Recognizing peptic ulcer disease

Keys to clinical and laboratory diagnosis

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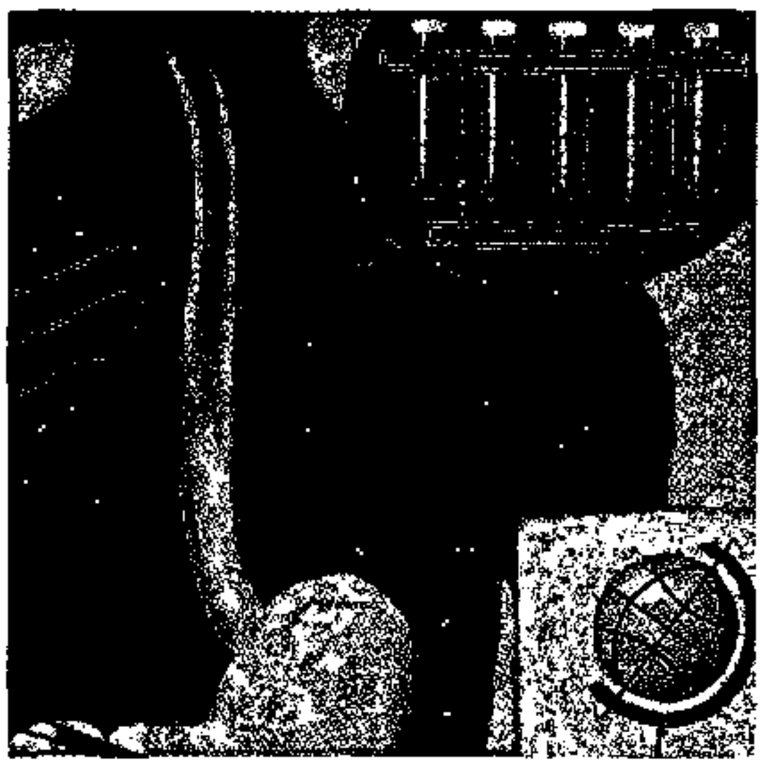
PREVIEW

Determining which patients to test and which to treat is the crux of management of peptic ulcer disease. A number of laboratory tests are now available to confirm initial clinical recognition of dyspepsia due to *Helicobacter pylori* infection. Fortunately, the disease can be cured with combination antisecretory and antibiotic therapy. However, the value of testing in patients in whom the presence of an ulcer is unconfirmed remains controversial. Nevertheless, it is generally agreed that confirmed cases of *H pylori* infection should be treated. In this article, the authors discuss clinical and laboratory diagnosis of peptic ulcer disease and provide an algorithmic approach to evaluation.

Most patients with peptic ulcer disease can now be treated as having an infectious illness caused by the bacterium *Helicobacter pylori*. Peptic ulcer disease due to *H pylori* infection can be cured with a combination of antimicrobial and antisecretory drugs.[1]



A cost-conscious approach to primary care management in patients with dyspepsia consists of determining the likelihood of peptic ulcer disease, detecting the presence of *H pylori* infection as inexpensively and reliably as possible, and prescribing appropriate therapy. It is also important to determine which patients need subspecialty consultation or referral (eg, those who are not cured after one or two courses of anti–*H pylori* therapy).

The presence of peptic ulcer disease is usually suspected on the basis of patient history and clinical findings. An important part of diagnosis is the ability to identify the signs, symptoms, and factors in the history that suggest *H pylori* infection. Equally important is the ability to determine which patients likely have gastroesophageal reflux disease (GERD), which would not be expected to respond to antimicrobial therapy for *H pylori*.

Although much has been written about diagnosis and treatment of *H pylori* infection and peptic ulcer disease, many physicians are uncertain or confused about when and how to test for *H pylori*, active ulcer disease, or both; how to select appropriate antimicrobial combination therapies; and what to tell patients about *H pylori* infection, peptic ulcer disease, and abdominal symptoms.[2]

Differential diagnosis

The most common differential diagnostic considerations in patients with dyspepsia are GERD, peptic ulcer disease, and functional (nonulcer) dyspepsia. An algorithmic approach to diagnosis (figure 1) begins with differentiation between peptic ulcer disease and

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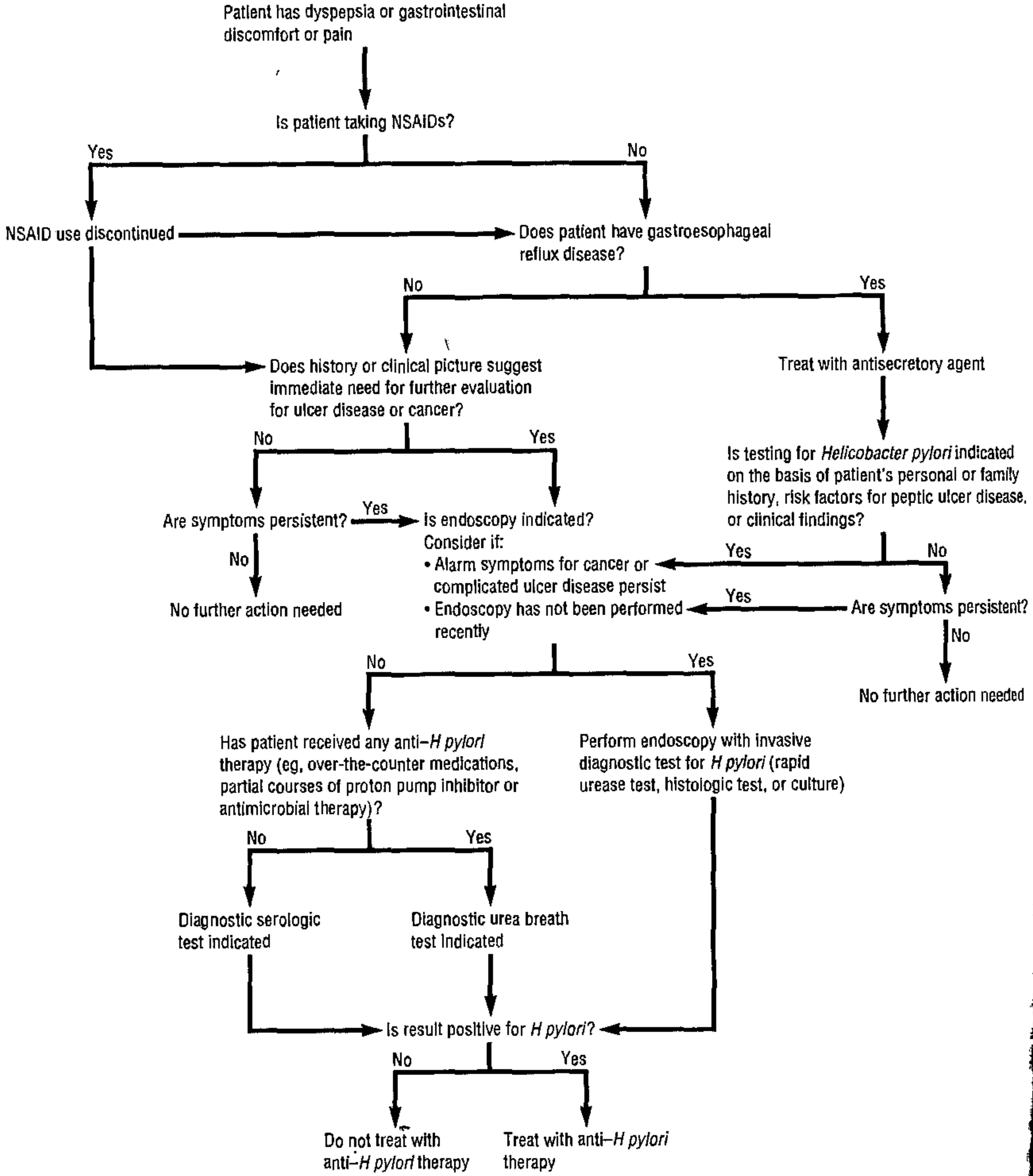

Figure 1. Algorithm for clinical evaluation of dyspepsia. NSAIDs, nonsteroidal anti-inflammatory drugs.

GERD, recognition of alarm signs and symptoms of gastric cancer, and elimination of use of nonsteroidal anti-inflammatory drugs (NSAIDs).

Symptoms suggesting GERD, nonulcer dyspepsia, or irritable bowel syndrome often coexist with those of peptic ulcer disease, making differential diagnosis difficult. For practical purposes in primary care, patients with dyspepsia can be classified immediately into one of three categories: (1) those with classic GERD, (2) those with alarm symptoms for cancer, and (3) those with another gastrointestinal condition (eg, peptic ulcer disease, NSAID-related gastrointestinal complications).

GERD and irritable bowel syndrome

GERD usually can be diagnosed solely on the basis of the patient's history. The typical profile consists of substernal reflux, regurgitation, and heartburn that are exacerbated when the patient lies supine or consumes citrus juices. Usually, antacids provide excellent, albeit temporary, relief. In patients with chronic symptoms of GERD, especially those over the age of 50, upper gastrointestinal endoscopy should be considered to exclude the premalignant condition Barrett's esophagus.

Irritable bowel syndrome occurs in about one in seven otherwise healthy adults. Symptoms are typically intermittent, are associated with emotional stress, and usually involve changes in bowel habits. Periods of constipation often alternate with periods of diarrhea, bloating, and cramping abdominal pain.

Gastric cancer

Although gastric cancer has become uncommon, it still occurs. The presence of one or more alarm features (table 1) is an indication for referral for early endoscopy or upper gastrointestinal radiology studies.

Peptic ulcer disease

The classic presentation of uncomplicated peptic ulcer disease is burning or deep epigastric pain that occurs 1 to 3 hours after eating and is relieved by ingestion of antacids or food. The pain also commonly awakens affected patients at night. Typically, the symptom pattern lasts for weeks to months and recurs over months to years (table 2).

Patients who have dyspepsia that is not unambiguous GERD and who have no alarm symptoms for

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Table 1. Indications for early endoscopy

Anorexia
Dysphagia
Gastrointestinal bleeding (gross or occult)
New-onset symptoms in persons ≥45 yr of age
Presence of a mass
Unexplained anemia
Unexplained weight loss
Vomiting (severe)

Table 2. Classic presentation of uncomplicated peptic ulcer disease

Epigastric pain (burning, vague abdominal discomfort, nausea)

- Often nocturnal
- Occurs with hunger or hours after meals
- Usually temporarily relieved by meals or antacids

Long-term characteristics

- Persistence or recurrence over months to years
- History of self-medication and intermittent relief

Other common factors

- Development of symptoms or persistence in absence of use of nonsteroidal anti-inflammatory drugs
- Previous treatment with histamine$_2$-receptor antagonist
- History of recent or current cigarette smoking

cancer should undergo prompt noninvasive testing for *H pylori* (ie, serologic test, urea breath test, or stool test for *H pylori* antigens). Noninvasive testing in symptomatic patients and treatment in those with positive test results are cost-effective.[3] It is also important to inquire about how often patients use NSAIDs and other over-the-counter preparations (many of which contain NSAIDs).

In the absence of alarm symptoms for gastric cancer, most patients with dyspepsia should undergo noninvasive testing for *H pylori* infection.

NSAID-related gastrointestinal complications

NSAID use and *H pylori* infection are independent risk factors for peptic ulcer disease. The risk is 5 to 20 times higher in persons who use NSAIDs than in the general population and 5 to 7 times higher in persons with *H pylori* infection.[4]

The relationship between NSAID use and *H pylori* infection still needs to be clarified; it is not known whether the combination poses a higher risk for peptic ulcer disease than either factor alone.[5] Elderly persons, the population that consumes the greatest amount of NSAIDs, are also most likely to be infected with *H pylori*.

NSAID use is a significant confounding factor in the diagnosis and management of peptic ulcer disease. More than a decade ago, enough NSAIDs were available in drugstores and hospitals to treat 3 million persons daily, and new agents become available every year.[6] It is now evident that even as *H pylori*–related peptic ulcer disease is coming under control, an epidemic of NSAID-induced ulcers and related complications is occurring.[5,7]

The risk of serious ulcers in persons taking NSAIDs has been reported to be 1% to 2% per year of NSAID use.[5,8-10] The Food and Drug Administration (FDA) estimates the risk to be 2% to 4% per year of use. NSAID-induced ulcer disease is more common in women than in men (presumably because more women take NSAIDs for arthritis and other rheumatic diseases), appears to affect an increased proportion of elderly persons, and occurs independently of the formulation or route of administration. For example, ketorolac tromethamine (Toradol) has been shown to produce ulcers within 5 days of parenteral administration in older patients. Also, as more nonprescription NSAIDs become available, the incidence of NSAID-induced ulcers is increasing.

NSAID-related gastrointestinal complications can develop at any time during NSAID therapy, even after long periods of trouble-free use. In addition, such complications are not necessarily heralded by gradual onset of symptoms or a preliminary period of minor discomfort; indeed, the first sign of an NSAID-induced gastric complication may be serious peptic ulcer disease with bleeding.

True NSAID-related ulcers are often recalcitrant even to long-term therapy with high-dose proton pump inhibitors.[5] Once healed, such ulcers are likely to recur with further NSAID use. The best combination therapy to prevent NSAID-induced ulcers is unclear. A recent study confirmed that histamine$_2$ (H_2) receptor antagonists are not helpful for prevention.[11] Misoprostol (Cytotec) has been shown to prevent both NSAID ulcers and related complications.[5,12-16]

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The minimum effective dosage appears to be 200 µg twice daily; total daily doses of 600 µg or 800 µg are significantly more effective.[17] A double-blind study[18] showed that 200 µg of misoprostol twice daily (the minimum effective dosage) was essentially identical to 20 mg of the proton pump inhibitor omeprazole for prevention of true NSAID ulcers (ie, ulcers in NSAID users without confounding *H pylori* infection). As yet, there is no evidence that higher doses of omeprazole are more effective. Nevertheless, combination therapy with a proton pump inhibitor should be considered for patients in whom preventive therapy is indicated and who are unable or unwilling to take misoprostol.

The availability of cyclooxygenase-2 (COX-2) selective inhibitors (eg, celecoxib [Celebrex]), a new class of NSAIDs, may make NSAID-induced ulcers much less of a problem. Other currently available NSAIDs have both COX-1 and COX-2 activity.

Laboratory and diagnostic testing

No abnormal laboratory values are typical of peptic ulcer disease, GERD, or nonulcer dyspepsia. The only laboratory tests useful for diagnosis of peptic ulcer disease are those that detect *H pylori* infection. As mentioned, alarm signs and symptoms that suggest gastric cancer are indications for early endoscopy or upper gastrointestinal radiology studies. Specialized testing, such as pH monitoring, may be indicated in evaluation of GERD that presents atypically or is unresponsive to initial antisecretory therapy and changes in diet and lifestyle.[19]

Factors to consider in selection of an appropriate test are reliability, specificity, sensitivity, cost, and local access and expertise. As a general rule, physicians should choose a test that has the best accuracy for the level of testing expertise available. The ideal test would have a sensitivity and specificity of at least 90% (preferably 95% for one of the parameters) and a positive or negative predictive value exceeding 95%.

Noninvasive testing

In the absence of alarm symptoms for gastric cancer, most patients with dyspepsia should undergo evaluation for *H pylori* infection with serologic testing, urea breath testing, or stool testing for *H pylori* antigens.

Serologic test: In the primary care setting, serologic tests to detect *H pylori* antibodies are often preferred. Serologic testing is highly sensitive, but it cannot be used for follow-up after therapy, because antibody titers fall slowly and may remain elevated for a year or longer (table 3).

The FDA-approved serologic assays all test for the presence of IgG antibodies. Tests for IgA or IgM antibodies have not been approved by the FDA, and they generally have poor specificity and sensitivity.[20] Unfortunately, these unapproved tests are readily available under the designation "for research use only" and are responsible for considerable confusion and misdirected therapy. They should not be used. Physicians should insist that their laboratory provider use only FDA-approved tests.

A number of rapid office-based serologic kits for use with either serum or whole blood have been introduced. These tests can usually be performed in less than 10 minutes at a cost of $10 to $40. They have a sensitivity in the 90% range and a specificity of at least 85%. Most FDA-approved commercial kits are roughly equivalent in accuracy.

Urea breath test: Urea breath tests measure the carbon dioxide produced when *H pylori* urease metabolizes urea labeled with radioactive carbon (^{13}C or ^{14}C). The ^{13}C test does not involve a radioactive isotope and, unlike the ^{14}C test, can be used in children and pregnant women. Both tests are available in kit form. With the ^{13}C test, exhaled breath samples are usually sent to a central testing facility equipped to perform mass spectrometric analysis on gaseous samples. The ^{14}C test, which exposes the patient to a small dose of radiation, can be analyzed in a hospital's nuclear medicine laboratory or sent to a central laboratory.

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Urea breath tests have the best sensitivity and specificity of any diagnostic test for *H pylori* (ie, 90% to 99%)[21] (table 3). Because active *H pylori* infection must be present for a positive result, false-negatives are possible in patients who recently received therapy with any drug that reduces the amount of *H pylori* in the stomach (eg, antibiotics, bismuth compounds, proton pump inhibitors). For best results, use of these agents should be prohibited for at least 1 week before testing. H_2-receptor antagonist therapy does not reduce the bacterial load and does not interfere with the ^{13}C test. However, for reasons unknown, such therapy can lead to false-positive results on the ^{14}C test; therefore, all antisecretory therapy must be stopped for at least a week before the ^{14}C test is performed. Urea breath testing is more expensive than serologic testing but less expensive than endoscopy.

Stool test: Recently, a stool test for *H pylori* antigens was approved for use in the United States. Although experience with the test is limited, its accuracy for pretreatment testing of *H pylori* appears to be similar to that of other available tests.

Biopsy-based testing

Mucosal biopsy performed at endoscopy can provide valuable information via histologic testing, rapid urease tests, and culture. For reliable histologic test results, three or more samples should be obtained from the gastric antrum and corpus.[22,23]

Histologic tests: The presence of *H pylori* can easily be detected at endoscopy with histologic testing. Unfortunately, special stains are required for best results, and many pathologists do not use them. The various staining techniques for identifying *H pylori* are hematoxylin-eosin (H&E), Genta, Giemsa, Diff-Quik, Warthin-Starry, and El-Zimaity.[22,24,25] Sensitivity of the tests ranges from 80% to 100%, and specificity exceeds 95% (table 3).

H&E is the simplest test to perform. However, it is prone to false-negatives, and results must be confirmed by one of the other tests. Many histopathologists prefer Diff-Quik or Giemsa stains because they are simple and inexpensive. Diff-Quik is probably the ideal second test when two stains are required. The Giemsa test is prone to false-positives. Because of the observed shortcomings of H&E and Giemsa stains, many physicians and histopathologists prefer the Genta stain, although it costs more and takes longer to perform. Genta staining alone is sufficiently diagnostic because of its high sensitivity, specificity, and positive predictive value. One advantage of the recently described El-Zimaity triple stain is that it can be used with an automatic slide stainer.[24] At a minimum, the pathologist should use a triple stain (eg, Genta or El-Zimaity) or perform a traditional H&E stain as well as a special stain, such as Diff-Quik, on a separate slide.

Rapid urease test: The rapid urease test detects changes in the pH of a medium as the urease produced by *H pylori* converts urea to ammonia and carbon dioxide. The color changes in the kit correspond to changes in pH. The test is inexpensive, and it provides rapid results with few false-positives. Specificity and sensitivity are about 95%[23,26,27] (table 3). As with other tests that require the presence of a high number of *H pylori* organisms, the sensitivity of rapid urease testing is reduced by recent therapy with antibiotics, bismuth preparations, or proton pump inhibitors.

Culture: Although not yet available in most primary care settings, culture has a valuable role in determining antimicrobial susceptibilities when previous courses of therapy for *H pylori* infection have been ineffective or antimicrobial resistance is suspected. Culture can achieve sensitivity as high as 95% and specificity of 100% (table 3).

Practical considerations in test selection

The basic principle underlying the practice of testing for *H pylori* is that patients should not undergo testing unless the physician is willing to treat on the basis of a positive test result.[28]

Recent reports have questioned the value of test-

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Table 3. Considerations regarding use of tests for *Helicobacter pylori*

Test	When to use	Why	Why not
Serologic test	Test of choice when endoscopy is not indicated and is not an option and when the patient has not received antimicrobial therapy for *H pylori* infection	Noninvasive; sensitivity of >80%, specificity of about 90%	Does not confirm eradication, because serologic "scar" remains for indefinite period after microbiologic cure
Urea breath test	Preferred for confirming cure of *H pylori* infection, but no sooner than 4 wk after completion of therapy	Simple; sensitivity and specificity of 90% to 99%	False-negatives possible if testing is done too soon after treatment with proton pump inhibitors, antimicrobials, or bismuth compounds; small radiation exposure with ^{14}C method; expensive
Histologic test	To directly ascertain presence of *H pylori* when endoscopy is being used; also used when determination of neoplastic status of lesion is necessary	Sensitivity of 80% to 100%, specificity of >95%; hematoxylin-eosin and Diff-Quik stains are simplest; Genta stain has sensitivity of >95% and specificity of 99%	Requires laboratory facilities and experience; when hematoxylin-eosin stain is nondiagnostic, second staining method is required
Rapid urease test	Simplest method when endoscopy is necessary	Simple; rapid (once biopsy specimen has been obtained); sensitivity of 80% to 95%, specificity of 95% to 100%	Invasive; false-negatives possible If testing is done too soon after treatment with proton pump inhibitors, antimicrobials, or bismuth compounds
Culture	After repeated failure of appropriate combination antibiotic therapy; when antimicrobial resistance is suspected or high level of resistance exists in the population	Allows determination of antibiotic susceptibility	Time-consuming; expensive; usually not necessary unless resistance is suspected

ing in symptomatic patients in whom the probability of peptic ulcer disease is high but the presence of ulcer is unconfirmed. In one study of 565 patients with endoscopically documented ulcer disease,[29] the investigators concluded that the overall cost of care would have been significantly lower if patients with a high pretest probability of infection had been treated empirically with bismuth, tetracycline, and metronidazole (Flagyl, Protostat) rather than undergoing endoscopy or noninvasive testing first. We strongly disagree. The decision to give antibiotic combination therapy must be based on confirmation of an *H pylori* infection. Neither the individual patient nor the general population benefits from antibiotic therapy when no infection is present. The only outcomes that can be expected are unnecessary complications and development of antibiotic resistance in other bacteria, and neither is beneficial.[30,31]

The outcome of asymptomatic *H pylori* infection is relatively poor: Peptic ulcers develop in one in six patients, and the lifetime risk of gastric cancer is 1% to 3%. Therefore, cure of the infection is a reasonable goal. It is less expensive to do noninvasive testing for *H pylori* infection in symptomatic patients and to administer therapy for peptic ulcer disease in all infected patients than it is to perform endoscopy on every patient in whom peptic ulcer disease is suspected.

Cost-effectiveness studies usually do not take into account the ancillary or societal costs, such as lost work time, the need for patients to be driven home after endoscopy (because of sedation), and the cost of histologic analysis. For endoscopy to be cost-competitive with breath testing, the actual total cost would need to fall to $200 to $300, and even then, from a societal standpoint, the test would not be competitive.

In general, regardless of the therapy first prescribed, failure of one or two rounds of treatment suggests the need for endoscopy with culture and sensitivity testing. Managed care organizations need to understand that restricting the use of endoscopy because of cost is not in their or the patient's best interests. In primary care, the key to cost-effective clinical management lies in rapid recognition of which patients need subspecialty consultation (eg, those who are not cured after one or two courses of anti–*H pylori* therapy). This approach ensures that peptic ulcer disease will be cured at the lowest possible cost. A delay in diagnosing gastric cancer of up to 6 weeks between presentation and endoscopy does not place patients without alarm signs and symptoms at a disadvantage.

Confirmation of cure of *H pylori* infection

Is it always necessary to confirm cure of *H pylori* infection? About 75% of patients presumed to have uncomplicated peptic ulcer disease due to *H pylori* infection are cured after one course of therapy. Treatment failure in the remainder of patients means that the ulcer will recur, resulting in additional pain and necessitating more physician visits, tests, and therapy. Also, such patients remain at risk for an ulcer complication, such as upper gastrointestinal hemorrhage (overall risk, about 3% per year), and they continue to be a reservoir for transmission of infec-

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tion to others in the community, especially family members. The decision not to confirm cure cannot be made by the physician alone. The potential outcome of failure to cure the infection should be discussed with the patient and documented in the chart.

The urea breath test is the best method for assessing the effectiveness of therapy. The stool antigen test appears to be only slightly less accurate, and its use should be considered, especially when breath testing is not available. Endoscopy is neither practical nor cost-effective for follow-up except when symptoms persist after one or two courses of antimicrobial combination therapy. It is also appropriate for follow-up of gastric ulcer or when suspicion of gastric cancer or other serious illness is high.

Confirmation of cure must be delayed until at least 4 to 6 weeks after completion of antimicrobial therapy. Treatment with proton pump inhibitors must be discontinued at least 1 week before urea breath testing to confirm cure. H_2-receptor antagonists have no effect on culture, histologic tests, or the ^{13}C urea breath test and need not be discontinued before confirmation testing. Because elevated antibody levels to *H pylori* persist indefinitely after eradication, serologic testing has no role in follow-up.

Summary

An algorithmic approach to evaluation of dyspepsia or abdominal discomfort begins with differentiation between peptic ulcer disease and gastroesophageal reflux disease as well as recognition of alarm signs and symptoms for gastric cancer, which are indications for early endoscopy. In the absence of alarm symptoms, most patients should undergo noninvasive testing for *H pylori* infection with a serologic, urea breath, or stool antigen test.

Factors to consider in selection of appropriate testing include reliability, specificity, sensitivity, cost, and local access and expertise. As a general rule, physicians should choose a test that has the best accuracy for the level of testing expertise available. The basic principle underlying testing for *H pylori* is that patients should not undergo testing unless the physician is willing to treat on the basis of a positive test result. In patients who receive treatment, confirmation of cure is important for preventing further morbidity and reducing risk of transmission of infection. **PGM**

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