taking NSAIDs long-term should be tested and treated for *H pylori* to reduce their risk of developing an ulcer remains controversial.

GERD. Another very controversial issue is

TABLE 2

Diagnostic tests for *H pylori*

Invasive tests
(require upper endoscopy and mucosal biopsy)

- Histology*
  - Done when biopsies are obtained for abnormal endoscopic findings
- Rapid urease testing*
  - Inexpensive, gives rapid results (1–24 hrs), less accurate in acute bleeding
- Culture*
  - Costly, limited availability, technically demanding
- Polymerase chain reaction*
  - Not commercially available

Noninvasive tests

- Antibody tests (quantitative and qualitative)
  - Inexpensive and widely available
  - Rapid results with office-based test
  - Most appropriate when pretest probability of infection is high (urban areas, immigrant populations, patients with peptic ulcers)
  - Remain positive after eradication
- Nonendoscopic urease tests (carbon 13 and carbon 14 urea breath and blood tests)*
  - Identify active infection
  - Accurate before and after treatment
- Fecal antigen test*
  - Identifies active infection
  - Accurate before and after treatment

*The sensitivity of all endoscopic and nonendoscopic tests that identify active infection is reduced by recent use of antibiotics, bismuth, or proton pump inhibitors.

whether patients with gastroesophageal reflux disease (GERD) should be tested and treated for *H pylori*. Until very recently, the controversy revolved around whether eradicating *H pylori* had no effect or even worsened symptoms of esophagitis in GERD patients.[22,23] More recently, the controversy has become more complicated, with evidence suggesting that a subset of patients with GERD-related symptoms may benefit from cure of *H pylori*.[24] Despite the lack of consensus on this issue, surveys suggest that among primary care physicians, GERD is one of the most frequent reasons for *H pylori* testing.[25]

At this time, practitioners are advised to proceed with testing and treatment in patients presenting with GERD symptoms *in association with* dyspepsia. On the other hand, in view of the currently available evidence, we do not feel that *H pylori* eradication predictably aggravates or improves GERD. Therefore, routine testing for *H pylori* in patients presenting with *only* GERD symptoms does not seem justified.

Long-term proton-pump inhibitor therapy. Kuipers et al[26] reported an increased risk of developing atrophic gastritis, a condition associated with a greater risk of gastric cancer, in patients with *H pylori* infection treated long-term with proton pump inhibitors. Subsequent studies have refuted this finding,[27] and a recent review concluded that there were no adverse gastrointestinal effects from the long-term use of these drugs in patients with *H pylori* infection.[28]

DIAGNOSIS OF *H PYLORI* INFECTION

Testing for *H pylori* should be undertaken only if the clinician is prepared to offer treatment for positive results.[29]

The diagnostic tests for *H pylori* can be divided into two groups, those that require endoscopy and those that do not (TABLE 2). The decision regarding which test to use in which situation relies heavily on whether the patient requires evaluation with upper endoscopy, and also on an understanding of the strengths and weaknesses of the individual tests. No single diagnostic test can be considered the gold standard for the diagnosis of *H pylori* infection,[30] although histology has historically been considered by some to be the most accurate single test.[31]

Endoscopic diagnostic tests

There are currently four diagnostic tests for *H pylori* infection that require mucosal biopsy at the time of endoscopy: the rapid urease test, histology, culture, and polymerase chain reaction (PCR).

The rapid urease test identifies active *H pylori* infection through the organism's urease activity. Gastric biopsies are obtained and placed into an agar gel or on a reaction strip containing urea, a buffer, and a pH-sensitive indicator. In the presence of urease (from *H*

pylori), urea is metabolized to ammonia and bicarbonate, leading to an increase in pH in the microenvironment of the organism. This in turn causes the pH-sensitive indicator to change color.[2] Results are available in 1 to 24 hours.

Commercially available rapid urease test kits include the HUT-test, CLOtest, HpFast, and PyloriTek. Their overall pretreatment sensitivity is 93% to 97%, and their specificity is greater than 95%.[32] Though the different tests are comparable in their overall performance, they have some practical differences. For example, PyloriTek yields a positive result more quickly than two of the agar gel-based tests, CLOtest and HpFast.[33]

Medications that decrease the density and/or urease activity of *H pylori*, such as bismuth-containing compounds, antibiotics, and proton pump inhibitors, can reduce the sensitivity of the rapid urease test by as much as 25%.[32] Additionally, acute ulcer bleeding at the time of testing also lowers the sensitivity and negative predictive value of the test.[34] Owing to the patchy distribution of *H pylori* infection after antibiotic or proton pump inhibitor therapy, it is recommended that biopsy samples for rapid urease testing be obtained from two sites, the body at the gastric angle and greater curvature of the antrum.[35]

Despite these potential limitations, the ease of use, relatively low cost, and rapid reaction time of the rapid urease test make it a practical and cost-effective means of diagnosing *H pylori* if endoscopy is necessary.

Histologic testing has been considered by some to be the gold standard for detecting *H pylori*.[31] Unfortunately, this is at best an imperfect gold standard, as the detection of *H pylori* depends upon a number of issues, including the site and number of biopsy samples, the method of staining, and the level of experience of the pathologist.[31]

A significant advantage of histologic testing over other diagnostic methods is the ability to evaluate for pathologic changes associated with *H pylori* infection, such as inflammation, atrophy, intestinal metaplasia, and malignancy.[36] In fact, some have argued that type B chronic gastritis (either nonatrophic diffuse antral gastritis or atrophic pangastritis) can be used as a surrogate marker for the infection when organisms are not identified.[2]

As the distribution and density of *H pylori* organisms varies throughout the stomach, the number of biopsy samples can influence the sensitivity of histologic testing. It has therefore been recommended that a minimum of three biopsy samples be obtained, one from the junction of the angulus corpus and antrum, one from the greater curvature of the corpus, and one from the greater curvature of the antrum, to maximize accuracy.[31]

As with the rapid urease test, the sensitivity of histologic testing is significantly affected by the use of medications such as bismuth-containing compounds, antibiotics, and proton pump inhibitors.[31]

Although widely available and capable of achieving sensitivity and specificity of greater than 95%, the cost and need for properly trained personnel are limitations of histologic testing in clinical practice.

Culture is another highly specific direct testing method for *H pylori*. Conceptually, culture is attractive because it not only can detect infection but also can characterize antimicrobial sensitivities.[2] Unfortunately, culture is not as sensitive as rapid urease testing or histologic testing. Furthermore, culture techniques for *H pylori* are demanding and costly and, as a consequence, are available only in a limited number of clinical laboratories.[37]

PCR is a DNA amplification technique that utilizes the rapid production of multiple copies of a target DNA sequence to identify *H pylori*. This testing method has demonstrated accuracy comparable to that of the other endoscopic tests, boasting a sensitivity of 93% and a specificity of 100%.[38] Although currently restricted to the research arena, this method may prove practical for antibiotic sensitivity testing, organism typing, and determining organism virulence in the future.[38]

Whether treating *H pylori* improves GERD symptoms is not clear

Nonendoscopic diagnostic tests

There are currently three nonendoscopic diagnostic testing methods for *H pylori* infection. Antibody testing identifies an immunological reaction to the infection, while the nonendoscopic urease tests and fecal antigen test identify active *H pylori* infection.

Serologic or antibody testing is the most commonly used form of testing for *H pylori* infection in primary care.[39] Antibody testing

relies on the detection of IgG antibodies specific for *H pylori* in serum, whole blood, or urine. These antibodies typically appear approximately 21 days after infection and can remain present long after eradication[40]; they can be quantitatively assessed using enzyme-linked immunosorbent (ELISA) and latex agglutination techniques or qualitatively assessed using office-based kits. The advantages of the antibody tests are their low cost, widespread availability, and rapid results.

Unfortunately, the antibody tests have important limitations. A meta-analysis evaluated the accuracy of a number of commercially available serologic kits and found their overall sensitivity to be 85% and their specificity to be 79%, with no differences among the various kits.[41] Three of the qualitative whole-blood antibody kits were directly compared in another study and demonstrated sensitivities ranging from 76% to 84% and specificities of 79% to 90%.[42]

Of importance: the positive predictive value of antibody testing is linked to the prevalence of *H pylori* infection.[43] This issue will be discussed in detail in a later section. Additionally, the serologic tests are of little benefit in documenting eradication, as results can remain positive for years following successful cure of the infection.[40]

The urea breath test, like the rapid urease test, identifies active *H pylori* infection through the organism's urease activity. If *H pylori* is present, the ingestion of urea labeled with either the nonradioactive isotope carbon 13 or the radioactive isotope carbon 14 results in production of labeled carbon dioxide, which can be detected in expired breath.[2] Although the amount of radiation in the carbon 14 urea breath test is less than the daily background radiation exposure,[44] the carbon 13 test is preferred in children and pregnant women.[45]

Overall, the performance characteristics of both tests are similar,[2] with sensitivity greater than 95%, specificity greater than 90%, and excellent test reproducibility.[44] The urea breath test also provides an accurate means of post-treatment testing.[46]

A urease blood test, which relies upon the detection of labeled bicarbonate in a blood sample, also reliably identifies active *H pylori* infection.[47]

As the nonendoscopic urease tests rely on robust urease activity by *H pylori*, their sensitivity is decreased by medications that reduce organism density or urease activity, including bismuth-containing compounds, antibiotics, and proton pump inhibitors. It is currently recommended that bismuth and antibiotics be withheld for at least 28 days and proton pump inhibitors for 7 to 14 days prior to the urea breath test.[48,49] It is controversial whether histamine-2–receptor antagonists affect the sensitivity of the urea breath test,[50,51] though our practice is to withhold these drugs for 24 to 48 hours before the test.

The fecal antigen test identifies *H pylori* antigen in the stool by enzyme immunoassay with the use of polyclonal anti-*H pylori* antibody. As this test detects bacterial antigen in ongoing infection, it can be used for screening for infection and as a predictor of eradication following therapy.

A multicenter European study[52] found that, before treatment, the specificity of the fecal antigen test was 94% and its sensitivity was 91%. Four weeks after treatment, its sensitivity was 92% and its specificity was 96%. Recent studies indicate that the fecal antigen test may be effective in confirming eradication as early as 14 days after treatment.[53,54] The fecal antigen test has been shown to be more cost-effective than serologic testing in populations with low *H pylori* prevalence (< 20%).[52,54]

Antibody tests should not be used to test for eradication

The sensitivity of the fecal antigen test is affected by recent use of bismuth compounds, antibiotics, or proton pump inhibitors, although to a lesser degree than the urea breath test.[55] A recent study also suggests that the specificity of the fecal antigen test is reduced in bleeding peptic ulcer disease, and for this reason, it should not be the sole diagnostic test used in this situation.[56]

Although the fecal antigen test shows great promise, issues slowing its widespread use include the unpleasantness of handling and storing stool, limited availability, and variable state-to-state reimbursement.[2]

H PYLORI TESTING IN CLINICAL PRACTICE

Once the clinician has decided to test a patient for *H pylori*, the next decision is whether endoscopy is needed.

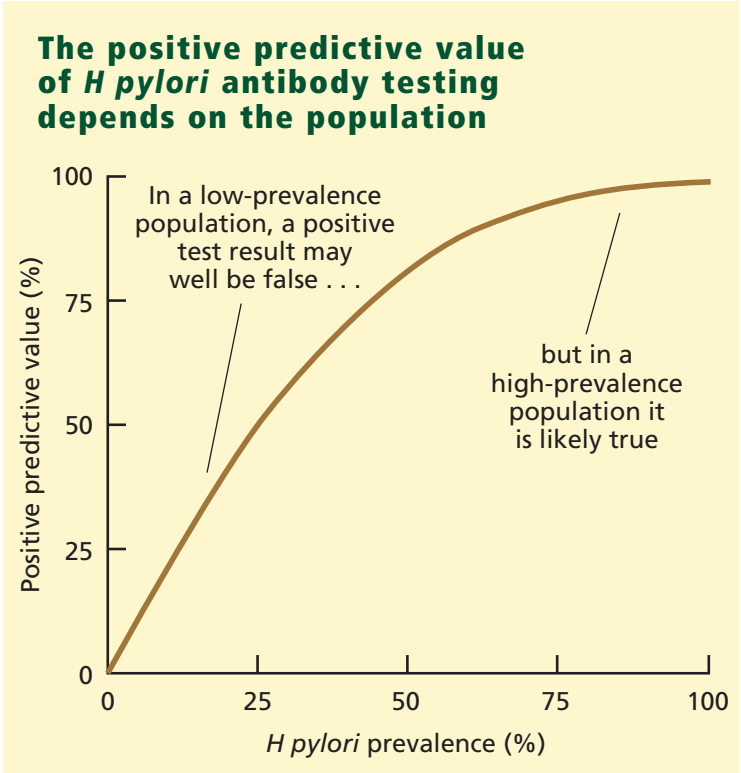

FIGURE 1. Effect of *H pylori* prevalence on the positive predictive value of antibody testing (the sensitivity is assumed to be 85% and specificity 79%)

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If endoscopy is needed

If endoscopy is necessary based upon the patient's clinical presentation, biopsy-based endoscopic tests will be most appropriate. If the patient has not recently been on bismuth, antibiotics, or a proton pump inhibitor, the rapid urease test offers the desirable combination of accuracy and low cost.[29] If mucosal abnormalities are identified at the time of endoscopy and require further histologic analysis, biopsy samples may be obtained for this purpose.[29]

Otherwise, if the patient has recently taken medications that could affect the sensitivity of the endoscopic tests, it is prudent to obtain biopsy samples for both rapid urease testing and histologic testing or to plan testing with a urea breath test or fecal antigen test at a later date after withholding antibiotics, bismuth, or proton pump inhibitor therapy for an appropriate period of time.

If the patient has an active bleeding ulcer, rapid urease testing and histologic testing are less reliable. Therefore, negative results should be confirmed with an antibody test. Because the pretest probability of *H pylori* infection is relatively high in a patient with an ulcer, the positive predictive value of an antibody test is reasonably high in this situation.[29]

If endoscopy is not needed

Uninvestigated dyspepsia is a common problem that primary care physicians encounter. In this situation, a number of organizations, including the American Gastroenterological Association,[14] endorse a strategy of testing for *H pylori* with a nonendoscopic test and treating it if present.[14,57] For the practical reasons noted earlier, antibody testing is the most commonly used *H pylori* test in primary care.

In parts of the United States where the prevalence of *H pylori* infection is high, such as urban areas or communities with large immigrant populations, the positive predictive value of antibody testing is reasonably high. Using the same logic, antibody testing is also an acceptable means by which to screen for *H pylori* in those with a bleeding ulcer, given the high pretest probability of infection.

However, in parts of the United States where *H pylori* prevalence is low, the positive predictive value of antibody testing is poor.[58] From a pragmatic standpoint, this means that if a physician practices in a community in which the prevalence of *H pylori* infection is less than 20% to 25% (eg, in much of the United States), a negative antibody test result suggests that infection is absent. However, a positive result is no better than a coin toss in predicting that active infection is present (**FIGURE 1**). As such, in low-prevalence populations, antibody tests should be avoided altogether or positive results should be confirmed with a test that identifies active infection prior to initiating therapy.[3,57,58]

PRIMARY TREATMENT OF *H PYLORI* INFECTION

The first course of therapy has the greatest likelihood of eradicating *H pylori*. After an initial trial of antibiotics has failed, subsequent

TABLE 3

Regimens for *H pylori* eradication

Proton pump inhibitor: standard dose* twice daily (esomeprazole is only once a day)
Clarithromycin 500 mg twice a day
Amoxicillin 1,000 mg twice a day
- Eradication rate: 80%–90%
- First line for patients not allergic to penicillin

Bismuth subsalicylate 525 mg orally four times a day
Metronidazole 250 mg orally four times a day
Tetracycline 500 mg orally four times a day
Ranitidine 150 mg orally twice daily or proton pump inhibitor in a standard dose once or twice daily
- Eradication rate: 75%–90%
- First line for penicillin-allergic patients
- High pill count
- Proton pump inhibitor may improve efficacy

Proton pump inhibitor: standard dose* twice daily
Clarithromycin 500 mg twice daily
Metronidazole 500 mg twice daily
- Eradication rate: 80%–90%
- *Consider only in penicillin allergy and those unable to tolerate bismuth quadruple therapy*

In general, all regimens should be used for 10 to 14 days.
*Standard dosages for proton pump inhibitors: lansoprazole 30 mg, omeprazole 20 mg, pantoprazole 40 mg, rabeprazole 20 mg, esomeprazole 40 mg.
Note: the above treatments are not all approved by the US Food and Drug Administration (FDA). The FDA-approved regimens are as follows:
- Bismuth 525 mg four times a day + metronidazole 250 mg four times a day + tetracycline 500 mg 4 times a day for 2 weeks + an H2-receptor antagonist as directed for 4 weeks
- Lansoprazole 30 mg twice a day + clarithromycin 500 mg twice a day + amoxicillin 1 g twice a day for 10 days
- Omeprazole 20 mg twice a day + clarithromycin 500 mg twice a day + amoxicillin 1 g twice a day for 10 days
- Esomeprazole 40 mg once a day + clarithromycin 500 mg twice a day + amoxicillin 1 g twice a day for 10 days
- Rabeprazole 20 mg twice a day + clarithromycin 500 mg twice a day + amoxicillin 1 g twice a day for 7 days

Prevalence of *H pylori* is higher in immigrants, in cities, and in patients with ulcer bleeding

therapies are less likely to succeed. Therefore, it is important to only use regimens that have been proven effective. In the United States, the following two regimens have consistently achieved high eradication rates[29]:

- Clarithromycin-based triple therapy: a proton pump inhibitor, clarithromycin, and amoxicillin
- Bismuth quadruple therapy: a proton pump inhibitor or histamine-2–receptor antagonist, bismuth, metronidazole, and tetracycline (TABLE 3).

Both of these regimens, when given for 1 to 2 weeks, have been shown to be effective first-line treatments, with eradication rates ranging from 75% to 90.[5] Treatment durations of less than 7 days are associated with lower eradication rates and are not recommended. A simple rule of thumb is to consider clarithromycin-based triple therapy in patients not allergic to penicillin, and bismuth quadruple therapy in those who are allergic to penicillin.

The currently available proton pump inhibitors perform comparably well when used in these regimens.[5,59] A recent meta-analysis of 13 studies suggests that twice-a-day dosing of a proton pump inhibitor in clarithromycin-based triple regimens may be more effective than once-daily dosing.[60]

Do not substitute ampicillin for amoxicillin, doxycycline for tetracycline, or erythromycin for clarithromycin. In clarithromycin-based triple therapy, some advocate using metronidazole in place of amoxicillin. In fact, this regimen is as effective as

TABLE 4

Common side effects of therapy for *H pylori*

DRUG	SIDE EFFECTS
Proton pump inhibitors	Headache, diarrhea
Clarithromycin	Gastrointestinal upset, diarrhea, altered taste
Amoxicillin	Gastrointestinal upset, headache, diarrhea
Metronidazole	Metallic taste, dyspepsia, disulfiram-like reaction with alcohol
Tetracycline	Gastrointestinal upset, photosensitivity, tooth discoloration in children under 8 years old
Bismuth	Darkened tongue and stool, nausea, gastrointestinal upset

the combination of a proton pump inhibitor, clarithromycin, and amoxicillin. However, it is important to realize that if the infection is not cured when a patient receives a proton pump inhibitor, clarithromycin, and metronidazole, the remaining *H pylori* is quite likely to be resistant to both clarithromycin and metronidazole, severely limiting the options for salvage therapy. Therefore, this regimen is best reserved for patients who are allergic to penicillin and cannot tolerate bismuth quadruple therapy.

Optimizing the chances of successful *H pylori* eradication

The factors that are most likely to reduce treatment success include poor patient compliance and antibiotic resistance.[61]

Increasing patient compliance. The importance of taking the medications as prescribed to minimize the likelihood of treatment failure and the development of antibiotic resistance must be stressed to patients.

Patients should also be informed of possible treatment-related side effects (TABLE 4). Significant side effects are reported in 5% to 20% of those taking the standard treatment regimens.[62]

The most common side effects of the proton pump inhibitors include headache and diarrhea, which occur in up to 10% of patients. More importantly, patients need to take the proton pump inhibitor 30 to 60 minutes before eating. Nevertheless, the proton pump inhibitor is generally prescribed to be taken with the antibiotics (as a means of convenience to enhance compliance), potentially impairing optimal acid suppression. It is unclear if such a reduction in acid suppression is enough to affect the efficacy of *H pylori* therapies.

The most common side effects of clarithromycin include gastrointestinal (GI) upset, diarrhea, and altered taste, which can be managed with a mint, chocolate, or flavored soda.[39]

Common side effects of amoxicillin include GI upset, headache, and diarrhea.[39]

Side effects of metronidazole are dose-related and include a metallic taste and dyspepsia, as well as a disulfiram-like reaction with alcohol consumption.[39]

Common side effects of tetracycline include GI upset and photosensitivity.[39] This antibiotic should not be used in children under 8 years of age, owing to possible tooth discoloration.

Treatment with bismuth compounds has been associated with darkening of the tongue and stool, nausea, and GI upset.[39] When patients are warned about such side effects, they are less likely to be alarmed when they occur and consequently are less likely to needlessly stop their treatment.

Antibiotic resistance must also be carefully considered when choosing the drug regimen. The current resistance rates of *H pylori* in the United States are 37% for metronidazole, 10% for clarithromycin, 3.9% with dual resistance to metronidazole and clarithromycin combined, and 1.4% for amoxicillin.[63]

Of note: clarithromycin resistance is absolute and associated with a high rate of treatment failure when clarithromycin-containing regimens are used.[64,65] On the other hand, metronidazole resistance appears to be more rel-

The first course of *H pylori* therapy is the one most likely to succeed

TABLE 5

Salvage therapy after an unsuccessful attempt to eradicate *H pylori*

Bismuth subsalicylate 525 mg four times a day Metronidazole 250 mg four times a day Tetracycline 500 mg four times a day A proton pump inhibitor twice a day
Levofloxacin 250 mg twice a day Amoxicillin 1,000 mg twice a day A proton pump inhibitor twice a day
Rifabutin 300 mg once a day Amoxicillin 1,000 mg twice a day A proton pump inhibitor twice a day

Comments

Do not use the same antibiotics that have failed previously
Treat for 10 to 14 days
Consider culture and sensitivity testing after two treatment failures

ative. Eradication rates can be improved in patients with metronidazole-resistant *H pylori* strains by using higher doses of metronidazole and/or by adding a proton pump inhibitor to bismuth, tetracycline, and metronidazole.[61]

Prior use of a macrolide or metronidazole increases the chances of resistance

A recent study suggests that previous use of either a macrolide or metronidazole for any infection significantly increases the likelihood of *H pylori* resistance to these agents. The authors recommend that bismuth quadruple therapy be considered in patients with a previous history of clarithromycin or metronidazole use.[66] Therefore, clinicians should routinely ask about previous macrolide or metronidazole use when deciding upon an *H pylori* treatment regimen.

PROVING ERADICATION

Proving that *H pylori* has been eradicated after therapy is not necessary in all cases[29]; however, it should be done in patients with any of the following:

- An *H pylori*-associated ulcer
- A remote history of peptic ulcer disease on chronic acid-suppressive therapy
- Persistent dyspeptic symptoms
- *H pylori*-associated MALT lymphoma
- Early gastric cancer that has been resected.

If confirmation of eradication is necessary, testing is generally recommended no sooner than 4 weeks after the completion of treatment.[3,4,29]

In view of its high cost, endoscopic testing should be used only if endoscopy is clinically indicated for other reasons. Most experts would advocate using histology or the combination of histology and a rapid urease test, as rapid urease testing alone has been shown to have reduced sensitivity after treatment.[67] If endoscopic follow-up is unnecessary, testing to prove eradication of *H pylori* infection can be accomplished with the urea breath test or fecal antigen test.[44,54] In general, the antibody tests are to be avoided after treatment.

OPTIONS WHEN PRIMARY *H PYLORI* THERAPY FAILS

When an initial course of therapy for *H pylori* has failed, the clinician should avoid using the same antibiotics again. In addition, therapy should be given for a minimum of 10 to 14 days.

The most frequently used rescue or salvage therapy is bismuth quadruple therapy including a proton pump inhibitor (TABLE 5). A recent pooled analysis of 16 studies and 24 abstracts demonstrated an average eradication rate of 76% (range 60%–100%) using quadruple salvage therapy.[68]

If quadruple therapy cannot be given or fails to eradicate the infection, referral to a gastroenterologist is appropriate.[57] Less-studied regimens using rifabutin, furazolidone, and fluoroquinolones such as levofloxacin may be used.[57,61,69–73]

Because *H pylori* culture and antibiotic sensitivity testing are expensive and not widely available, they are not typically done unless at least two courses of therapy have failed.

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