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TESTING FOR *HELICOBACTER PYLORI* IN THE CLINICAL SETTING

Jeremy M. Lake, and William D. Chey

Division of Gastroenterology, Department of Internal Medicine, University of Michigan Health System, Ann Arbor, MI

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1. ABSTRACT

There are a variety of tests available to identify *Helicobacter pylori* infection. These tests can be divided into those that do not require and those that do require endoscopy. This review provides a detailed discussion of the available diagnostic tests for *H. pylori* infection. Special attention is paid to the role of diagnostic testing in the management of patients with *H. pylori*-related disease. The potential advantages and disadvantages of various tests and the role of testing to confirm eradication after treatment for *H. pylori* is also discussed.

2. CURRENT INDICATIONS FOR THE DIAGNOSIS OF *H. PYLORI*

In the past, clinicians have asked the question, " Which patients with *Helicobacter pylori* infection should we *treat*?". However, once identified, it is difficult to withhold therapy for an infection known to be associated with a number of clinically important diseases. If found to be infected, regardless of the reason for diagnostic testing, the clinician should be prepared to offer treatment. As such, the only relevant question is, "Which patients should we *test* for *Helicobacter pylori* infection?".

There is a clear link between *H. pylori* infection and the pathogenesis of peptic ulcer disease (PUD) (1). Cure of this infection is the most cost-effective means of managing patients with PUD (2). A consensus conference statement from the National Institutes of Health recommended that all patients with PUD as well as those on long-term medical therapy for a history of PUD should be tested for *H. pylori* (3).

The incidence of *H. pylori* infection in patients with *gastric* adenocarcinoma, non-Hodgkin's lymphoma, and mucosa associated lymphoid tissue lymphoma (MALToma), is significantly higher than in controls (4). Because many patients with low-grade gastric MALToma will experience tumor regression following *H. pylori* eradication (5), all patients with MALToma should be tested for *H. pylori*. In addition, the Japanese have reported that eradication of *H. pylori* infection reduces the likelihood of recurrence following the endoscopic resection of early gastric adenocarcinoma (6).

A recent medical position statement by the American Gastroenterological Association recommended that dyspeptic patients, primarily those with ulcer-like dyspepsia or pain centered in the upper abdomen as their predominant symptom, under the age of 45-50 years with no "alarm features" (weight loss, evidence of bleeding, vomiting, dysphagia, anemia) undergo a "test and treat" strategy for *H. pylori* (7). In this strategy, patients undergo a non-endoscopic test for *H. pylori* and those with a

Table 1. Indications for *H. pylori* testing and treatment

Accepted Indications
? Documented gastric or duodenal ulcer
? History of peptic ulcer disease
? Gastric mucosa associated lymphoid tissue lymphoma
? Following resection of early gastric adenocarcinoma
? Dyspepsia in the primary care setting
Controversial Indications
? Nonulcer dyspepsia
? Patients to be treated with non-steroidal anti-inflammatory medications
? Patients to be treated long-term with a proton pump inhibitor
? Patients with a family history of gastric cancer
? Patients residing in countries or of ethnic background where gastric cancer is common
Not Currently Indicated
? Asymptomatic individuals
? Gastroesophageal reflux disease
? Irritable bowel syndrome

Table 2. Tests for *H. pylori*

Nonendoscopic Tests for *H. pylori*
? Antibody tests
– Quantitative (ELISA)
– Qualitative (serum or whole blood)
? Active tests
– Urease tests
▪ $^{13}C/^{14}C$-urea breath
▪ ^{13}C-blood test
– Fecal antigen test
Endoscopic Tests for *H. pylori*
? Rapid urease tests
? Histology
? Culture
Polymerase Chain Reaction

positive test receive antimicrobial therapy. The test and treat strategy may reduce the utilization of upper endoscopy (EGD) and expenditures associated with the care of dyspeptic patients (8,9). The cost-effectiveness of this strategy will require periodic re-evaluation given the changing costs of specific diagnostic tests and the falling prevalence of *H. pylori* in the western world.

Patients with non-ulcer dyspepsia (NUD) suffer with epigastric pain or discomfort but have no evidence of PUD at the time of endoscopy. A relationship between *H. pylori* and NUD has been suggested but remains quite controversial. Several recent, large, randomized, double-blind, controlled trials assessing the potential benefits of treating patients with NUD for *H. pylori* infection with a standard regimen versus placebo or a short course with a proton pump inhibitor (PPI) have yielded conflicting results (10-13). The degree of confusion regarding this issue was recently highlighted by the publication of two meta-analysis' which arrived at opposite conclusions – one finding a statistically significant benefit associated with the eradication of *H. pylori* (14) and the other finding no statistically significant advantage to curing this infection (15). Though the conclusions of the available studies have been conflicting, the reported likelihood of symptom response has been remarkably consistent ranging from 21-46%. Even if the reader accepts the premise that there is a statistically significant benefit to curing *H. pylori* in NUD patients, the incremental benefit over placebo or a short course with a PPI is likely to be modest.

Currently, there is no indication to test asymptomatic individuals for *H. pylori*. In addition, the available literature would suggest that the classic symptoms of gastroesophageal reflux disease (GERD), including heartburn and regurgitation, are not indications to test for *H. pylori* infection. Recent studies suggest that eradication of *H. pylori* infection either has no effect or may even worsen GERD in a subset of patients (16,17). There is currently no data to suggest that *H. pylori* eradication improves GERD symptoms or esophagitis. Recommended indications for testing and treating *H. pylori* are presented in table 1.

3. DIAGNOSTIC TESTS FOR *H. PYLORI*

No single test can be considered the "gold standard" for the diagnosis of *H. pylori* infection. It is convenient to divide the diagnostic tests into those that do and those that do not require EGD (table 2). Non-endoscopic tests can be further divided into those that identify the presence of an antibody response to *H. pylori* infection (antibody testing) and those that identify active infection, either on the basis of *H. pylori*'s urease activity or through the detection of fecal antigen. The endoscopic tests, including the rapid urease test, histology, and culture, identify only patients with active *H. pylori* infection.

3.1. Non-endoscopic Methods of *H. pylori* Diagnosis:

3.1.1. Antibody tests

The enzyme-linked immunosorbent assay (ELISA) provides a widely available means of determining the serum IgG antibody titre to *H. pylori*. A recent meta-analysis of 21 studies reported an overall sensitivity of 85% and specificity of 79% for ELISA (18). Disadvantages of the ELISA include the need for a CLIA-approved laboratory and a delay between the time of testing and the availability of results.

Office-based, qualitative kits utilizing serum or whole blood are also available. The sensitivity and specificity of the serum-based qualitative tests are similar to those yielded by ELISA (19). Whole blood, qualitative antibody tests, which require 2-3 drops of blood obtained by a fingerstick, are quick, easy to perform, and do not require centrifugation. Unfortunately, the current generation of whole blood antibody tests appears to be less sensitive than other methods of *H. pylori* testing. In a recent US, multi-center trial, 3 different fingerstick whole blood antibody tests were evaluated against a histological gold standard (20). Sensitivities for the 3 antibody tests ranged from 76-84% and specificities from 79-90%. Though the first generation whole blood antibody tests are not as sensitive as the ELISAs, newer whole blood tests appear to provide improved sensitivity (21,22).

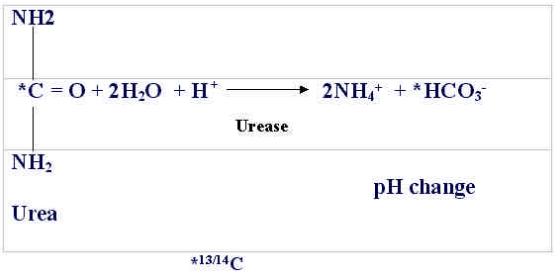

Figure 1. Effects of *H. pylori's* urease activity. Urease metabolizes $^{13/14}$C-labeled urea to ammonia and bicarbonate. Labeled bicarbonate is promptly excreted in the breath as labeled CO_2.

Antibody tests are most useful in patients not previously treated for *H. pylori* infection. Unlike the noninvasive tests that detect active infection, including the urea breath test and stool antigen test, the sensitivity of antibody tests in patients with *H. pylori* infection is not affected by the recent use of proton pump inhibitors (PPIs), bismuth containing compounds, or antibiotics. Unfortunately, antibody tests cannot distinguish between active and recent (previously treated) infection. The importance of this point is discussed later in this manuscript.

3.1.2. Non-endoscopic urease tests (NUT)

The non-endoscopic urease tests (NUT) include the $^{13/14}$Carbon-urea breath tests and ^{13}Carbon-urea blood test. These tests rely upon the identification of *H. pylori*'s urease activity (figure 1). Since urease is not present in normal human tissues, and since other urease-producing bacteria do not colonize the stomach, the presence of urease in the stomach can be equated with *H. pylori* infection. When a patient with active *H. pylori* infection takes an oral dose of labeled urea, urease hydrolyzes the urea to ammonia and labeled bicarbonate. Ammonia migrates toward the gastric lumen while labeled bicarbonate is rapidly absorbed into the bloodstream where it can be converted to water and labeled carbon dioxide. The labeled bicarbonate can be measured in the serum, while the majority of labeled CO_2 is excreted in the breath where it can be collected and quantitated using mass spectrometry (^{13}C) or a standard scintillation counter (^{14}C). Unlike the antibody-based tests, the NUTs only identify patients with active *H. pylori* infection and are accurate in both the pre- and post-treatment setting.

The ^{13}C-urea breath test (UBT) utilizes a non-radioactive, stable isotope. Breath samples are analyzed by mass spectrometry. The test that is currently commercially available requires a meal to slow gastric emptying of the ^{13}C-urea and takes approximately an hour to perform (Meretek, Nashville, TN). A simplified version of the ^{13}C-urea breath test that requires no test meal and the collection of a single 15 minute breath sample will be available some time in 2001(personal communication: David Graham, Baylor University, Houston, TX). Another version of the ^{13}C-UBT which provides real-time results is currently in development (23). In the near future, infrared spectrometry will provide an alternative means of breath analysis to mass spectrometry (24). Infrared spectrometry may offer advantages over mass spectrometry in terms of decreasing need for quality control, space, and cost.

The ^{14}C-urea breath test (Ballard Medical Products, Draper, UT) requires no test meal and takes <30 minutes to perform. This test does require the ingestion of a small dose of radioactive isotope (1 microcurie). However, a single ^{14}C-urea breath test results in radiation exposure equivalent to 1/60 of a chest radiograph (20 mrem) and less than daily background radiation exposure (25). In addition, 86-97% of the ^{14}C is excreted in the breath and urine within 3 days of ingestion (26). Nonetheless, as non-radioactive alternatives are currently available, this test is not recommended in pregnant females. The role of the ^{14}C-urea breath test in children remains controversial.

The ^{13}C-urea blood test (Metabolic Solutions, Nashua, NH) has recently been approved by the US Food and Drug Administration. This study involves measuring labeled bicarbonate via a single blood sample obtained by standard phlebotomy 30 minutes after the ingestion of ^{13}C-urea (27). An increase in the concentration of labeled serum bicarbonate indicates the presence of active *H. pylori* infection.

The NUTs are accurate as primary diagnostic methods and for confirming eradication after a course of antimicrobial therapy (28,29). The NUTs are functional tests and therefore, can be adversely affected by drugs known to decrease the absolute number of *H. pylori* organisms or urease activity. The recent use of antibiotics, bismuth compounds, or agents that potently suppress gastric acid production can lead to false negative NUT results (25,30).

It is currently recommended that antibiotics and bismuth containing compounds be withheld for 2-3 weeks prior to performing the NUTs (25). PPIs have been found to decrease the sensitivity of the NUTs (31,32,33). Several investigators have found that standard doses of omeprazole and lansoprazole can induce false negative NUT results. Based upon these observations, it is currently recommended that patients withhold a PPI for 7-14 days prior to urease testing. The mechanisms by which PPIs affect the sensitivity of the NUTs remain incompletely defined. However, it appears that individuals with the greatest increase in intragastric pH with a PPI are the most likely to develop a false negative UBT result (32). A recent study found that intragastric acidification with citrate at the time of urea ingestion decreases the likelihood of false negative UBT results in patients taking a PPI (34). Whether histamine-2-receptor antagonists influence the sensitivity of the NUTs remains controversial (32,35). A recent study in a large number of subjects with *H. pylori* infection reported that standard and high doses of ranitidine induced false negative breath test results in 15% and that this effect resolved within 2 weeks of discontinuing therapy (36).

3.1.3. Fecal antigen test (FAT)

Recently, a test which identifies *H. pylori* antigens in stool has become commercially available. The

fecal antigen test (FAT) utilizes polyclonal anti-*H. pylori* capture antibody adsorbed to microwells. Diluted stool and a peroxidase conjugated polyclonal antibody are added followed by substrate one hour later. In infected patients, enzyme-substrate binding leads to a color change which can be detected visually or spectrophotometrically. After collection, stool samples can be stored at 2-8°C for 3 days and at –20°C indefinitely.

Studies have reported sensitivity and specificity for the FAT of >90% in patients not previously treated for *H. pylori* infection (29). Like the NUTs, the stool antigen test identifies patients with active *H. pylori* infection. Preliminary studies suggest that the stool antigen test may be useful as a means of establishing cure after antimicrobial therapy (37). The sensitivity of the stool test is decreased by the recent use of antibiotics, bismuth, or PPIs, though to a lesser degree than the NUTs (30). Issues which have slowed the widespread use of this test include the inherent unpleasantness associated with the handling and storing of stool, limited availability, and highly variable state to state reimbursement.

3.2. Endoscopic methods of *H. pylori* diagnosis

3.2.1 . Rapid urease tests (RUT)

The rapid urease tests (RUTs) rely upon the identification of *H. pylori*'s urease activity. These tests utilize either a gel matrix (CLO test, Ballard Medical Products; HP fast, GI supply) or reaction strip (Pyloritek, Serim Research) embedded with urea and a pH-sensitive indicator. If *H. pylori* is present, urease cleaves urea leading to an increase in pH and consequent color change in the test medium. The RUT is sensitive (>89%) and specific (>90%) (38). Like the NUTs, RUT sensitivity can be decreased by the recent use of antibiotics, bismuth, or PPIs. The CLO test and the HP fast provide rapid results in most instances (75% positive within 20 minutes) but can take up to 24 hours to become positive (39). An advantage of Pyloritek is the ability to obtain formal results 1 hour after inoculation with gastric tissue. The RUT is the least costly means of *H. pylori* diagnosis at the time of EGD (≈$5-10).

The rapidity with which the RUT becomes positive is dependent upon the quantity of urease, or *H. pylori*, inoculated into the test medium. In addition, the recent use of a PPI decreases the sensitivity of RUT when using a single antral mucosal biopsy. As such, it is reasonable to obtain two mucosal biopsies (one from the body and one from the antrum of the stomach) when performing the RUT. Recent studies suggest that the sensitivity of the RUT may be compromised in patients who have suffered an acute upper gastrointestinal bleed (40). In such patients, obtaining biopsies for histology or blood for ELISA testing may be a more appropriate diagnostic choice than RUT.

3.2.2. Histology

In *experienced* hands, histological identification of *H. pylori* is highly sensitive (>90%) and specific (>90%) (41). *H. pylori* is best identified by silver, Giemsa, and/or Genta stains. The Genta stain, which is a combination of H&E, Steiner, and Alcian Blue stains, allows identification of *H. pylori* and a review of histological architecture of the gastric mucosa with a single stain. Standard H&E staining is also reasonably sensitive and specific in the hands of an experienced pathologist. Factors other than the direct demonstration of the organism can support the histological diagnosis of *H. pylori*. The demonstration of chronic antral gastritis (Type B gastritis) is highly sensitive but not specific for *H. pylori* infection (21,41). In other words, all *H. pylori* infected patients have some degree of chronic antral gastritis, but not all chronic antral gastritis is caused by *H. pylori* infection. In addition to direct demonstration of the organism or surrogate markers such as chronic antral gastritis, histology allows the identification of concurrent mucosal pathology such as gastric malignancy and can provide clues regarding the etiology of lesions caused by nonsteroidal anti-inflammatory agents.

3.2.3. *H. pylori* culture

Identification of *H. pylori* is made on the basis of colony morphology (≈ 3 mm translucent colonies) that contain Gram negative, curved rods that test positive for urease, catalase, and oxidase. Culture is arguably the most specific means of diagnosing *H. pylori* infection. Culture also allows the determination of antibiotic sensitivity profiles. However, the usefulness of culture is hampered by limited availability, the fastidious nature of *H. pylori*, the need for properly trained personnel, and the delay between obtaining tissue and receiving formal results (3-6 days) (42). In addition, sensitivity can be affected by sampling error, recent antibiotic use, ingestion of topical anesthetics or simethicone, and contamination of specimens with glutaraldehyde during biopsy acquisition (43). In the best hands, sensitivity is approximately 85% (44). As is the case with histology, the need for endoscopy and associated expense are further factors weighing against culture. For these reasons, culture remains confined to the setting of clinical research in the US. However, it is conceivable that culture will acquire a more important role in the years to come as resistance to commonly used antimicrobial agents increases.

4. *H. PYLORI* TESTING IN CLINICAL PRACTICE

When considering the diagnostic options for *H. pylori*, the first decision involves whether a patient does or does not require EGD. If EGD is needed and a patient has not had recent antibiotics, bismuth, or a PPI, RUT is the most cost-effective choice. In patients who have recently taken medications known to affect *H. pylori* viability, some have advocated obtaining biopsies for RUT and histology, and only sending histology if the RUT is negative. Unfortunately, this is cumbersome in clinical practice. As such, if a patient is taking antibiotics, bismuth, or a PPI or if there are macroscopic findings which require microscopic evaluation, histology with or without RUT should be performed.

Due largely to issues of availability, convenience, and cost, antibody tests are currently the most widely utilized non-endoscopic tests for *H. pylori*. However, choosing the most appropriate non-endoscopic test for *H.*

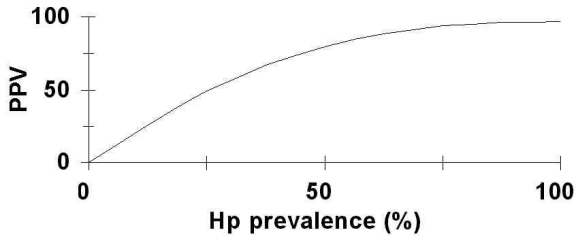

Figure 2. Effect of *H. pylori* prevalence on the positive predictive value (PPV) of antibody testing (where sensitivity = 85% and specificity = 79%, Adapted from 18).

pylori requires an explicit understanding of the tradeoffs between the lower acquisition cost of antibody testing and the superior accuracy of active testing.

We recently developed a decision analytic model in patients with uninvestigated dyspepsia to compare the clinical benefits of active testing versus the lower costs of antibody testing (45) . For this model, we assumed a background *H. pylori* prevalence of 30% and used 1999 Medicare reimbursements for antibody testing ($25) and the urea breath test ($100). We assumed the cost of therapy to be $200. Our model found that active testing led to a substantial reduction in unnecessary treatment for dyspeptic patients without active *H. pylori* infection (antibody = 23.7, active = 1.4 per 100 patients) at an incremental cost of $37/patient. The decrease in unnecessary therapy has important implications for patients, payers, and society. For the patient, it makes no sense to ingest multiple medications without an expectation of clinical benefit. For the payer, the costs associated with the prescribing of therapy in uninfected patients can be substantial. From a societal perspective, antimicrobial resistance is a growing problem in the westernized world (46,47). Limiting the inappropriate use of antimicrobials may slow the development of resistance not only for *H. pylori* but for other bacteria as well. For these reasons, it is likely that tests which detect active *H. pylori* infection will gain popularity amongst clinicians.

Several other factors should be taken into consideration when choosing a non-endoscopic test for *H. pylori*. Recent studies suggest that the accuracy of various antibody tests may differ based upon geographical location (48). Antigenic variability in *H. pylori* strains may explain some of the observed geographical differences in test accuracy (49). The pretest probability of finding *H. pylori* infection (background prevalence of *H. pylori* infection) influences the predictive value of antibody testing in a given population (18) (figure 2). These observations have several potentially important consequences. First, local validation of different antibody tests and/or the development of antibody tests based upon local *H. pylori* strains may be necessary. In addition, antibody testing may be less useful in populations with a low prevalence of *H. pylori* infection or where the prevalence of *H. pylori* infection is rapidly decreasing.

The widespread use of antibiotics for indications unrelated to *H. pylori* is also likely to influence the usefulness of antibody testing in developed countries. Treatment with single antibiotics, such as clarithromycin, results in the cure of *H. pylori* infection in up to a third of infected patients (50). This incidental *H. pylori* eradication in combination with the purposeful cure of the infection with multi-drug regimens will lead to a population of antibody positive but *H. pylori* uninfected individuals. In composite, the weight of the evidence strengthens the economic and clinical arguments for active as opposed to antibody testing in patients with dyspepsia in the primary care setting.

5. TESTING TO PROVE CURE OF *H. PYLORI* INFECTION AFTER TREATMENT

Currently, testing to prove cure of *H. pylori* infection is recommended in only selected clinical situations including recalcitrant or complicated (significant bleeding, perforation, penetration, obstruction) ulcers in the hopes of preventing future ulcer-related morbidity and mortality, in patients suffering with refractory dyspeptic symptoms despite an appropriate course of therapy, in patients with gastric MALT lymphoma, and after resection of early gastric cancer (51). However, the recommendations for testing following therapy for *H. pylori* are now becoming more inclusive. Given the possibility of future ulcer-related morbidity and mortality in those with persistent infection, most would agree that all patients with *H. pylori*-related PUD should undergo some form of follow-up testing.

Unfortunately, many if not most patients with dyspepsia and *H. pylori* infection remain symptomatic despite an appropriate course of antimicrobial therapy. In patients with ongoing symptoms despite therapy, it is important to establish the presence or absence of persistent infection prior to deciding upon the need for further therapy for *H. pylori*. This recommendation can be supported by several arguments. Accepted 10-14 day regimens for *H. pylori* result in a cure rate of 80-90% (52). It is reasonable to expect that <50% of patients subjected to the "test and treat" strategy for dyspepsia will experience symptom resolution following therapy for *H. pylori* (53). Therefore, even if one were to assume that all patients with persistent infection remained symptomatic, a substantial percentage of patients with symptoms will not have persistent infection. In addition, testing, unlike therapy, is unlikely to be associated with adverse events or the development of antimicrobial resistance. Finally, a course of *H. pylori* therapy is typically more expensive than a non-endoscopic test. Of course, arguments founded on the basis of cost are less relevant in situations where endoscopy is deemed to be necessary.

The role of follow-up testing in dyspeptic patients rendered asymptomatic after *H. pylori* therapy is much less clear. Some percentage of patients with *H. pylori* and dyspepsia will have PUD. As the clinician cannot know which dyspeptic patients have PUD, one could argue that follow-up testing may be of benefit to identify those with persistent *H. pylori* infection given the associated risk of ulcer recurrence. However, given the

Table 3. Sensitivity of Biopsy-Based *H. pylori* Tests

	Pretreatment	Posttreatment
A/B histology	322/323 (100%)	103/111 (93%)
A/B culture	273/309 (88%)	90/108 (83%)
A-CLO test	326/326 (100%)	88/113 (78%)
Histology/CLO		109/112 (97%)

A = antrum, B = body *Adapted from 44).*

high likelihood of eradication with *H. pylori* therapy and the low likelihood of PUD, this recommendation is not likely to be cost-effective.

A very real consideration is that many patients will want to know that their *H. pylori* infection has been eliminated even if there is not an absolute medical indication for such testing. Fendrick and colleagues recently found that >70% of patients with PUD would be willing to commit >$50 of their own funds to obtain the peace of mind provided by follow-up testing (54).

There are now several tests which can be used to confirm cure of *H. pylori* infection. In general, testing to establish *H. pylori* cure should be performed >4 weeks after the completion of therapy, regardless of the type of test chosen (25,51). The endoscopic methods including histology and RUT can be used, but cannot be routinely recommended on the basis of their high overall cost and the small, but definable risk associated with endoscopy. When a follow-up endoscopy is clinically indicated, it is important to realize that the sensitivity of the RUT is reduced in the post-treatment setting. A recent study found that antral CLO testing had a sensitivity of only 78% eight weeks after the completion of therapy for *H. pylori*. Combining RUT with histology increased sensitivity to 97% eight weeks following therapy (44) (table 3).

Antibody tests can remain positive for years following the successful eradication of *H. pylori* (55). Because of this, these tests are not a practical means of establishing cure in clinical practice. The NUTs provide a reliable means of establishing cure of *H. pylori* infection. Recent studies have found that the NUTs have sensitivity and specificity exceeding 90% in the post-treatment setting (28,37). Another study recently reported that a UBT performed 2 weeks after therapy yielded results comparable to testing done 4-6 weeks after therapy (56).

The fecal antigen test can also be used to establish cure of *H. pylori* infection. A multi-center study from Europe found the FAT to be both sensitive and specific as a means of establishing *H. pylori* eradication (37). However, results from other studies have yielded conflicting results (57). The timing and optimal cut-off for the stool test in the post-treatment setting remains controversial.

6. SUMMARY

There are clear indications for *H. pylori* testing. Testing should not be undertaken unless the clinician is prepared to offer appropriate therapy. A number of accurate tests for *H. pylori* are currently available though no single test can be considered the "gold standard." The choice of diagnostic test relies heavily upon whether or not an EGD is required and an understanding of the accuracy and costs associated with specific tests. It is important to consider overall costs associated with disease management (including costs for inappropriate therapy and its consequences or lack thereof) rather than only the acquisition costs associated with a specific test. Particularly in areas of low *H. pylori* prevalence, tests that identify active infection are the most logical choice. Recommendations for post-treatment testing are becoming more inclusive. In general, post-treatment testing should be performed no less than 4 weeks after the completion of therapy.

7. REFERENCES

1. Nomura A, GN Stemmermen, P Chyou, GI Perez-perez, M Blaser: *Helicobacter pylori* infection and the risk of duodenal and gastric ulceration. *Ann Intern Med* 120, 977-81 (1994)

2. Sonnenberg A, JS Schwartz , AF Cutler, N Vakil, BS Bloom: Cost savings in duodenal ulcer therapy through *Helicobacter pylori* eradication compared with conventional therapies: results of a randomized, double-blind, multi-center trial. Gastrointestinal Utilization Trial Study Group. *Arch Intern Med* 158, 852-60 (1998)

3. NIH Consensus Development Panel on *Helicobacter pylori* in Peptic Ulcer Disease. *Helicobacter pylori* in peptic ulcer disease. *JAMA.* 272, 65-9 (1994)

4. Parsonnet J, S Hansen, L Rodriguez, AB Gelb, RA Warnke, E Jellum, N Orentreich, JH Vogelman, GD Friedman: *Helicobacter pylori* infection and gastric lymphoma. *N Engl J Med* 330, 1267-71 (1994)

5. Steinbach G, R Ford, G Glober, D Sample, FB Hagemeister, PM Lynch, PW McLaughlin, MA Rodriguez, JE Romaguera, AH Sarris, A Younes, R Luthra, JT Manning, CM Johnson, S Lahoti, Y Shen, JE Lee, RJ Winn, RM Genta, DY Graham, FF Cabanillas: Antibiotic treatment of gastric lymphoma of mucosa-associated lymphoid tissue. An uncontrolled trial. *Ann Intern Med* 131, 88-95 (1999)

6. Uemura N, T Mukai, S Okamoto, S Yamaguchi, H Mashiba, K Tanuyama, N Sasaki, K Haruma, K Sumii, G Kajiyama: Effect of *Helicobacter pylori* eradication on subsequent development of cancer after endoscopic resection of early gastric cancer. *Cancer Epidemiol Biomarkers Prev* 6, 639-42 (1997)

7. Talley NJ, MD Silverman, L Agreus, A Sonnenberg, G Holtmann: AGA Technical Review: Evaluation of Dyspepsia. *Gastroenterol* 114, 582-95 (1998)

8. Heaney A, JSA Collins, RGP Watson, RJ McFarland, KB Bamford, TCK Tham: A prospective randomised trial of "test and treat" policy versus endoscopy based management in young *Helicobacter pylori* positive patients with ulcer-like dyspepsia, referred to a hospital clinic. *Gut* 45, 186-190 (1999)

9. Lassen AT, FM Pedersen, P Bytzer, OS de Muckadell: *Helicobacter pylori* test-and-eradicate versus prompt endoscopy for management of dyspeptic patients: randomised trial. *Lancet* 356, 455-460 (2000)

10. McColl K, L Murray, E El-Omar, A Dickson, A El-Nujumi, A Wirz, A Kelman, C Penny, R Knill-Jones, T

Hilditch: Symptomatic benefit from eradicating *Helicobacter pylori* infection in patients with nonulcer dyspepsia. *N Engl J Med* 339, 1869-74 (1998)
11. Blum AL, NJ Talley, C O'Morain, S Veldhuyzen van Zanten, J Labenz, M Stolte, JA Louw, A Stubberod, A Theodors, M Sundin, E Bolling-Sternevald, N Dip, O Junghard: Lack of effect of treating *Helicobacter pylori* infection in patients with nonulcer dyspepsia. *N Engl J Med* 339, 1875-82 (1998)
12. Talley NJ, N Vakil, ED Ballard, MB Fennerty MB: Absence of benefit of eradicating *Helicobacter pylori* in patients with nonulcer dyspepsia. *N Engl J Med* 341, 1106-1111 (1999)
13. Malfertheiner P, W Fischback, P Layer, J Moessner, M Stolte, A Leodolter, K Demleitner, WA Fuchs: Elan study proves symptomatic benefit of *Helicobacter pylori* eradication in functional dyspepsia (FD). *Gastroenterol* 118, A440 (2000)
14. Moayyedi P, S Soo, J Deeks, D Forman, J Mason, M Innes, B Delaney: Systemic review and economic evaluation of *Helicobacter pylori* eradication treatment for non-ulcer dyspepsia. *BMJ* 321, 659-664 (2000)
15. Laine L, P Schoenfeld, MB Fennerty: Therapy for Helicobacter pylori in patients with nonulcer dyspepsia. A meta-analysis of randomized, controlled trials. *Ann Intern Med* 134, 361-369 (2001)
16. McColl KE, A Dickson, A El-Nujumi, E El-Omar, A Kelman: Symptomatic benefit 1-3 years after *H. pylori* eradication in ulcer patients: Impact of gastroesophageal reflux disease. *Am J Gastroenterol* 95, 101-105 (2000)
17. Koike T, A Masamune: *Helicobacter pylori* infection in reflux esophagitis and atrophic gastritis: Clinical implications. *Medscape Gastroenterology* 3 (2001)
18. Loy CT, LM Irwig, PH Kateralis, NJ Talley: Do commercial serological kits for *Helicobacter pylori* infection differ in accuracy? A meta-analysis. *Am J Gastroenterol* 91, 1138-44 (1996)
19. Graham DY, DJ Evans, J Peacock, JT Baker, WH Schrier: Comparison of rapid serological tests (FlexSure HP and QuickVue) with conventional ELISA for detection of *Helicobacter pylori* infection. *Am J Gastroenterol* 91, 942-8 (1996)
20. Chey WD, W Linscheer, A Zawadski, J Montague, W Linscheer, L Laine: A comparison of three fingerstick whole blood antibody tests for *Helicobacter pylori*: A United States, multicenter trial. *Am J Gastroenterol* 94, 1512-6 (1999)
21. Hahn M, B Fennerty, CL Corless, N Magaret, DA Lieberman, DO Faigel: Noninvasive tests as a substitute for histology in the diagnosis of *Helicobacter pylori* infection. *Gastrointest Endosc* 52, 20-26 (2000)
22. Chey WD, U Murthy, W Linscheer, C Barish, D Riff, H Rubin, M Safdi, H Schwartz, U Shah, L Wruble, MT El-Zimaity: The ChemTrak Hp Chek™ fingerstick, whole blood serology test for the detection of *H. pylori* infection. *Am J Gastroenterol* 93, 16-19 (1998)
23. Shirin H, O Shevah, G Kenet, Y Wardi, M Shahmurov, R Bruck: Evaluation of a novel continuous real time ^{13}C urea breath analyzer. Comparison to urease test and histopathological detection of *H. pylori*. *Gastroenterol* 118, A507 (2000)
24. Leodolter A, U von Arnim, C Gerards, S Kahl, P Malfertheiner: Pre- and post-treatment diagnosis of *H. pylori* infection by the ^{13}C-urea breath test ($^{13C\text{-}UBT}$): Validation of a new isotope-selective infrared spectrometer (ISIS). *Gastroenterol* 118, A506 (2000)
25. Chey WD: Accurate diagnosis of H. pylori: Breath tests (^{14}C). *Gastroenterol Clin North Am* 29, 895-902 (2000)
26. Munster DJ, BA Chapman, MJ Burt, BR Dobbs, RA Allardyce, PF Bagshaw, WD Troughton, HB Cook: The fate of ingested ^{14}C-urea in the urea breath test for *Helicobacter pylori* infection. *Scand J Gastroenterol* 28, 661-6 (1993)
27. Chey WD, U Murthy, P Toskes, S Carpenter, L Laine: The ^{13}C-urea blood test accurately detects active *H. pylori* infection: a US, multicenter trial. *Am J Gastroenterol* 94, 1522-4 (1999)
28. Leodolter A, E Dominguez-Munoz, U von Arnim, S Kahl, U Peitz, P Malfertheiner: Validity of a modified ^{13}C-urea breath test for pre- and post-treatment diagnosis of *Helicobacter pylori* infection in the routine clinical setting. *Am J Gastroenterol* 94, 2100-2104 (1999)
29. Vaira D, P Malfertheiner, F Megraud, ATR Axon, M Deltenre, AM Hirschl, G Gasbarrini, C O'Morain, JM Pajares Garcia, M Quina, GNJ Tytgat: Diagnosis of *Helicobacter pylori* infection with a new non-invasive antigen-based assay. HpSA European study group. *Lancet* 354, 30-3 (1999)
30. Bravo LE, JL Realpe, C Campo, R Mera, P Correa: Effects of acid suppression and bismuth medications on the performance of diagnostic tests for *Helicobacter pylori* infection. *Am J Gastroenterol* 94, 2380-2383 (1999)
31. Chey WD, M Spybrook, S Carpenter, TT Nostrant, GH Elta, JM Scheiman: Prolonged effect of omeprazole on the ^{14}C-urea breath test. *Am J Gastroenterol* 91, 89-92 (1996)
32. Chey WD, M Woods, JM Scheiman, TT Nostrant, J Del Valle: Lansoprazole and ranitidine affect the accuracy of the ^{14}C-urea breath test by a pH dependent mechanism. *Am J Gastroenterol* 92, 446-50 (1997)
33. Laine L, R Estrada, M Trujillo, K Knigge, MB Fennerty: Effect of proton pump inhibitor therapy on diagnostic testing for *Helicobacter pylori*. *Ann Intern Med* 129, 547-50 (1998)
34. Chey WD, K Chathadi, J Montague, F Ahmed, U Murthy: Intragastric acidification reduces the occurrence of false negative urea breath test results in patients taking a proton pump inhibitor. *Am J Gastroenterol* (in press)
35. Cutler AF, M Elnagger, E Brooks, K O'Mara: Effect of standard and high dose ranitidine on [13C]urea breath test results. *Am J Gastroenterol* 93, 1297-99 (1998)
36. Savarino V, D Tracci, P Dulbecco, MR Mele, P Zentilin, C Mansi, S Vigneri: Negative Effect of Ranitidine on the Results of Urea Breath Test for the diagnosis of *Helicobacter pylori*. *Am J Gastroenterol* 96, 348-52 (2001)
37. Vaira D, P Malfertheiner, F Megraud, ATR Axon, M Deltenre, G Gasbarrini, C O'Morain, JM Pajares Garcia, M Quina, GNJ Tytgat, The European *Helicobacter pylori* HpSA Study Group: Noninvasive antigen-based assay for assessing *Helicobacter pylori* eradication: A European multicenter study. *Am J Gastroenterol* 95, 925-929 (2000)
38. Laine L, D Lewin, W Naritoku, R Estrada, H Cohen: Prospective comparison of commercially available rapid urease tests for the diagnosis of *Helicobacter pylori*. *Gastrointest Endosc* 44, 523-526 (1996)

39. Marshall BJ, JR Warren, GJ Francis, SR Langton, CS Goodwin, ED Blincow: Rapid urease test in the management of Campylobacter pyloidis-associated gastritis. *Am J Gastroenterol* 82, 200-4 (1987)
40. Lee JM, NP Breslin, C Fallon, CA O'Morain: Rapid urease test lack sensitivity in *Helicobacter pylori* diagnosis when peptic ulcer disease presents with bleeding. *Am J Gastroenterol* 95, 1166-70 (2000)
41. Cutler AF, S Havstad, CK Ma, MJ Blaser, GI Perez-Perez, TT Schubert: Accuracy of invasive and noninvasive tests to diagnose *Helicobacter pylori* infection. *Gastroenterol* 109, 136-41 (1995)
42. Marshall BJ: Helicobacter pylori. *Am J Gastroenterol* 89, S116-28 (1994)
43. Brown KE, DA Peura: Diagnosis of *Helicobacter pylori* infection. *Gastro Clin N America* 22, 105-15 (1993)
44. Laine L, J Sugg, L Suchower, G Neil: Endoscopic biopsy requirements for post-treatment diagnosis of *Helicobacter pylori*. *Gastrointest Endosc* 51, 664-669 (2000)
45. Chey WD, M Fendrick: Non-invasive *H. pylori* testing for the test and treat strategy: a decision analysis to assess the impact of past infection on test choice. *Arch Intern Med* (in press)
46.Whitney CG, MM Farley, J Hadler, LH Harrison, C Lexau, A Reingold, L Lefkowitz, PR Cieslak, M Cetron, ER Zell, JH Jorgensen, A Schuchat: Increasing prevalence of multidrug resistant *Streptococcus pneumoniae* in the United States. *N Engl J Med* 343, 1917-24 (2000)
47. Donskey CJ, TK Chowdhry, MT Hecker, CK Hoyen, JA Hanrahan, AM Hujer, RA Hutton-Thomas, CC Whalen, RA Bonomo, LB Rice: Effect of antibiotic therapy on the density of vancomycin-resistant Enterococcus in the stool of colonized patients. *N Engl J Med* 343, 1925-32 (2000)
48. Leung WK, EK Ng, FK Chan, JY Sung: Evaluation of three commercial enzyme-linked immunosorbent assay kits for diagnosis of *Helicobacter pylori* in Chinese patients. *Diagn Microbiol Infect Dis* 34, 13-7 (1999)
49. Hook-Nikanne J, GI Perez-Perez, MJ Blaser: Antigenic characterization of *Helicobacter pylori* strains from different parts of the world. *Clin Diagn Lab Immunol* 4, 592-7 (1997)
50. Walsh JH, WL Peterson: The treatment of *Helicobacter pylori* infection in the management of peptic ulcer disease. *N Engl J Med* 333, 984-991 (1995)
51. Howden CW, RH Hunt: Guidelines for the management of *Helicobacter pylori* infection. *Am J Gastroenterol* 93, 2330-8 (1998)
52. Chey WD: Treatment of *H. pylori*. *Curr Treat Options Gastroenterol* 2, 171-81(1999)
53. Stanghellini V, C Tosetti, R De Giorgio, G Barbara, B Salvioli, R Corinaldesi: How should *Helicobacter pylori* negative patients be managed? *Gut* 45(Suppl 1), I32-35 (1999)
54. Fendrick AM, WD Chey, N Magaret, J Palaniappan, MB Fennerty: Symptom status and the desire for *Helicobacter pylori* confirmatory testing after eradication therapy in patients with peptic ulcer disease. *Am J Med* 107, 133-136 (1999)
55. Cutler AF, VH Prasad: Long term follow-up of *Helicobacter pylori* serology after successful eradication. *Am J Gastroenterol* 31, 85-8 (1996)
56. Chey WD, DC Metz, S Shaw, D Kearney, J Montague, U Murthy: Appropriate timing of the ^{14}C-urea breath test to establish eradication of *H. pylori* infection. *Am J Gastroenterol* 95, 1171-4 (2000)
57. Forne N, J Dominquez, F Fernandez-Banares, J Lite, M Esteve, N Gali, JC Espinos, S Quintana, JM Vivir: Accuracy of an enzyme immunoassay for the detection of *Helicobacter pylori* in stool specimens in the diagnosis of infection and posttreatment check-up. *Am J Gastroenterol* 95, 2200-5 (2000)

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Send correspondence to: William D. Chey, MD, 3912 Taubman Center, Ann Arbor, MI 48109-0362, Tel: 734-936-4775, Fax: 734-936-7392, E-mail: wchey@umich.edu