Guidelines for the Management of *Helicobacter pylori* Infection


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for and on behalf of the Ad Hoc Committee on Practice Parameters of the American College of Gastroenterology

**PREAMBLE**

Guidelines for clinical practice are intended to suggest preferable approaches to particular medical problems as established by interpretation and collation of scientifically valid research, derived from extensive review of published literature. When data are not available that will withstand objective scrutiny, a recommendation may be made based on a consensus of experts. Guidelines are intended to apply to the clinical situation for all physicians without regard to specialty. Guidelines are intended to be flexible, not necessarily indicating the only acceptable approach, and should be distinguished from standards of care that are inflexible and rarely violated. Given the wide range of choices in any health care problem, the physician should select the course best suited to the individual patient and the clinical situation presented. These guidelines are developed under the auspices of the American College of Gastroenterology and its practice parameters committee. These guidelines are also approved by the governing boards of the American Gastroenterological Association, the American Society for Gastrointestinal Endoscopy, and the American Association for the Study of Liver Diseases. Expert opinion is solicited from the outset for the document. Guidelines are reviewed in depth by the committee, with participation from experienced clinicians and others in related fields. The final recommendations are based on the data available at the time of the production of the document and may be updated with pertinent scientific developments at a later time. The following guidelines are intended for adults and not for pediatric patients.

**INTRODUCTION**

The realization that *H. pylori* infection is the single most common cause of peptic ulcer has had an enormous impact on our approaches to the management of ulcer disease. The National Institutes of Health (NIH) Consensus Development Conference of 1994 and the American Digestive Health Foundation (ADHF) International Update Conference of 1997 recommended that all ulcer patients with *H. pylori* infection be treated for the infection. Today, there is no longer any serious debate about the value or appropriateness of such treatment that is based on overwhelming evidence from clinical trials reinforced by several years of clinical practice. Furthermore, there are enormous economic benefits from successfully treating the infection in ulcer patients. Successful eradication of the infection can be equated with cure of the ulcer disease in most individuals who are not exposed to any other known ulcerogen such as aspirin or a nonsteroidal anti-inflammatory drug (NSAID). Patients who are cured of ulcer disease will consume fewer health care resources.

*H. pylori* infection has been implicated as a risk factor for gastric adenocarcinoma and low grade gastric lymphoma of mucosa-associated lymphoid tissue (MALT). The risk of either of these conditions in any one infected individual in the US is very low, and possibly unquantifiable. Of more direct importance to the American population is the possible association between *H. pylori* infection and dyspeptic symptoms—either uninvestigated (*i.e.*, dyspepsia) or after a negative upper GI endoscopy (*i.e.*, nonulcer dyspepsia [NUD]). These issues will be discussed in this article.

There is enormous interest by the general public about *H. pylori* and its disease associations. Gastroenterologists and primary care physicians are increasingly likely to be consulted by patients requesting further information about the infection and advice about issues of testing and treatment.

**PRINCIPLES OF TESTING FOR *H. PYLORI* INFECTION**

*Recommendation*

*Diagnostic testing for H. pylori infection should only be performed if treatment is intended.*

*H. pylori* infection is common in the general population.
Most infected individuals are asymptomatic and unlikely to develop a serious medical problem from the infection. At present, treatment of the infection is of proven value only for those patients who have peptic ulcer disease or gastric MALT lymphoma. These patients represent a minority of all infected individuals.

*Helicobacter pylori* is classified as a group I (or definite) carcinogen by the World Health Organization’s International Agency for Research on Cancer (1). It will, therefore, be difficult for physicians to withhold treatment for the infection in any individual with a positive test result. This is despite the general lack of evidence of any sustained medical benefit in most infected people. Therefore, it is recommended that some form of confirmation of *H. pylori* infection not be done except in specific clinical situations will now be discussed.

### Recommendation

**Testing for H. pylori infection is indicated in patients with active peptic ulcer disease, a past history of documented peptic ulcer, or gastric MALT lymphoma.**

As stated above, testing for the infection should only be performed in patients to be offered treatment for a positive test result. Testing should only be performed as part of overall management and as a prelude to treatment. Available tests are summarized in Table 1. The rationale for testing in specific clinical situations will now be discussed.

#### Nonbleeding duodenal ulcer seen at endoscopy

Although most duodenal ulcers are the result of *H. pylori* infection, there is increasing awareness of the “*H. pylori*-negative ulcer.” In two recent large, multicenter US-based clinical trials, 23% and 27% of patients with an endoscopic diagnosis of duodenal ulcer had three negative tests for *H. pylori* infection (2). In Rochester, NY, 42% of 261 patients with duodenal or gastric ulcer were *H. pylori*-negative (3). Therefore, it is recommended that some form of confirmatory testing for *H. pylori* infection be done when the diagnosis of duodenal (or gastric) ulcer is made endoscopically.

A biopsy urease test is the most appropriate method if the patient is not taking a proton pump inhibitor (PPI) or any other medication that might interfere with the performance of this test (see later here). Although it is unlikely that a patient with a new endoscopic diagnosis of duodenal ulcer would be taking a PPI, it is possible that such treatment might have been initiated shortly before endoscopy. In that situation, diagnosis of *H. pylori* infection might have to be made by alternative means.

#### Nonbleeding gastric ulcer seen at endoscopy

Biopsies will be taken from around the ulcer crater to exclude the possibility of malignancy. Further biopsies should be taken from at least two separate sites in the gastric mucosa distant from the ulcer for histological evaluation for *H. pylori* infection. Absence of *H. pylori* on biopsies taken from different gastric sites should suggest the possibility of aspirin or an NSAID as the causative factor for the gastric ulcer. This is especially true if there is a relative paucity of histological inflammation seen in the biopsy specimens. Aspirin use may be surreptitious (4) or unrecognized.

#### Recently bleeding ulcer seen at endoscopy

It is strongly recommended that physicians test for *H. pylori* infection in patients with recent upper gastrointestinal bleeding who are found to have a peptic ulcer. In patients with a duodenal ulcer, biopsies may be taken from the antrum for a rapid urease test. However, this test may be compromised if there is blood in the gastric lumen (5), or if the patient had been taking any medication that might invalidate a biopsy urease test (see later here). In that case, biopsies should be taken from both the antrum and corpus for histology. In a patient with a recently bleeding gastric ulcer, biopsies of the gastric mucosa distant from the ulcer crater should be examined histologically.

In some patients with active upper GI tract hemorrhage, biopsy of the gastric mucosa at the time of upper endoscopy might be difficult or be considered clinically inappropriate, and may be unreliable. If so, a venous blood sample should be taken as soon as possible after endoscopy for determination of *H. pylori* status by serology. Serology is probably the most reliable method for determination of *H. pylori* status in patients with ulcer bleeding, assuming they have not previously been treated for the infection.

#### Past history of peptic ulcer

Any previous endoscopic or radiological studies should be reviewed to confirm the presence of peptic ulcer. Assuming that the patient had never received treatment for *H. pylori* infection, a serological test should be performed to document the infection before initiating antimicrobial treatment.

### Table 1

<table>
<thead>
<tr>
<th>Test</th>
<th>Average Sensitivity</th>
<th>Average Specificity</th>
<th>Cost (approx.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>In-Office, serum</td>
<td>88–94%</td>
<td>74–88%</td>
<td>$10–30</td>
</tr>
<tr>
<td>In-office whole blood</td>
<td>67–88%</td>
<td>75–91%</td>
<td>$10–30</td>
</tr>
<tr>
<td>Laboratory, serum</td>
<td>86–94%</td>
<td>78–95%</td>
<td>$40–100</td>
</tr>
<tr>
<td>ELISA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salivary antibody</td>
<td>65–89%</td>
<td>72–90%</td>
<td>N/A</td>
</tr>
<tr>
<td>UBT</td>
<td>90–96%</td>
<td>88–98%</td>
<td>$250–350 (13C)</td>
</tr>
<tr>
<td>Biopsy urease test</td>
<td>88–95%</td>
<td>95–100%</td>
<td>$6–20</td>
</tr>
<tr>
<td>(plus endoscopy)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Histology</td>
<td>93–96%</td>
<td>98–99%</td>
<td>$60–250</td>
</tr>
<tr>
<td>Culture</td>
<td>80–98%</td>
<td>100%</td>
<td>$150</td>
</tr>
</tbody>
</table>

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**Gastric MALT lymphoma**

This is a rare tumor in the United States. There is good evidence that *H. pylori* infection is causally associated, as areas with a high incidence of this lymphoma have a high prevalence of *H. pylori* infection. The bacterium is almost always present on gastric mucosa adjacent to the tumor. Infection with *H. pylori* precedes development of the tumor. Furthermore, *H. pylori* infection is only associated with this tumor in the stomach and not at other sites (6, 7). It is recommended that all patients with gastric MALT lymphoma be tested for *H. pylori* infection. Further management is discussed later here.

**Recommendation**

Testing for *H. pylori* infection is not indicated in asymptomatic individuals without a past history of peptic ulcer disease, or in patients on long term treatment with a proton pump inhibitor for gastroesophageal reflux disease (GERD).

**Asymptomatic individuals**

Asymptomatic individuals should not be tested for *H. pylori* infection. However, in any person testing positive for the infection, treatment may be offered after a full discussion about its potential risks and benefits. One group of asymptomatic individuals in whom testing might be justified would be those of Japanese, Korean, or Chinese descent with either a family history, or a perceived fear, of gastric adenocarcinoma. It would be difficult to refuse testing in any such individual who requested it. Again, treatment should be offered to any individual who tests positive.

**Long term treatment with a proton pump inhibitor**

One nonrandomized study from Europe has suggested that continuous PPI treatment increases the risk of chronic atrophic gastritis (CAG) in patients infected with *H. pylori*, and that no alterations to the labeling of either PPI were necessary.

There is currently no need to test for *H. pylori* infection in GERD patients on long term treatment with a PPI or those being considered for PPI treatment. However, if a patient has previously tested positive for *H. pylori* infection, appropriate treatment should be given. GERD patients who also have duodenal or gastric ulcer should be tested for *H. pylori* infection and treated appropriately if positive.

**NONULCER DYSPEPSIA**

**Recommendation**

There is no conclusive evidence that eradication of *H. pylori* infection will reverse the symptoms of nonulcer dyspepsia. Patients may be tested for *H. pylori* on a case-by-case basis, and treatment offered to those with a positive result.

By definition, patients with nonulcer dyspepsia have had an upper gastrointestinal endoscopy that has shown no evidence of peptic ulcer disease. However, before endoscopy, it is difficult to classify dyspepsia and to reach a meaningful clinical diagnosis. On clinical history, dyspepsia can be classified as “reflux-like,” “ulcer-like,” “dysmotility-like,” or nonspecific. Patients in any of these categories may or may not be infected with *H. pylori*. There is some evidence that the prevalence of infection is increased in dyspeptic patients (11). There is no particular symptom profile that is consistent with, or diagnostic of, *H. pylori* infection (12), although some studies have shown a high prevalence of the infection in “ulcer-like,” and a lower than expected prevalence in “dysmotility-like,” dyspepsia.

A careful history and appropriate investigations should identify patients with probable GERD and those with irritable bowel syndrome or other conditions not known to be related to *H. pylori* infection, such as cholelithiasis or pancreatic disease. Testing for *H. pylori* infection is not indicated in these patients. In others, a blood test for *H. pylori* has been used as triage for determining which patients require endoscopy (13). A negative serological test for *H. pylori* infection in a patient with uninvestigated dyspepsia makes the diagnosis of peptic ulcer unlikely, assuming the patient is not taking aspirin or an NSAID.

Patients presenting with dyspepsia in primary care are increasingly likely to be tested for *H. pylori* infection. This is despite the fact that there is no conclusive evidence that the infection is causal for their symptoms, or that its eradication will cure their symptoms. Any patient with a positive test result for *H. pylori* infection should be offered treatment for the infection. Patients should be counseled that such a test does not prove that *H. pylori* infection is the explanation for their symptoms, and that treatment of the infection will not necessarily cure their symptoms. Potential risks of treatment should also be presented to the patient including the possibility of *Clostridium difficile* infection from antibiotic use as well as more minor adverse events such as taste...
disturbance and diarrhea. Cure of *H. pylori* infection might be associated with the onset of new GERD-like symptoms either with or without the development of erosive esophagitis (14, 15). This may be particularly likely in men who had a severe corpus gastritis from their *H. pylori* infection, and who gain considerable weight after cure of the infection (14). This controversial association is unproven and has yet to be confirmed in prospective US-based studies. There are other possible explanations for the apparent development of esophagitis after eradication of *H. pylori* infection in ulcer patients. For example, patients may increase their dietary intake after alleviation of ulcer-related symptoms. Alternatively, patients may have had symptoms of GERD that went unrecognized before the elimination of *H. pylori*. However, given the possibility of the new onset of reflux symptoms with or without esophagitis, it is important that any treatment for *H. pylori* infection is for appropriate clinical indications.

If upper GI endoscopy is undertaken as part of the investigation of dyspepsia and no evidence of peptic ulcer is found, the diagnosis is that of NUD. Although the practitioner has the opportunity to test for *H. pylori* infection during endoscopy, it is difficult to give any firm recommendations concerning the utility of this. However, if biopsies are taken to test for *H. pylori* infection, it is assumed that treatment will be offered to anyone with a positive result after appropriate discussion.

**PARTICULAR DIAGNOSTIC STRATEGIES FOR *H. PYLORI* INFECTION**

**Recommendation**

The diagnostic test to use in a particular patient depends on the clinical setting, particularly if upper GI endoscopy is performed.

Tests for *H. pylori* infection that require endoscopy include biopsy urease tests, histology, and culture (16). Those that do not require endoscopy include the determination of the presence of antibodies to *H. pylori* in blood, serum, or saliva, and functional tests of the bacterium’s urease enzyme with a carbon-labeled urea breath test (UBT) (17). String tests represent an alternative nonendoscopic, although invasive, method (17–19); the sensitivity of these tests is likely to be variable and poor and it is doubtful whether they will be accepted by patients. They are not currently recommended.

**Recommendation**

When endoscopy is indicated, the test of first choice is a urease test on an antral biopsy. If a biopsy urease test is negative, *H. pylori* infection may be diagnosed by histology or serology. Biopsy urease tests have reduced sensitivity in patients taking PPIs and in patients with recent or active bleeding. Histology is not generally necessary and is expensive. When endoscopy is not performed, an office-based serological test is the least expensive means of evaluating for evidence of *H. pylori* infection. A urea breath test is the best nonendoscopic test for documenting *H. pylori* infection.

**Biopsy urease tests**

These tests depend on the activity of bacterial urease. Any detectable urease activity on gastric mucosal biopsies is presumed to have come from *H. pylori*, which has the highest urease activity of any known bacterium to infect man. Rarely, the human stomach may be colonized by another urease-producing bacterium—*Helicobacter heilmannii* (20). It is not currently known how frequently this organism contributes to inaccuracies of the biopsy urease test or whether it can sometimes be a cause of *H. pylori*-negative peptic ulcer.

Three biopsy urease tests are currently available in the US (Clotest, Pyloritek, and Hp-fast). They have similar operating characteristics and may suitably be used in the endoscopy suite, as they all have CLIA-waived (CLIA: Clinical Laboratories Improvement Act) status. The Pyloritek has the advantage of being read after 1 h, whereas the others are designed to be read at 24 h, although a positive result may be obtained sooner. There is very close agreement between the different tests (21, 22). Although these tests are of low cost, they add to the total cost of the endoscopic procedure, which is automatically “up-coded” once a biopsy is taken for any reason.

Because these tests have such excellent specificity, a positive result can be taken as conclusive evidence of *H. pylori* infection. However, because their sensitivity is reduced under certain circumstances, a negative result does not necessarily mean absence of infection with *H. pylori*. The test may produce a false negative result in patients with active or recent bleeding from the upper gastrointestinal tract if gastric contents are contaminated with blood (5). Furthermore, and of importance clinically, they may give a false negative result in patients who have recently been taking PPIs, *H_2*-receptor antagonists (*H_2*RAs), antibiotics, or bismuth-containing compounds.

During treatment with a PPI, the distribution of *H. pylori* within the stomach probably changes so that the density in the antrum is reduced and that in the corpus is relatively increased (23). This means that a negative biopsy urease test on an antral biopsy in a patient taking a PPI is insufficient evidence of the absence of *H. pylori* infection. The Clotest on a single antral biopsy had a sensitivity of 97% in 35 patients on no antisecretory medication, 76% in 34 patients on an *H_2*RA, and 41% in 12 patients on a PPI (24). Eleven patients with known *H. pylori* infection who were receiving a PPI had multiple gastric biopsies taken for Clotest (25). The sensitivity of a single Clotest from an antral biopsy was as low as 9%, and rose to only 45% when multiple samples were taken from different sites in the stomach.

In patients on a PPI, practitioners may choose to avoid a biopsy urease test and document the presence of infection by a serological test, preferably one performed in a laboratory.
Alternatively, if the PPI is stopped before scheduling the endoscopy, a urease test on an antral biopsy specimen can be used to assess \textit{H. pylori} status. The optimum time for the patient to be off of the PPI is not established; 4 wk is the most conservative recommendation that can be made, although 1 wk may conceivably be enough. Ideally, patients should not be taking an H$_2$RA at the time of endoscopy if a biopsy urease test is to be used as the sole method for determining \textit{H. pylori} status (24). In patients on an H$_2$RA or PPI, it is recommended that biopsies for urease testing be taken from both the antrum and fundus of the stomach to increase sensitivity (26).

**Histology**

As well as documenting the presence of the organism, histology allows evaluation of the underlying gastritis. In the absence of chronic inflammation, \textit{H. pylori} infection can be reliably excluded (27). Shortly after successful eradication of \textit{H. pylori} infection, there will be resolution of the acute inflammatory component of the gastritis; however, it takes longer for chronic inflammation to resolve, and lymphoid follicles may still be present up to 1 yr later. In routine practice, hematoxylin and eosin staining is usually adequate. Specialized stains such as the Warthin-Starry, Genta, and Giemsa may be useful in cases in which no bacteria are visible on hematoxylin and eosin staining but there is evidence of inflammation on histology (28).

As with biopsy urease tests, there may be reduced sensitivity of histology in patients taking antisecretory drugs. Histological evaluation of an antral biopsy had a sensitivity of 91% in 35 patients not taking an acid-suppressing drug, 91% in 34 patients on an H$_2$RA, and 75% in 12 patients on a PPI (24). However, histology on biopsies taken from the corpus was more reliable, with a sensitivity of 83% in patients on a PPI, 91% in patients on an H$_2$RA, and 94% in patients not taking an antisecretory drug.

Histology increases total cost because of the pathologist’s professional fee and the cost of processing the biopsies in the pathology laboratory. As for the biopsy urease test, the endoscopic procedure is “up-coded” to include the charge for the biopsy. As a potential cost saving measure, physicians may take biopsies for a urease test and histology but may send the histology samples for processing only if the biopsy urease test is negative. Histology samples can be discarded if that test is positive, assuming that histology is not required for other reasons such as exclusion of malignancy in a gastric ulcer or assessment of IM. An alternative, less costly approach to follow up a negative biopsy urease test is to check the \textit{H. pylori} status by a blood test. However, this would be appropriate only in patients who had not been treated previously for the infection (see later here).

**Culture**

Culturing \textit{H. pylori} is difficult, time consuming, and expensive, and is an impractical means of establishing the diagnosis of infection. Not all hospital laboratories have the necessary expertise or resources available to offer culture routinely. Culture is used in controlled clinical trials of treatment of the infection but, in that situation, is usually performed centrally in a single reference laboratory. Culture is seldom required in routine clinical practice but may be helpful in determining \textit{in vitro} patterns of antimicrobial resistance and sensitivity in planning treatment for a patient in whom two or more attempts at eradication had proven unsuccessful. However, an equally acceptable approach to managing a patient with failed eradication would be to re-treat with a different antibiotic regimen without recourse to biopsy, culture, and sensitivity testing.

As for other biopsy-based tests, there may be a reduced sensitivity of culture as a means of diagnosing \textit{H. pylori} infection in patients on antisecretory therapy. Using an antral biopsy, the sensitivity of culture was 85% in 35 patients on no acid-suppressing medication, 50% in 12 patients on a PPI, and 74% in 34 patients on an H$_2$RA (24). Culture of a biopsy from the corpus was not associated with the same level of reduced sensitivity; corresponding rates were 80%, 76%, and 67%, respectively.

**Serology**

Enzyme-linked immunosorbent assays (ELISA) for IgG antibodies to \textit{H. pylori} are widely available (29). Measurement of IgG is all that is necessary because it is of more use and applicability than IgA. Although typically reported as an antibody titer, these tests are best viewed as qualitative rather than quantitative. A number of office-based serum antibody tests are also available (30).

Serological tests can only diagnose the infection and not any specific condition such as peptic ulcer or gastric cancer. Furthermore, these tests are unreliable indicators of \textit{H. pylori} status in patients who have received treatment for the infection. Although antibody titers fall in most patients after successful eradication, the rate and extent of the decline are highly variable and unpredictable (17). If used as a means of determining cure of infection, it would be necessary to perform the identical ELISA at the same time on a 6-month posttreatment serum sample and on a stored pretreatment sample. This makes serology inconvenient and impractical for documenting cure of infection.

**Whole blood tests**

In addition to laboratory-based ELISA tests and other office-based tests on serum, a variety of office-based tests have been developed using whole blood. These tests, based on latex agglutination or solid-phase ELISA, generally have lower levels of sensitivity and specificity than laboratory-based ELISA tests (Table 1). Largely developed and validated in hospital settings, they may not perform as well in office-based practice. Although local validation is essential for the proper interpretation and application of any test, this may not always be appreciated or carried out.

The main attractions of these tests are their simplicity and low cost. The main disadvantage to their more widespread
use is that many patients could have them performed inappropriately or unnecessarily. Patients testing positive would then receive treatment for H. pylori infection, which may not have been responsible for their presenting problem. More widespread application of treatment of H. pylori infection will lead to an increased occurrence of adverse events and will promote the development of antimicrobial resistance.

Salivary antibody tests

These tests have poor sensitivity and specificity and are not widely available in the United States. Their exact role in clinical practice is undefined and their use cannot currently be recommended.

Urea breath tests

In a urea breath test (UBT), a small dose of urea in which $^{13}$C has been replaced with $^{13}$C or $^{14}$C is given by mouth. In the presence of H. pylori infection, bacterial urease splits the urea to produce CO$_2$ and ammonia. The CO$_2$ will carry the $^{13}$C or $^{14}$C label. $^{13}$CO$_2$ or $^{14}$CO$_2$ diffuses into the bloodstream and is excreted by the lungs. $^{13}$CO$_2$ is detected by mass spectroscopy, $^{14}$CO$_2$ by scintillation counting. Because the normal human stomach is devoid of urease, any gastric urease activity is considered to be derived from H. pylori. Therefore, demonstration of urease activity in the stomach is a reliable surrogate marker of active H. pylori infection (17).

Two UBTs are currently FDA-approved. The first to gain approval was a nonradioactive, $^{13}$C-based test (Meretek). Subsequently, a radioactive $^{14}$C-based test (Tri-Med) has also been approved. The $^{13}$C-UBT and the $^{14}$C-UBT have similar performance characteristics. Although the $^{14}$C-UBT is radioactive, the dose of radiation can be as low as 1 μCi (31). The main advantage of the $^{14}$C-UBT over the nonradioactive $^{13}$C-UBT is that it is less expensive (Table 1). However, the $^{14}$C-UBT should not be administered to children or to women of child-bearing potential. Both the $^{13}$C- and the $^{14}$C-UBT should be regarded as qualitative rather than quantitative. In neither test is it possible to interpret the absolute level of expired labeled CO$_2$ as an indicator of the likelihood of specific pathology (32–34).

UBTs have high accuracy and reproducibility (17, 35). Because they are functional tests that essentially “sample” the entire stomach, they are not prone to the same level of sampling error as biopsy-based tests may be (see above). False positive results are uncommon with UBTs but may occur if there is intraoral hydrolysis of urea by oral bacteria. However, this will usually produce an early peak in labeled CO$_2$ excretion and should not cause confusion. False-negative tests may occur if the patient is currently taking, or has recently been taking, an antisecretory drug, bismuth, or an antibiotic, whether given for the treatment of H. pylori infection or for some unrelated reason. For routine clinical purposes, it is recommended that a UBT to ascertain success or failed eradication of H. pylori infection be delayed for 4 wk after completing eradication treatment.

PPIs reduce the sensitivity of UBTs and may produce a false negative result (36–38). Although the test usually reverts to true positive within 5 days of stopping treatment (38), this may be delayed for up to 4 wk in isolated patients. The 1 μCi $^{14}$C-UBT became false negative in five of 31 patients with known H. pylori infection during 2 wk of treatment with omeprazole 20 mg b.i.d. The test was still false-negative 4 wk after stopping omeprazole in one of the five patients (39). H$_2$RAs may also reduce the sensitivity of the UBT, although the test reverts to true positive within 5 days of stopping treatment (38).

The main benefit of these tests is in determining whether infection has been successfully eradicated in patients in whom there was a clinical need to know, but in whom repeat endoscopy was not justified, not feasible, or not approved by a third party payer.

TREATMENT OF H. PYLORI INFECTION

Recommendation

The highest eradication rates are achieved with the following regimens:

- a PPI, clarithromycin, and either amoxicillin or metronidazole for 2 wk
- ranitidine bismuth citrate, clarithromycin, and either amoxicillin, metronidazole, or tetracycline for 2 wk
- a PPI, bismuth, metronidazole, and tetracycline for 1 to 2 wk.

Given the importance of eradicating H. pylori infection in patients with ulcer disease, it is vital that the infection be treated optimally with a combination regimen that has an acceptably high eradication rate. These have been variably defined. Reasonable targets would be $\geq$90% cure rate on per-protocol analysis, and $\geq$80% cure rate on intent-to-treat analysis (40). Additional important factors to be taken into account when planning treatment include compliance and the likelihood of adverse events. Combination drug regimens are essential to maximize the chance of eradicating the infection and to minimize the risk of promoting antimicrobial resistance. Metronidazole resistance is increasing in the US and was recently reported to be present in 54% of strains (41). In contrast, rates of clarithromycin resistance in the US are 7–11% (41). In France, where there has been greater and more prolonged use of clarithromycin and other macrolides, clarithromycin resistance in H. pylori has remained stable at around 10% (42). Resistance to amoxicillin is rare (43); resistance to tetracycline has never been adequately documented.

At the time of writing, five combination regimens had received approval from the FDA for the treatment of H. pylori infection in patients with ulcer disease (44). Three of these are dual treatment regimens that can no longer be recommended because they have been superceded by more...
TABLE 2
Suggested Regimens for the Treatment of H. pylori Infection

<table>
<thead>
<tr>
<th>Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PPI (lansoprazole 30 mg OR omeprazole 20 mg) + amoxicillin 1000 mg + clarithromycin 500 mg</strong> (each drug given twice daily for 2 wk)</td>
</tr>
<tr>
<td><strong>PPI (omeprazole 20 mg OR lansoprazole 30 mg) + metronidazole 500 mg + clarithromycin 500 mg</strong> (each drug given twice daily for 2 wk)</td>
</tr>
<tr>
<td><strong>RBC 400 mg + clarithromycin 500 mg + amoxicillin 1000 mg OR metronidazole 500 mg OR tetracycline 500 mg</strong> (each drug given twice daily for 2 wk)</td>
</tr>
<tr>
<td>Bismuth subsalicylate 525 mg q.i.d. + metronidazole 500 mg t.i.d. + tetracycline 500 mg q.i.d. + PPI (lansoprazole 30 mg q.day OR omeprazole 20 mg q.day) (each drug given in the dosage and frequency indicated daily for 2 wk)</td>
</tr>
<tr>
<td>Bismuth subsalicylate 525 mg q.i.d. + metronidazole 250 mg q.i.d. + tetracycline 500 mg q.i.d. + H2-receptor antagonist (each drug given in the dosage and frequency indicated daily for 2 wk with the H2-receptor antagonist continued for a further 2 wk)</td>
</tr>
</tbody>
</table>

Not all of the above regimens are FDA-approved.

FOLLOW-UP OF PATIENTS AFTER TREATMENT FOR H. PYLORI INFECTION

Recommendation

Currently, routine posttreatment testing is only recommended in patients with a history of ulcer complications, gastric MALT lymphoma, or early gastric cancer. Patients with recurrent symptoms after treatment of H. pylori infection will also need further evaluation.

Ordinarily, documentation of eradication of infection is unnecessary, assuming that the patient received treatment with an appropriate regimen with an acceptably high eradication rate (see above) and was compliant. It has not been established that routine posttreatment testing is either necessary or cost-effective. However, many physicians feel that confirmation of eradication is desirable. Therefore, this recommendation could conceivably change when reliable, noninvasive, and inexpensive testing becomes widely available.

Patients with a history of ulcer complication

In a patient with a complication of peptic ulcer disease, it is important to know the H. pylori status after treatment to plan further long term management and to give an accurate prognosis. In those patients, a UBT would be the test of choice unless repeat endoscopy was clinically necessary (e.g., as follow-up of a gastric ulcer in a patient in whom adequate biopsies had not been obtained at the initial endoscopy). The UBT is highly sensitive for determining H. pylori status after treatment of the infection, and is at least as accurate as endoscopic testing (27) as long as patients are off treatment with any of the medicines discussed above (50).

Gastric MALT lymphoma

Cure of H. pylori infection has been associated with complete or partial regression of localized, low grade gastric MALT lymphoma in the majority of patients (51–55). Work-up of patients with suspected MALT lymphoma must demonstrate that the neoplasm is low grade and confined to the stomach. Endoscopic ultrasound, when available, has a valuable role in staging. Once H. pylori infection has been documented and treated in patients with this condition, it will be necessary to confirm successful eradication. Because the patient will require further endoscopy and biopsies to follow the neoplasm, H. pylori status is best determined by histology. All patients must subsequently receive expert surveillance by a gastroenterologist and an oncologist experienced in the management of lymphoid neoplasms (55).

REFERENCES

2. Webb D. Data on file, Glaxo Wellcome Inc.


