

Clinical Roundtable Monograph

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Contemporary Diagnostic Strategies for the Detection of *Helicobacter pylori* Infection

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Abstract

Helicobacter pylori infection is highly prevalent, affecting approximately half of the world's population. While the majority of infected individuals are asymptomatic, *H. pylori* infection is associated with certain diseases, including peptic ulcers (either duodenal or gastric), gastritis, and 2 malignancies—gastric cancer and gastric mucosa-associated lymphoid tissue lymphoma. Many of the epidemiologic associations between these diseases and *H. pylori* infection have been further validated by treatment studies, which show that effective eradication therapy correlates with a decreased risk of disease. A variety of testing strategies are used to detect *H. pylori* infection. Serologic techniques are widely available and inexpensive, but they are no longer preferred as they have low sensitivities and specificities, and they may show a positive result for a long period following effective therapy. The remaining testing methods are divided into 2 categories: invasive tests (which require endoscopy) and noninvasive tests. Noninvasive test methods such as the urea breath test and stool antigen test have gained popularity due to their high sensitivities and specificities. Further, both of these methods may be used to confirm the absence of infection following eradication therapy. Due to the increasing incidence of treatment failure (caused in part by antibiotic resistance), post-treatment testing is recommended to confirm *H. pylori* eradication.

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Helicobacter pylori: History, Prevalence, and Association with Disease

Adam B. Elfant, MD, FACC

H*elicobacter pylori* was first identified in 1982 by Robin Warren and Barry Marshall in Perth, Western Australia. These physicians observed a small, curved bacteria colonizing the antrum of patients with gastric inflammation; they reported the successful isolation of this unidentified bacilli in a Letter to the Editor published in a 1983 edition of *The Lancet*.¹ They further noted the strong association between the presence of this bacteria and the presence of gastritis or duodenal ulcer. Shortly thereafter, in 1983, Marshall inoculated himself with an isolate of this bacteria taken from a 66-year-old male with known dyspepsia.² Subsequent to his self-inoculation, Marshall developed a mild gastrointestinal illness in the following weeks; a biopsy confirmed the presence of gastritis.

At the turn of the next decade, in 1990, researchers in the Netherlands made a key discovery. They reported the cure of duodenal ulcers with eradication of *H. pylori* infection.³ A total of 50 patients were included in this study, all of whom had intractable duodenal ulcers. Patients were randomly assigned to 4 weeks of treatment with colloidal bismuth subcitrate, given alone or in combination with amoxicillin and metronidazole. Five patients in the triple therapy group withdrew from the study due to side effects. Among the remaining 45 patients, 17 experienced eradication of *H. pylori* infection with no ulcer relapse during 12 months of follow-up. Among 21 patients who remained positive for *H. pylori*, the 12-month ulcer relapse rate was 89%. Nine of these patients were subsequently treated with the triple therapy regimen, 7 of whom demonstrated *H. pylori* eradication and no ulcer relapse in the 12-month follow-up period. The study results caused the authors to conclude that *H. pylori* eradication would become a key component in the treatment and cure of duodenal ulcers.

This conclusion was supported in 1994, when the National Institutes of Health convened an expert consensus panel to develop recommendations for the treatment of patients with *H. pylori* infection.⁴ A key component of the panel's recommendations was the suggestion that ulcer patients with *H. pylori* infection be treated with antimicrobial agents in addition to antisecretory drugs. Further, the panel concluded that there appeared to be an "interesting relationship" between *H. pylori* infection and gastric cancers, an association that would require further research.

The key contributions made by Warren and Marshall were recognized in 2005, when the 2 researchers were awarded the Nobel Prize in Physiology or Medicine "for their discovery of *H. pylori* and its role in gastritis and peptic ulcer disease."⁵ This award noted that, thanks to their discovery, peptic ulcer disease was no longer a chronic and frequently disabling condition, but instead could often be cured with treatment. Ongoing research continues to evaluate the importance of *H. pylori* infection as a contributing factor in various conditions. In addition to peptic ulcer disease, *H. pylori* is also associated with gastric cancer and gastric mucosa-associated lymphoid tissue (MALT) lymphoma, both of which are discussed in further detail below.⁶

Prevalence of *Helicobacter pylori* Infection

At least half of the world's population is estimated to be infected with *H. pylori*.⁷ However, the prevalence of this infection varies widely across both geographic regions and ethnic groups. Overall, rates of *H. pylori* infection are markedly higher in developing countries compared to developed countries. For example, prevalence rates that approach or even exceed 90% have been reported in multiple studies conducted in Bangladesh, Egypt, Russia, Siberia, and Africa. In contrast, prevalence rates are much lower in developed regions, including the United States (6.8–79%), Europe (7.3–70%), and Australia (15.5–23%). These patterns may reflect the known association between low socioeconomic status and increased risk of *H. pylori* infection.

Substantial disparities in the prevalence of *H. pylori* infection occur across racial and ethnic groups. This disparity was demonstrated in an analysis of *H. pylori* seroprevalence rates among adults (aged 20 years or older) enrolled in the National Health and Nutrition Examination Survey (1999–2000).⁸ In an analysis of 4,145 participants, the age-standardized proportion of seropositivity for *H. pylori* was 30.7% (95% confidence interval [CI], 27.9–33.6). When the population was stratified by racial and ethnic groups, a higher seropositivity rate was observed among non-Hispanic blacks and Mexican Americans compared to non-Hispanic whites (Figure 1). Further, a multivariate analysis demonstrated that non-Hispanic blacks and Mexican Americans had

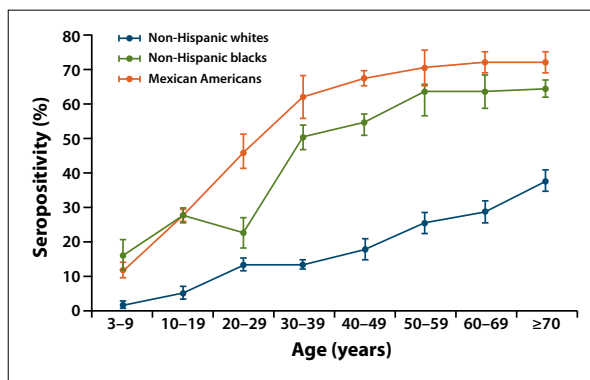


Figure 1. Race and ethnic disparities in *Helicobacter pylori* seropositivity in the United States.

Grad YH, et al. *Am J Epidemiol.* 2011;175:54-59.

a significantly higher odds ratio (OR) for *H. pylori* infection even after adjusting for factors such as age, socioeconomic status, and country of origin. The OR for *H. pylori* infection was 3.12 among non-Hispanic blacks (95% CI, 2.46–3.94) and 3.05 among Mexican Americans (95% CI, 2.10–4.44; both comparisons versus non-Hispanic whites). The factors driving the higher prevalence of seropositivity among non-Hispanic blacks and Mexican Americans remain unclear and require further exploration.

Studies have also consistently found the prevalence of *H. pylori* infection to be higher in adults than in children. This observation is likely due to 2 factors: First, infection with *H. pylori* typically occurs early in life and, second, becomes chronic if the bacteria are not eradicated, allowing infection to persist into adulthood. This trend may also reflect a birth cohort effect, with poor living conditions and sanitation in prior decades resulting in a higher prevalence of *H. pylori* infection in the past.

Risk Factors for Infection

The primary mode of *H. pylori* transmission is person-to-person passage, occurring via gastric-oral, oral-oral, or fecal-oral routes. Thus, risk factors associated with person-to-person transmission of infection have been linked to *H. pylori*; these factors include infected family members, increased number of siblings, crowded living conditions, and poor sanitation and hygiene.^{9,10} For example, when the concordance of *H. pylori* infection was compared among 241 sibling and nonsibling children (aged 2–18 years), the odds of infection increased from 1.2 (95% CI, 0.52–2.9) among children residing with at least 1 infected nonsibling to 3.2 (95% CI, 1.14–9.1) among children residing with at least 1 infected sibling and to 9.4 (95% CI, 3.1–28.5) among children residing with at least 1 infected sibling and 1 infected nonsibling.¹¹

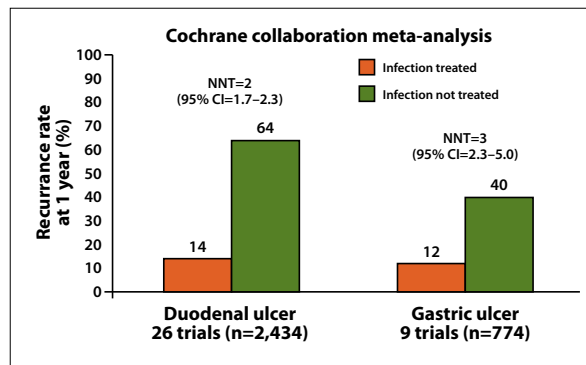


Figure 2. Decreased ulcer recurrence after treatment of *Helicobacter pylori* infection.

Ford AC, et al. *Am J Gastroenterol.* 2004;99:1833-1855.

CI=confidence interval; NNT=number needed to treat.

Association Between *Helicobacter pylori* Infection and Disease

Although the vast majority of infected individuals are asymptomatic, *H. pylori* infection is a cofactor in the development of several diseases. Peptic ulcers (either duodenal or gastric) occur in 10–15% of individuals infected with *H. pylori*.¹² Ford and colleagues conducted a systemic review of eradication therapy for the treatment of *H. pylori*-positive peptic ulcer disease; a total of 52 trials were included in the final meta-analysis.¹³ For healing duodenal ulcers, eradication therapy proved to be superior to treatment with either an ulcer-healing drug only or no treatment; the relative risks for the persistence of the ulcer were 0.66 (95% CI, 0.58–0.76) and 0.37 (95% CI, 0.26–0.53), respectively. For gastric ulcers, in contrast, the relative risk of the ulcer persisting was not significantly superior for eradication therapy versus treatment with an ulcer-healing drug only (relative risk, 1.32; 95% CI, 0.92–1.90).

The study by Ford and colleagues also showed that eradication therapy was associated with markedly lower recurrence rates for both duodenal ulcers (14% with treatment vs 64% with no treatment) and gastric ulcers (12% with treatment vs 40% with no treatment; Figure 2). Additionally, the number needed to treat (NNT) was calculated as the reciprocal of the risk difference from the meta-analysis; the NNT to prevent 1 duodenal ulcer recurrence within 1 year was 2 (95% CI, 1.7–2.3), and the NNT to prevent 1 gastric ulcer recurrence was 3 (95% CI, 2.3–5.0). However, even with treatment of *H. pylori* infection, an appreciable recurrence rate remained; these recurrences were likely due to failed *H. pylori* eradication as well as other ulcerogenic factors, such as use of aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs).

Mounting epidemiologic evidence suggests that *H. pylori* infection has an important role in the etiology

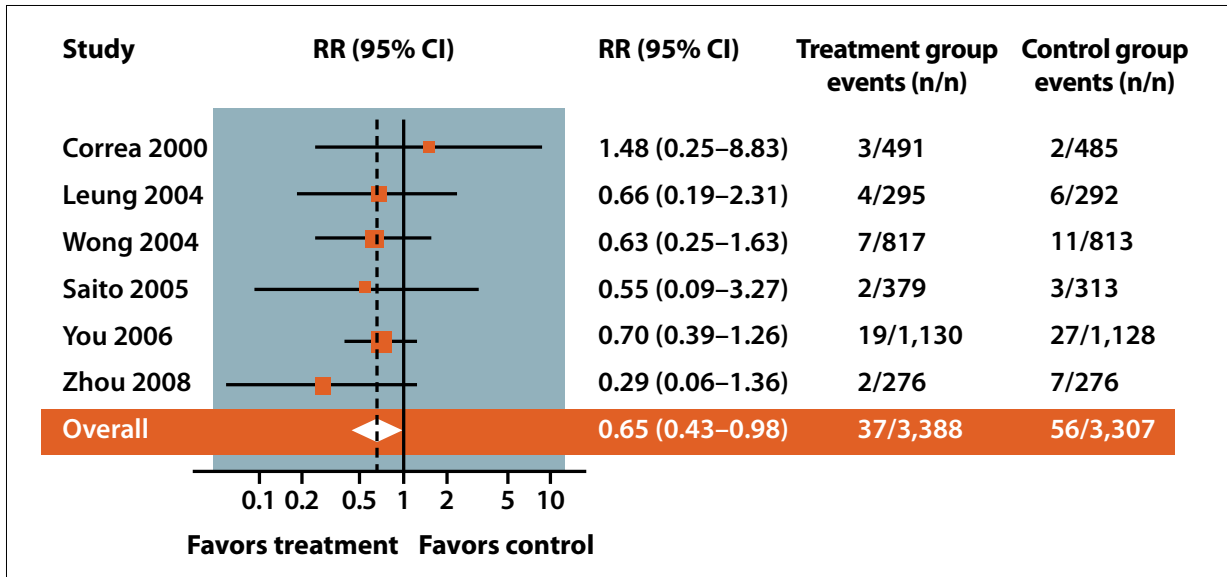


Figure 3. Effect of *Helicobacter pylori* eradication on risk of gastric cancer.

Fuccio L, et al. *Ann Intern Med.* 2009;151:121-128.

CI=confidence interval; RR=relative risk.

of 2 malignancies: gastric adenocarcinoma and gastric MALT lymphoma. *H. pylori* infection may initiate the critical sequence of phenotypic changes in gastric mucosa that lead to cancer, which begins with inflammation and then proceeds to superficial gastritis, chronic atrophic gastritis, intestinal metaplasia, dysplasia, and, finally, carcinoma. Given its role in the pathogenesis of these malignancies, *H. pylori* infection is recognized by the World Health Organization as a Group 1 carcinogen.¹⁴ Overall, *H. pylori* infection is associated with a 2-fold to 3-fold increased risk for the development of gastric adenocarcinoma, although the lifetime risk of developing the disease still remains relatively low (<1%).^{12,15} The risk of developing gastric MALT lymphoma, a rarer malignancy, is even lower.^{6,16}

Wong and colleagues conducted a prospective, randomized, placebo-controlled, population-based trial to determine whether treatment of *H. pylori* infection could reduce the incidence of gastric cancer.¹⁷ A total of 1,630 healthy, *H. pylori*-positive, Chinese patients were included in this study and were followed for a mean of 7.5 years. Patients were randomized to receive *H. pylori* eradication therapy (combination therapy with omeprazole, amoxicillin, clavulanate potassium, and metronidazole) or placebo. Eighteen new cases of gastric cancer developed during the follow-up period, but the incidence of gastric cancer did not differ significantly between patients who received eradication therapy and those who did not (7 vs 11 cases, respectively; *P*=.33). However, a subgroup analysis of the patients who had no precancerous lesions at the time of study enrollment (*N*=988) demonstrated that no cases of gastric cancer developed

among patients who were treated with eradication therapy, compared to 6 cases of cancer occurring among patients in this subgroup who were treated with placebo (*P*=.02).

More recently, Fuccio and coauthors conducted a meta-analysis of randomized trials in which they aimed to determine the ability of *H. pylori* eradication therapy to reduce the risk of gastric cancer (Figure 3).¹⁸ This meta-analysis included 6 studies, all of which were conducted in areas that had a relatively high incidence of gastric cancer. In total, 3,388 patients received eradication therapy, while 3,307 untreated patients served as a control group. The authors reported that 1.1% of patients treated with eradication therapy developed gastric cancer, compared to 1.7% of untreated patients. This difference translated to a relative risk of 0.65 (95% CI, 0.43–0.98) for gastric cancer developing after eradication therapy.

Development of Gastritis

Based on histologic evidence, all patients with *H. pylori* infection develop gastritis. Other gastrointestinal conditions may also be related to *H. pylori* infection, although these associations are more controversial; for example, *H. pylori* infection and associated inflammation have been reported in biopsy specimens of gastric mucosa from patients with nonulcerative dyspepsia. However, this finding is mitigated by the fact that signs of *H. pylori* infection are commonly observed in asymptomatic patients.

Once *H. pylori* infection occurs, several factors are important in determining the outcome of the infection— notably, the level of acid secretion and the distribution of

the gastritis. An antral-predominant distribution is associated with a high level of gastric acid secretion, which leads to an increased risk for the development of duodenal ulcers. In contrast, corpus-predominant gastritis (or pangastritis) is associated with a lower level of gastric acid secretion and increased risk for both gastric ulcers and gastric cancer.

Importantly, the level of acid secretion and the gastritis distribution are themselves affected by multiple factors acting at various levels: the host level (such as changes in immune response and gene polymorphisms), the bacteria level (such as virulence factors), and the environmental level (including smoking, alcohol use, NSAID use, and proton pump inhibitor [PPI] use). At the host level, an emerging determinant of gastric distribution and acid secretion is the proinflammatory cytokine interleukin (IL)-1 β .¹⁹ Polymorphisms in the IL-1 β gene have been shown to be linked to the risk of developing *H. pylori*-induced gastric cancer. At the environmental level, an important determinant may be the use of PPIs, which are pharmacologic inhibitors of acid secretion. Among *H. pylori*-infected patients, PPIs have been shown to result in redistribution of gastritis from an antral-predominant location to a corpus-predominant location.²⁰

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Testing for *Helicobacter pylori* Infection

Neil Stollman, MD, FACP, FACC, AGAF

According to guidelines from the American College of Gastroenterology (ACG), established indications for *H. pylori* testing include: peptic ulcer disease (either duodenal or gastric ulcer, regardless of whether the patient has active disease or a documented history of previously untreated disease), a diagnosis of low-grade gastric MALT lymphoma, and following endoscopic resection of early gastric cancer.¹ Importantly, these guidelines note that testing should only be performed in patients who will subsequently be offered *H. pylori* eradication therapy.

Other guidelines from the ACG list possible or probable indications for *H. pylori* testing. For example, while there is no established evidence that eradication of *H. pylori* infection will cure nonulcer dyspepsia, testing may be performed in such patients on a case-by-case basis, and treatment may be offered to patients with a positive test result.² Similarly, testing and treating for *H. pylori* infection may be beneficial for preventing NSAID-related ulcer complications, especially in patients planning to undergo long-term NSAID therapy.³

The American Gastroenterological Association (AGA) has also published official recommendations on the evaluation of dyspepsia, which include an algorithm for determining which patients should undergo *H. pylori* testing (Figure 1).⁴ According to this algorithm, patients who present with dyspepsia in the absence of gastroesophageal reflux disease or NSAID use are first divided into 2 groups: those who require immediate endoscopy and those who are suitable candidates for noninvasive testing. Patients who are over the age of 55 years or who exhibit certain alarm features should undergo immediate investigation with endoscopy in order to rule out peptic ulcer diseases or upper gastrointestinal tract malignancy. Alarm features include gastrointestinal bleeding, unexplained iron-deficiency anemia, unintended weight loss, family history of upper gastrointestinal cancer, dysphagia, and odynophagia. In contrast, dyspeptic patients who are 55 years or younger and who have no alarm features should undergo *H. pylori* testing using a validated, noninvasive test. *H. pylori*-positive patients should then undergo eradication therapy and a trial of PPI therapy, if symptoms persist. In all cases, endoscopy may be considered if patients do not respond to therapy.

Current Strategies for *Helicobacter pylori* Testing

A variety of testing strategies are available to assess for *H. pylori* infection (Tables 1 and 2).¹ Of these strategies, serologic tests are capable of determining whether the patient has a history of previous exposure to *H. pylori*, as

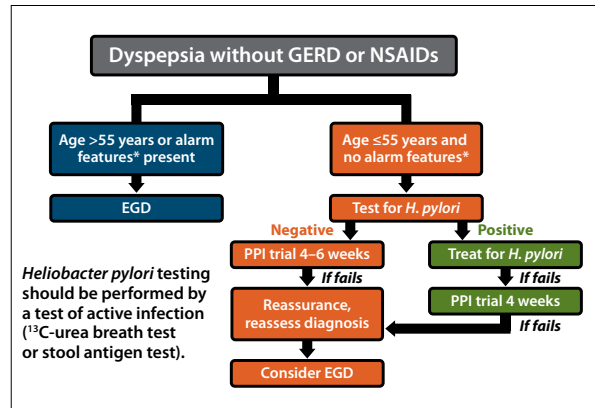


Figure 1. American Gastroenterological Association algorithm for the management of dyspepsia.

Talley NJ, et al. *Gastroenterology*. 2005;129:1753-1755.

EGD=esophagogastroduodenoscopy; GERD=gastroesophageal reflux disease; NSAID=nonsteroidal anti-inflammatory drug; PPI=proton pump inhibitor.

*Alarm features include gastrointestinal bleeding, unexplained iron-deficiency anemia, unintended weight loss, family history of upper gastrointestinal cancer, dysphagia, and odynophagia.

	Active infection	History of exposure
Endoscopic	<ul style="list-style-type: none"> • Biopsy urease test • Histology • Culture 	—
Nonendoscopic	<ul style="list-style-type: none"> • Urea breath test <ul style="list-style-type: none"> – ¹³C – nonradioactive – ¹⁴C – radioactive • Stool antigen test 	Serology*

Table 1. Methods of testing for *Helicobacter pylori* infection.

*American College of Gastroenterology practice guidelines: In populations with a low pretest probability of *H. pylori* infection, nonendoscopic tests such as the urea breath test and stool antigen test offer superior positive predictive values compared to antibody tests. Chey WD, et al. *Am J Gastroenterol*. 2007;102:1808-1825.

these tests measure the formation of anti-*H. pylori* antibodies. They are widely available and are the least expensive of the testing strategies currently in use. However, because positive results may reflect a previous, rather than current infection, use of these tests is not recommended in low-prevalence populations due to their low positive predictive value, nor when clinicians are seeking to confirm the success of *H. pylori* eradication therapy.

The nonserologic tests can be divided into 2 categories: invasive (or endoscopic) versus noninvasive (nonendoscopic).⁵ Endoscopic detection methods include biopsies, histology, or culture. Nonendoscopic methods for detecting *H. pylori*—which are more commonly used for routine testing—include the urea breath test (UBT) or a

Test	Advantages	Disadvantages
Serology	<ul style="list-style-type: none"> • Widely available • Least expensive of available tests 	<ul style="list-style-type: none"> • Positive results may reflect previous rather than current infection • Not recommended for confirming eradication
Urea breath test	<ul style="list-style-type: none"> • High negative and positive predictive values • Useful before and after treatment 	<ul style="list-style-type: none"> • False negative results are possible in the presence of PPIs or with recent use of antibiotics or bismuth preparations • Specialized equipment is required to perform the test
Stool antigen test	<ul style="list-style-type: none"> • High negative and positive predictive values with monoclonal antibody test • Useful before and after treatment 	<ul style="list-style-type: none"> • Process of stool collection may be distasteful to patients • False negative results are possible in the presence of PPIs or with recent use of antibiotics or bismuth preparations

Table 2. Nonendoscopic tests for *Helicobacter pylori*.

Adapted from McColl KE. *N Engl J Med.* 2010;362:1597-1604.

PPI=proton pump inhibitor.

	Urea breath test (BreathTek UBT for <i>H. pylori</i>)*†		Stool antigen test (HpSA)*	Endoscopic biopsy‡ (routine histology)	Serology (ELISA)*
	Initial diagnosis	Post-eradication			
Sensitivity	95%	95.5%	93%	93%	85%
Specificity	90%	96%	93%	90%	79%

Table 3. Sensitivity and specificity of tests for *Helicobacter pylori*.

ELISA=enzyme-linked immunosorbent assay.

*Vaira D, et al. *Gut.* 2001;48:287-289; †BreathTek UBT [package insert]; Rockville, Md; Medical Device Division of Otsuka America Pharmaceutical, Inc.; 2012;

‡Maconi G, et al. *Aliment Pharmacol Ther.* 1999;13:327-331.

stool antigen test. For the UBT assay, the patient drinks a solution containing ^{13}C -labeled or ^{14}C -labeled urea, which is converted to labeled carbon dioxide by the urease in *H. pylori*. The labeled gas is then measured in a breath sample. The other noninvasive test, the stool antigen detection method, uses polyclonal or monoclonal antibodies to identify *H. pylori*-specific antigens in a stool sample.

Both UBT and stool antigen detection assays are associated with high negative and positive predictive values, and both are useful either prior to or following eradication therapy. Also, the ACG practice guidelines note that the UBT and stool antigen detection tests both offer superior positive predictive values compared to serologic testing when used in patients with a low pretest probability of *H. pylori* infection.¹ This group includes individuals from high socioeconomic status areas and/or regions with a low background prevalence of ulcer or *H. pylori* infection.

The disadvantage of the UBT method is that it requires specialized equipment to perform the test; the disadvantage of stool antigen detection methods is their requirement that patients provide stool samples, which can be pragmatically challenging for some patients. Another disadvantage of both UBT and stool antigen detection assays is that recent treatment with a PPI, an antibiotic, or a bismuth preparation may lead to a false-negative result.

Despite their various advantages and disadvantages, all of these testing strategies have relatively high rates of sensitivity and specificity (Table 3).⁶⁻⁸ For example, the BreathTek® UBT for *H. pylori* Kit (Otsuka America Pharmaceutical, Inc.) is associated with sensitivity and specificity rates of 95% and 90%, respectively, for initial diagnosis with the BreathTek UBT Kit. Similarly, the HpSA stool antigen assay has

a 93% sensitivity rate and a 93% specificity rate. Similarly, endoscopic biopsy followed by routine histology has a 93% sensitivity rate and a 90% specificity rate. Because of a higher propensity for false positives with serologic techniques, this method is associated with slightly lower sensitivity and specificity rates: 85% and 79%, respectively.

BreathTek® UBT for *H. pylori* Testing

The BreathTek UBT Kit is intended to be used for the qualitative detection of urease activity associated with *H. pylori* infection present in the human stomach and is indicated as an aid in the initial diagnosis and post-treatment monitoring of *H. pylori* infection in adult patients. It is for administration by a healthcare professional, as prescribed by a physician.⁸ This test is based on the fact that all *H. pylori* strains produce the enzyme urease, which cleaves urea into ammonium ions and carbon dioxide. Normally, the human stomach is devoid of urease, so any detectable urease activity in the human stomach is likely due to the presence of *H. pylori*. The BreathTek UBT is indicated for use in adult patients both to aid in the initial diagnosis of *H. pylori* infection and for post-treatment monitoring.

The diagnostic pharmacologic agent in the BreathTek UBT Kit is ^{13}C -urea. This agent is a synthetic urea that becomes orally available after reconstitution with water. The ^{13}C component of this compound is a stable, naturally occurring, nonradioactive carbon isotope. Taken orally, the ^{13}C -urea is degraded by the bacterial urease, if present. The resulting, isotopically-labeled carbon dioxide product will then equilibrate with body fluids

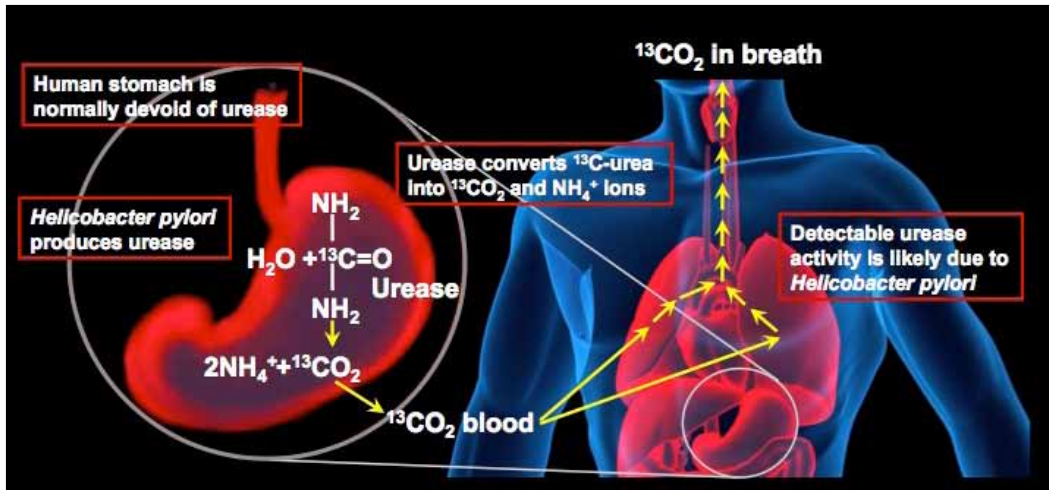


Figure 2. Principles of the urea breath test.

CO₂=carbon dioxide; H₂O=water; NH₂=amine group; NH₄⁺=ammonium ion.

and will ultimately be expired from the lungs (Figure 2). In the absence of *H. pylori*, the ¹³C-urea is not converted into labeled carbon dioxide, and the ratio of ¹³C-labeled carbon dioxide in the post-dose breath sample remains similar to the level detected in the baseline sample.

In clinical practice, the testing process begins with the patient providing a baseline breath sample. The patient then ingests a solution containing the ¹³C-urea agent, and 15 minutes later the patient provides a post-test breath sample. Both the baseline and post-test samples can be analyzed immediately, or they can be stored and tested at any time within 7 days. Once the samples are ready for testing, the BreathTek UBT assay uses an infrared spectrophotometer to measure the ratio of ¹³C-labeled carbon dioxide to ¹²C-labeled carbon dioxide in both the pretest and post-test breath samples.

Before undergoing the BreathTek UBT, patients must fast for at least 1 hour. Additionally, patients must wait at least 4 weeks after the end of *H. pylori* eradication therapy before undergoing post-treatment testing. False-negative results may occur in patients who recently received PPI acid suppression therapy and/or bismuth compounds or antibiotics; therefore, patient should not have received any of these agents within the 2 weeks prior to use of the BreathTek UBT. Another potential cause of false-negative test results is a premature post-dose breath collection. In contrast, false-positive results may be caused by the presence of urease produced by other gastric spiral organisms, such as *H. heilmannii*. Conditions such as achlorhydria may also lead to a false-positive test result.

Several precautions should be followed when administering this test. Patients with phenylketonuria should be cautioned that the test solution contains phenylalanine in an amount approximately equivalent to a typical 12-ounce diet cola soft drink. Additionally, because the drug solution contains Aspartame, it should be used with caution in diabetic patients. Patients who are hypersensitive to mannitol, citric

acid, or Aspartame should also avoid the drug solution. Use with caution in patients with difficulty swallowing or who may be at a high risk of aspiration due to medical or physical conditions. No information is available on the use of the ¹³C drug agent during pregnancy. Finally, several adverse events have been identified in postapproval use of the BreathTek UBT. These voluntarily reported reactions included anaphylactic reaction, hypersensitivity, rash, a burning sensation in the stomach, tingling in the skin, vomiting, and diarrhea.

Acknowledgement

Neil Stollman, MD, FACP, FACG, AGAF, was paid by Otsuka America Pharmaceutical, Inc. for participation in this roundtable and development of this monograph, and he is a promotional speaker for BreathTek® UBT for *Helicobacter pylori* (*H. pylori*) Kit. He has also received speaking honoraria from Aptalis Pharmaceuticals, Optimer Pharmaceuticals, and Warner Chilcott, and he receives research support from Warner Chilcott.

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Treatment and Post-Treatment Testing for *Helicobacter pylori* Infection

Colin W. Howden, MD

A variety of drug regimens are used in the treatment of *H. pylori* infection.¹ The most widely used is a triple combination of a PPI, clarithromycin, and amoxicillin, each of which is dosed twice daily for 10 or 14 days. For patients who are allergic to amoxicillin, metronidazole can be substituted. Especially in areas with a high prevalence of clarithromycin resistance, a quadruple drug regimen may also be used for *H. pylori* eradication; this option includes a PPI plus tetracycline, metronidazole, and a bismuth salt.

The success rates for *H. pylori* eradication are relatively similar with triple and quadruple therapy; per-protocol analyses show eradication rates of 85% and 87%, respectively, and intent-to-treat analyses show eradication rates of 79% and 80%, respectively (Table 1).² To further compare triple versus quadruple drug regimens, Fischbach and colleagues conducted a meta-analysis of 93 studies (N=10,178).³ This study found a higher rate of eradication with quadruple therapy among populations with higher rates of resistance to either clarithromycin or metronidazole. Quadruple therapy regimens were consistently found to eradicate over 80% of *H. pylori* infections.

A more recent meta-analysis of 9 studies (N=1,679), which was conducted by Luther and colleagues, demonstrated that per-protocol eradication rates were similar for triple and quadruple therapy; the intent-to-treat eradication rates were also similar for the 2 regimens (77.0% vs 78.3%, respectively; risk ratio, 1.00; 95% CI, 0.94–1.07).⁴ This same meta-analysis reported no statistically significant differences between triple and quadruple drug regimens in terms of either patient compliance or side effects.

Benefits of *Helicobacter pylori* Eradication

Several randomized, controlled studies have demonstrated that *H. pylori* eradication therapy is superior to short-term treatment with placebo or an acid-suppressing drug for the treatment of dyspepsia among patients in the primary care setting. A meta-analysis of 3 such studies (N=1,106) reported a relative risk of 0.82 (95% CI, 0.73–0.91) and an NNT of 9 (95% CI, 6–20; Figure 1).⁵ In another study, Chiba and colleagues used a test-and-treat strategy to assess improvements in symptoms among primary care patients with uninvestigated dyspepsia.⁶ A total of 294 *H. pylori*-positive patients with moderately severe dyspep-

	Per-protocol eradication rate	Intent-to-treat eradication rate
PPI + clarithromycin + amoxicillin/metronidazole	85%	79%
PPI + bismuth + tetracycline + metronidazole	87%	80%

Table 1. Success rates of standard treatments for *Helicobacter pylori* infection.

Saad RJ, et al. *Nat Clin Pract Gastroenterol Hepatol.* 2006;3:20-21.

PPI=proton pump inhibitor.

sia were randomized to either omeprazole, metronidazole, and clarithromycin or to omeprazole and placebo. Compared to the omeprazole-placebo combination, eradication therapy resulted in a significantly higher rate of treatment success (36% vs 50%, $P=.02$), defined as no or minimal dyspepsia at the end of 1 year. Eradication therapy successfully cured *H. pylori* infection in 80% of evaluable patients.

In another study, Stevens and colleagues evaluated *H. pylori* eradication therapy among primary care patients presenting with ulcer-like symptoms; this study excluded patients with a confirmed ulcer.⁷ Of the 543 patients enrolled in this study, 364 were found to be positive for *H. pylori* infection. These patients were then randomized to receive either lansoprazole, clarithromycin, and amoxicillin or lansoprazole and placebo. The 179 patients who were negative for *H. pylori* infection underwent open-label treatment with lansoprazole. Over the 1-year follow-up period, patients who received *H. pylori* eradication therapy demonstrated significantly lower average numbers of gastrointestinal consultations ($P<.02$) and prescriptions ($P=.05$) compared to patients who received lansoprazole and placebo. Further, the relapse rate was significantly lower among patients who received eradication therapy compared to patients who received lansoprazole and placebo (37.0% vs 51.4%; $P=.02$).

Finally, a meta-analysis by Vergara and colleagues sought to determine whether *H. pylori* eradication therapy was associated with the prevention of peptic ulcers among NSAID users (Figure 2).⁸ Five studies with a total of 939 patients were included in this meta-analysis. All of these studies compared eradication therapy with either no therapy or PPI therapy. Nearly twice as many patients

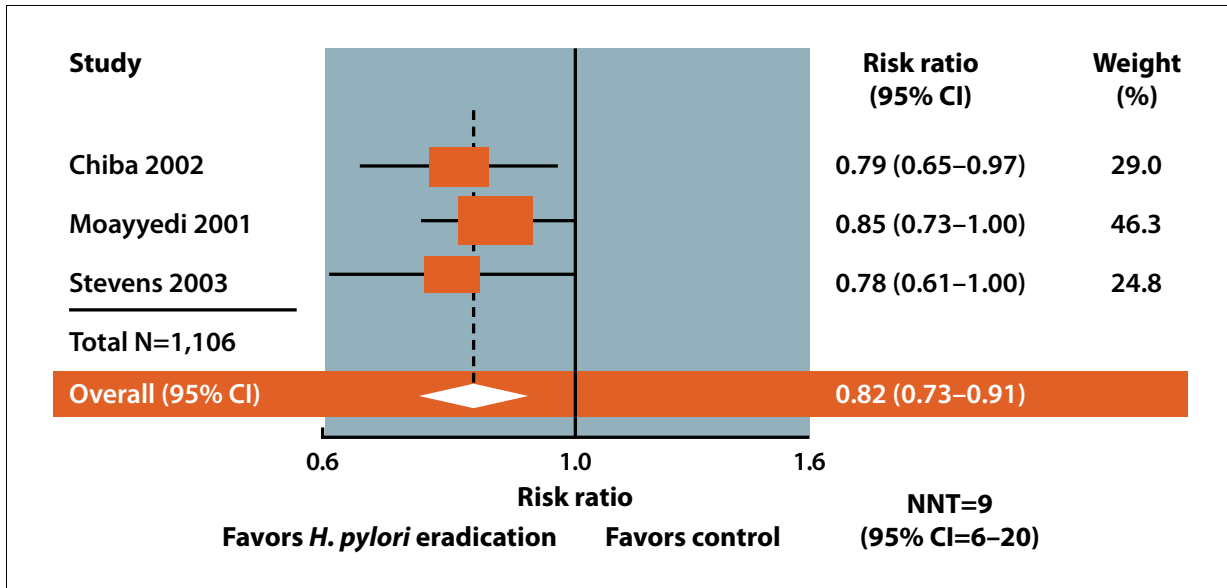


Figure 1. *Helicobacter pylori* eradication is superior to short-term acid suppression in patients with dyspepsia.

Talley NJ, et al. *Gastroenterology*. 2005;129:1756-1780.
 CI=confidence interval; NNT=number needed to treat.

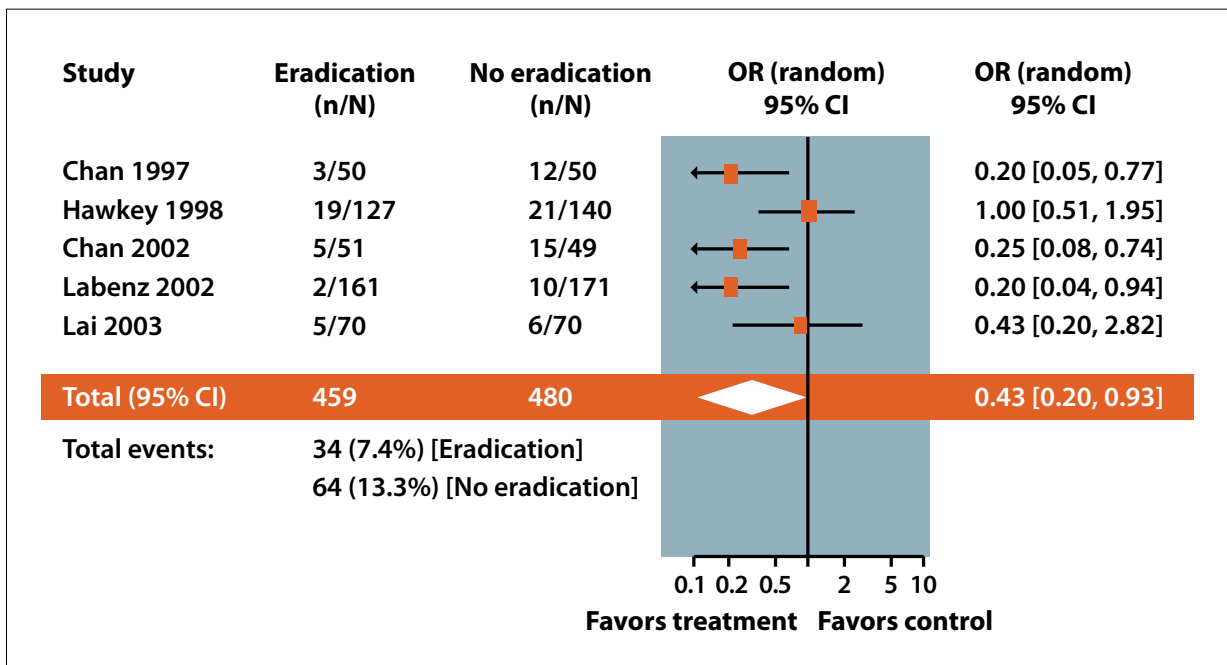


Figure 2. *Helicobacter pylori* eradication reduces the risk of ulcers in NSAID users.

Vergara M, et al. *Aliment Pharm Ther*. 2005;21:1411-1418.
 CI=confidence interval; NSAID=nonsteroidal anti-inflammatory drug; OR=odds ratio.

in the control group developed a peptic ulcer compared to patients in the eradication therapy group (13.3% vs 7.4%; OR, 0.43; 95% CI, 0.20–0.93). Interestingly, a subanalysis of the data demonstrated a significant reduction in the risk of developing a peptic ulcer among

NSAID-naïve patients (OR, 0.26; 95% CI, 0.14–0.49) but not among patients who had been previously treated with NSAIDs (OR, 0.95; 95% CI, 0.53–1.72).

Based on these and other data, ACG practice guidelines recognized a potential advantage for *H. pylori* testing

Study	Regimen										Duration of therapy (days)	Intent-to-treat eradication rate	95% CI	
	A	C	T	B	M	E	O	L	P	R				
Laine 1998												10	75%*	(70–81)
Fennerty 1998												10	81%	(74–88)
												14	82%	(74–88)
Laine 2000												10	78%*	(70–85)
Laine 2003												10	88%	(82–93)
												10	83%	(77–90)
Bochenek 2003												7	65%*	(57–73)
												7	77%*	(69–84)
Vakil 2004												7	77%	(71–83)
												10	78%	(72–84)
												10	73%	(67–79)

Table 2. Traditional therapies for *Helicobacter pylori* fail in up to 30% of patients.

Vakil N, et al. *Gastroenterology*. 2007;133:985-1001.

A=amoxicillin; B=bismuth; C=clarithromycin; CI=confidence interval; E=esomeprazole; L=lansoprazole; M=metronidazole; O=omeprazole; P=pantoprazole; R=rabeprazole; T=tetracycline.

Usual doses: Proton pump inhibitor twice daily, clarithromycin 500 mg twice daily, amoxicillin 1 gram twice daily. Esomeprazole was studied in a single daily dose.

* Mean of 2 studies.

among individuals who will require long-term NSAID therapy, with treatment of the infection in patients who test positive.⁹ Thus, the ACG recommendation is to consider *H. pylori* testing (and treatment, if positive) for all patients prior to initiation of long-term NSAID therapy.

Importance of Confirmatory Post-Treatment Testing

Following therapy, symptoms alone are not a reliable indicator of whether a patient's *H. pylori* infection has been eradicated. The ACG's updated practice guidelines for the management of *H. pylori* infection recommend post-treatment testing for patients with *H. pylori*-associated ulcers, patients with persistent dyspepsia, patients with *H. pylori*-associated MALT lymphoma, and patients who have undergone endoscopic resection of lesions of early gastric cancer.¹⁰ Post-treatment testing should be performed with a test of active infection a minimum of 4 weeks following the completion of therapy.

Strategies for post-treatment testing are generally similar to those used prior to eradication therapy, with the important exception that serology is definitely not appropriate in the post-treatment setting. For patients in whom endoscopic follow-up is necessary, post-treatment *H. pylori* testing can be performed endoscopically. For all

other patients, the ACG guidelines recommend use of the UBT, as this method is the most reliable nonendoscopic test for proving eradication of *H. pylori* infection. Alternatively, the stool antigen test may be used for post-treatment testing, although the ACG guidelines note that the timing and reliability of this method have not been demonstrated as clearly as they have been for the UBT.

When Initial Treatment Fails

H. pylori eradication rates in recent trials are lower than those reported in the late 1990s (Table 2). The primary causes of initial treatment failure are antimicrobial resistance and poor adherence.¹¹ Indeed, eradication rates with triple therapy have been declining as resistance rates to commonly used antimicrobials have risen. One study reported clarithromycin resistance in approximately one third of patients who failed therapy.¹²

To address concerns about antibiotic resistance in the United States, researchers and clinicians formed the *Helicobacter pylori* Antimicrobial Resistance Monitoring Program, a prospective, multicenter network that tracked national incidence rates of *H. pylori* antimicrobial resistance.¹³ Among 347 clinical isolates collected through this network between 1998 and 2002, 29.1% were found to be resistant to 1 antimicrobial agent, and

5% to 2 or more. When resistance to specific drugs was analyzed, 25.1% of isolates were found to be resistant to metronidazole, 12.9% to clarithromycin, and only 0.9% to amoxicillin; none was resistant to tetracycline. A multivariate analysis found that black race was the only significant risk factor for infection with an antibiotic-resistant strain of *H. pylori*.¹³

Antimicrobial resistance to *H. pylori* is particularly prevalent in Alaska, as shown by data from the Alaska Sentinel Surveillance Study conducted by the Centers for Disease Control and Prevention; this study involved hospitals in 5 Alaska regions.¹⁴ An analysis of isolates collected from 531 *H. pylori*-positive patients between 2000 and 2008 showed high rates of resistance to metronidazole (42%), clarithromycin (30%), and levofloxacin (19%), while resistance to amoxicillin was only 2%. Again, no isolates were resistant to tetracycline. Fifteen percent of clinical isolates were found to be resistant to both metronidazole and clarithromycin. Of note, the rates of resistance to metronidazole and clarithromycin reported in this Alaskan study were approximately 2-fold and 3-fold higher, respectively, than the rates observed in the general US population.

When initial eradication therapy for *H. pylori* infection fails, several subsequent treatment options may be considered. If a patient has already been treated with a clarithromycin-containing regimen, this drug should be avoided in subsequent therapy. Salvage regimens may include amoxicillin even if it had been previously used, due to the very low prevalence of amoxicillin resistance. Finally, although antimicrobial susceptibility testing might appear logical for the evaluation of treatment failure, such testing is not widely available in the United States.

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opment of this monograph, and he is a promotional speaker for BreathTek® UBT for *Helicobacter pylori* (*H. pylori*) Kit. He has also been a paid consultant for Perrigo and Takeda, and he has received speaking honoraria from GlaxoSmithKline International and Takeda.

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Question-and-Answer Forum

G&H A 45-year-old man is referred for epigastric pain. He had a bleeding duodenal ulcer that required hospitalization and transfusion years ago. He takes intermittent ibuprofen for headaches. There is no nausea or evidence of gastrointestinal bleeding, and a physical examination reveals only mild epigastric tenderness. What would you do next?

Colin W. Howden, MD The patient must be tested for *H. pylori* infection in accordance with practice guidelines. Assuming he is not currently taking a PPI, he could be tested at the time of referral using the UBT or a stool antigen test. If he is taking a PPI, that drug would need to be stopped for at least 14 days before testing. There is no pressing need for a repeat endoscopy at this stage. If he tests positive for *H. pylori*, the infection should be treated appropriately, and a post-treatment test of eradication should be performed at least 4 weeks after completion of therapy.

Neil Stollman, MD, FACP, FACG, AGAF I agree. The indication for testing is very clear in this case. The fact that he is taking ibuprofen is also a consideration, especially if testing shows that he is negative for *H. pylori*. He should be educated about minimizing his NSAID use regardless of his test result, but if he is positive for *H. pylori*, then eradicating this infection will drastically lower his risk of recurrent ulcers even if he continues to use NSAIDs occasionally.

Adam B. Elfant, MD, FACG There is no question that this patient requires testing for *H. pylori*. Given his history of a clinically significant gastrointestinal bleed, I would also ask him to discontinue NSAID use and consider less ulcerogenic agents instead.

G&H How did the discovery of *H. pylori* by Warren and Marshall change physicians' understanding of peptic ulcer disease?

CWH The discovery of *H. pylori*—which was initially called a “*Campylobacter*-like organism”—ultimately proved to be revolutionary. Although the association between *H. pylori* and peptic ulcer disease was initially viewed with great skepticism, *H. pylori* infection is now universally accepted as the most common (but not the only) cause of peptic ulcers.

NS Physicians used to think that ulcers were due to stress, alcohol, and tobacco use. Thus, we blamed patients for their ulcers: We thought that ulcers were caused by what the patient was doing, and we believed that if patients changed their lifestyle, then they would not get ulcers. As we later learned, ulcers had little to do with lifestyle and had everything to do with bacteria. Ultimately, this discovery led to a sea change in our conception of ulcer disease.

ABE Acid was also thought to be a prime culprit in the development of peptic ulcers. In fact, the old dogma of “no acid no ulcer” was held for many years. Now, the important etiologic role of *H. pylori* is no longer disputed, and eradication has become the mainstay of successful management of this disease.

G&H Of the various types of *H. pylori* tests available—UBT, stool antigen test, endoscopy, and serology—which do you most commonly use in your practice?

NS I use breath testing almost exclusively, in part, because it is my most convenient option; my office has an instrument for analyzing breath samples from the BreathTek UBT test, which allows me to get a result in just 20 minutes. Stool testing is accurate, but compliance can be a problem because of the substantial patient effort required to collect and transport a sample. Serology testing for *H. pylori* is nearly obsolete, in my opinion; the specificity of serology is very poor, and a positive serology result can be a marker of prior exposure rather than active infection. Finally, endoscopy is a great way to test for *H. pylori* if the patient actually needs an endoscopy. I would never do an endoscopy *just* to look for *H. pylori*, but if the patient happens to need this procedure, then endoscopy is a perfect way to look for *H. pylori*; it is accurate, inexpensive, and safe.

ABE In my practice, we only utilize tests of active infection due to their higher sensitivity and specificity. If a patient requires endoscopy, then a biopsy will be obtained during the procedure. It is important to remember that *H. pylori* may colonize the human stomach in different areas based on ethnicity, acid exposure, and medication history. These factors need to be taken into consideration when obtaining biopsies from various areas of the stomach. Otherwise, I use both breath testing and stool antigen testing, based on patient preference.

G&H What are the advantages and disadvantages of the UBT when testing for *H. pylori* infection?

CWH Advantages of the UBT include its simplicity, its reliability, and the fact that it can be applied both before and after treatment for *H. pylori* infection. It is noninvasive, and, assuming the ¹³C-UBT is used, it does not involve the administration of any radioactive material. Also, it can be administered in the clinic setting by a healthcare professional, such as nursing personnel. A potential disadvantage of the UBT is the fact that it should not be used in patients who have been taking a PPI, an antibiotic, or a bismuth preparation within the preceding 14 days.

ABE I think that the major advantage is the ease of testing, whether you perform it in the office or send the patient to an outpatient lab. I would echo Dr. Howden's comments on the disadvantages.

NS Urea breath testing has high sensitivity and specificity, and it is a test for active infection—these are important advantages. If clinicians have the testing instrument in their office, then it also offers patients the convenience of real-time results. There is a risk of false-negative test results due to premature post-dose breath collection. False-positive results may also be caused by the presence of urease produced by other gastric spiral organisms, such as *H. heilmannii*, or achlorhydria.

G&H Are you concerned about encountering antibiotic resistance when treating *H. pylori* infection? How can this concern be addressed?

NS Yes, antibiotic resistance is definitely a concern and, unfortunately, it is already a problem. Resistance is rapidly increasing, and we are already seeing very significant and clinically meaningful levels of clarithromycin resistance. We are also seeing metronidazole resistance, but this is less clinically relevant. The result of this resistance is markedly decreased eradication rates; when we first started treating *H. pylori* infection, we were eradicating the infection 90–95% of the time, but more recent numbers suggest we are now eradicating it only 60–75% of the time.

CWH I agree. Antimicrobial resistance is a major problem when treating *H. pylori* infection. The most important means of addressing this problem is to have some information about a particular patient's antibiotic history. Patients who have received clarithromycin or another macrolide antibiotic in the past—either for the treatment of *H. pylori* infection or for some other reason—must not be given this drug as part of their *H. pylori* treatment regimen.

ABE Antibiotic resistance is a concern, but this is an issue that we deal with daily when treating *H. pylori* infection, as when treating many other infectious diseases. As physicians, we need to be cognizant that inappropriate prescribing practices exacerbate the problem of antibiotic resistance, and we need to be more vigilant in our use of broad-spectrum antibiotic therapy. Increasing resistance also means that we must take a careful medication history and try to utilize agents that the patient has not been treated with previously.

G&H What is your preferred first-line treatment for *H. pylori* infection? Your preferred second-line therapy?

CWH My preferred treatment depends upon which antibiotic(s) the patient has received previously. If a patient was given clarithromycin in the past, I would opt for a quadruple regimen consisting of a PPI, tetracycline, metronidazole, and bismuth as my first choice.

ABE My preferred regimen is also guided by the patient's previous antibiotic exposure history. I will use a clarithromycin-based regimen if the patient has not previously been exposed to this drug. My alternatives would be either tetracycline or a quinolone antibiotic, along with bismuth and metronidazole.

NS Treatment of *H. pylori* infection is an ongoing evolution. Fifteen years ago, quadruple therapy was the standard regimen. Like most other practitioners, I then migrated to triple therapy, which includes clarithromycin, mainly for reasons of convenience and tolerability. Now that we are seeing such high rates of clarithromycin resistance, however, I am in the process of migrating back to quadruple therapy. My second-line therapy is whichever regimen I did not use initially; if the patient was previously treated with quadruple therapy, then I use triple therapy for the second-line regimen, and vice versa.

Acknowledgement

Drs. Elfant, Howden, and Stollman were paid by Otsuka America Pharmaceutical, Inc. for participation in the roundtable and development of this monograph and are promotional speakers for BreathTek® UBT for Helicobacter pylori (H. pylori) Kit. Dr. Howden has also been a paid consultant for Perrigo and Takeda, and he has received speaking honoraria from GlaxoSmithKline International and Takeda. Dr. Stollman has also received speaking honoraria from Aptalis Pharmaceuticals, Optimer Pharmaceuticals, and Warner Chilcott, and he receives research support from Warner Chilcott.

BRIEF SUMMARY

INTENDED USE:

The BreathTek® UBT for *H. pylori* Kit (BreathTek UBT Kit) is intended for use in the qualitative detection of urease associated with *H. pylori* in the human stomach and is indicated as an aid in the initial diagnosis and post-treatment monitoring of *H. pylori* infection in adult patients. The test may be used for monitoring treatment if used at least 4 weeks following completion of therapy. For these purposes, the system utilizes an Infrared Spectrophotometer for the measurement of the ratio of ¹³CO₂ to ¹²CO₂ in breath samples, in clinical laboratories or point-of-care settings.

The BreathTek UBT Kit is for administration by a health care professional, as prescribed by a physician.

WARNINGS AND PRECAUTIONS:

1. For in vitro diagnostic use only. The Pranactin®-Citric solution is taken orally as part of the diagnostic procedure.
2. Phenylketonurics: Contains Phenylalanine (one of the protein components of Aspartame), 84 mg per dosage unit. (For reference, 12 ounces of typical diet cola soft drinks contain approximately 80 mg of Phenylalanine.)
3. Blood glucose: Use with caution in diabetic patients. Pranactin-Citric contains Aspartame.
4. A negative result does not rule out the possibility of *H. pylori* infection. False negative results do occur with this procedure. If clinical signs are suggestive of *H. pylori* infection, retest with a new sample or an alternative method.
5. False negative test results may be caused by:
 - Ingestion of antimicrobials, proton pump inhibitors, and bismuth preparations within 2 weeks prior to performing the BreathTek UBT
 - Premature POST-DOSE breath collection time for a patient with a marginally positive BreathTek UBT result
 - Post-treatment assessment with the BreathTek UBT less than 4 weeks after completion of treatment for the eradication of *H. pylori*.
6. False positive test results may be caused by:
 - Urease associated with other gastric spiral organisms observed in humans such as *Helicobacter heilmannii*
 - Achlorhydria.
7. If particulate matter is visible in the reconstituted Pranactin-Citric solution after thorough mixing, the solution should not be used.
8. Hypersensitivity: Patients who are hypersensitive to mannitol, citric acid or Aspartame should avoid taking the drug solution as this drug solution contains these ingredients.
9. Risk of Aspiration: Use with caution in patients with difficulty swallowing or who may be at high risk of aspiration due to medical or physical conditions.
10. Pregnancy: No information is available on use of the Pranactin-Citric solution during pregnancy.

POSTMARKETING EXPERIENCE:

During post-approval use of the BreathTek UBT, the following adverse events have been identified: anaphylactic reaction, hypersensitivity, rash, burning sensation in the stomach, tingling in the skin, vomiting and diarrhea. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to establish a causal relationship to drug exposure.

LIMITATIONS:

1. The BreathTek UBT should not be used until 4 weeks or more after the end of treatment for the eradication of *H. pylori* as earlier post-treatment assessment may give false negative results.
2. The specimen integrity of breath samples and reference gases stored in breath bags under ambient conditions has not been determined beyond 7 days.
3. A correlation between the number of *H. pylori* organisms in the stomach and the BreathTek UBT result has not been established.

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April 2012

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