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# TESTING FOR *HELICOBACTER PYLORI*:

## WHY IT STILL MATTERS, HOW IT HAS EVOLVED

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SUPPLEMENT

# Testing for *Helicobacter pylori*: Why It Still Matters, How It Has Evolved

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ALTHOUGH INFECTION WITH *Helicobacter pylori* is no longer the hot topic it was in the 1990s, it remains clinically relevant in primary care, particularly in light of the continued significant influx of immigrants to the United States.

To update primary care physicians on recent changes in the epidemiology and diagnosis of *H pylori* infection, the *Cleveland Clinic Journal of Medicine* convened a roundtable discussion in January 2005 among a panel of physicians representing gastroenterology, primary care, and managed care perspectives.

The session began with overviews of the current clinical relevance of *H pylori* and noninvasive methods of *H pylori* testing, reflected in the two short review articles here that set the stage for the roundtable discussion that follows. The tables and figures throughout this supplement were developed by consensus of the roundtable panel.

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REVIEW

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# *Helicobacter pylori*: Why it still matters in 2005

*Helicobacter pylori* still matters clinically in 2005. Although *H pylori* infection rates are falling in the developed world and its associated diseases are decreasing in prevalence, *H pylori* is still widespread in many populations, especially within the United States, and still causes significant morbidity. Fortunately, treatment regimens combining antibiotic and antisecretory agents can be effective in eradicating *H pylori* and improving outcomes in most of the conditions in which the organism has been clearly implicated.

This article briefly reviews the clinical relevance of *H pylori* infection today, with a focus on its evolving epidemiology and the state of the evidence on the organism's role in various conditions in which it has been clearly or theoretically implicated.

## WHO IS INFECTED WITH *H PYLORI*?

*H pylori* is an extremely common bacterium in humans, infecting an estimated one half of the world's population. Its primary reservoir is the stomach, and person-to-person contact is believed to be its principal mode of transmission. Infection is often associated with poor sanitation, crowded living conditions, and poor water supplies. For this reason, the prevalence of *H pylori* is much higher in less developed countries than in developed countries (Figure 1), although there are subgroups within many developed nations in which the prevalence is considerably higher than in the general population. Prevalence varies by geographic location (Table 1),[1] ethnic background, socioeconomic status, and age. Recent studies indicate that *H pylori* prevalence is declining in developed countries and in those with rapid socioeconomic improvement.[2,3]

*DISCLOSURE: Dr. Fennerty has served as a consultant to AstraZeneca Pharmaceuticals, Eisai, Meridian Bioscience, Santarus, and TAP Pharmaceutical Products.*

### Differing epidemiologies in the United States

The prevalence of *H pylori* infection in the United States was estimated at 30% to 40% in the 1990s.[4] Since most people acquire the organism during childhood and since *H pylori* infection rates during childhood are falling,[2,3,5] it is believed that the US prevalence is currently somewhat lower than this and will continue to decline in the coming years.

Nevertheless, given the racial and ethnic diversity of the United States and its large numbers of recent immigrants from the developing world, it is important to recognize that there are differences in the epidemiology of *H pylori* within the United States. Graphical plotting of *H pylori* prevalence data in the United States (Figure 2) shows that the African American and Hispanic subpopulations have curves similar to that of a developing country, whereas the white subpopulation demonstrates the cohort effect curve of a developed country (see Figure 1). In light of the higher *H pylori* prevalence rates in their countries of origin, immigrants from Asia, Eastern Europe, and Africa have rates of *H pylori* infection that are more like those of US African Americans and Hispanics than of US whites. Native Americans from Alaska are another population at elevated risk of *H pylori* infection.[6,7]

**The epidemiology of *H pylori* in the United States varies profoundly among different racial and ethnic groups**

Clinicians should recognize this variable epidemiology of *H pylori* infection within the United States and be prepared to stratify their patients for *H pylori* risk accordingly.

## WHAT ARE THE EFFECTS OF *H PYLORI* INFECTION?

*H pylori* causes histologic gastritis in all those infected with it. It is the most common cause of chronic gastritis, but most infected individuals have no reportable symptoms.[8] The organism can directly damage epithelial cells in the gastric mucosa as well as induce an inflammatory response in the host. Both host factors and organism factors determine the phenotypic expression of the infection over time. It is in this

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Please see original source figure (figure 1, page S117) in: *Marshall BJ.* Helicobacter pylori. *Am J Gastroenterol 1994; 89(8 Suppl):S116–S128.*

**FIGURE 1.** Typical prevalence curves for *Helicobacter pylori* infection in less economically developed and more economically developed nations. The steep curve for the developing world reflects rapid and widespread acquisition in childhood. The curve for the developed world reflects a cohort effect, with a low incidence of new infections in young people and a "carrier state" from pre-1945 childhood infection in older people. Adapted from *Am J Gastroenterol*, Vol. 89 (8 Suppl), Marshall BJ, "*Helicobacter pylori*," pages S116–S128, copyright 1994, with permission from the American College of Gastroenterology.

**TABLE 1**

**Worldwide prevalence of *H pylori* infection in the mid-1990s***

| | |
|---|---|
| United States and Canada | 30%–40% |
| Mexico and Central/South America | 70%–90% |
| Western Europe | 30%–50% |
| Eastern Europe | 70% |
| Africa | 70%–90% |
| Asia | 70%–80% |
| Australia | 20% |

*Data are from reference 1.

phenotypic expression that the significance of *H pylori* lies, and the rest of this review will summarize our current understanding of established, controversial, and theoretical phenotypic manifestations of *H pylori* infection.

## DISEASES IN WHICH *H PYLORI* HAS AN ESTABLISHED ROLE

### Peptic ulcer disease

*H pylori* is the major cause of peptic ulcer disease, and peptic ulcer disease remains the chief driver of interest in the organism in the United States. *H pylori* has been found in up to 95% of patients with duodenal ulcers and 80% of patients with gastric ulcers in some regions of the world.[9] In the United States, the percentage is closer to 75%,[10,11] which likely reflects a larger role for ulcers induced by nonsteroidal anti-inflammatory drugs (NSAIDs). Rates vary somewhat among different regions of the United States.

The causative role of *H pylori* in peptic ulcer disease has been confirmed by studies showing that *H pylori* eradication markedly reduces peptic ulcer recurrence. A meta-analysis of *H pylori* treatment trials demonstrated an odds ratio of 0.20 (95% confidence interval [CI], 0.13 to 0.31) for ulcer recurrence at 6 months in patients in whom *H pylori* had been eradicated.[11]

However, clinicians must recognize that *H pylori* eradication does not necessarily mean that a patient's ulcer symptoms will disappear. Indeed, the above meta-analysis showed a pooled ulcer recurrence rate of 20% at 6 months even in patients with successful *H pylori* eradication.[11] This recurrence of ulcer symptoms may be attributable to NSAID-induced ulcers, idiopathic ulcers, or other causes; regardless, the much higher likelihood of symptom resolution, together with other reasons for *H pylori* eradication (discussed below), clearly justifies testing for and treatment of *H pylori* in patients with peptic ulcer disease. Patients should be warned, however, that *H pylori* eradication will not always make their ulcer symptoms go away.

### Gastric cancer

A series of epidemiologic and case-control studies[12–14] support an association between *H pylori* infection and gastric adenocarcinoma, an association that is also supported by animal studies. One of the epidemiologic studies, conducted in Japan, found *H pylori* to be associated with a twofold- to threefold-higher risk of gastric cancer among men but with no increased risk among women.[12]

Despite this epidemiologic evidence of a connection between *H pylori* and gastric can-

cer, it is not clear whether *H pylori* eradication, at least in adults, reduces the risk of gastric cancer development. There are currently no randomized trials showing a reduction in gastric cancer incidence in individuals who received treatment for *H pylori* eradication. Uemura et al[15] conducted a nonrandomized comparison of *H pylori* eradication vs no eradication following endoscopic resection of early gastric cancer in *H pylori*–positive patients. After 3 years of follow-up, the incidence of gastric cancer recurrence was 0% in the eradication group vs 9% in the control group, but the design of this observational study was poor and its findings require confirmation in a randomized trial. A South American study assessing *H pylori* eradication in patients with precursor lesions for gastric cancer suggested that eradication was associated with regression only at more advanced stages of disease (multifocal atrophic gastritis and intestinal metaplasia).[16] Wong et al[17] recently reported no reduction in gastric cancer incidence with *H pylori* eradication in high-risk Chinese patients, although a subgroup analysis (not prespecified) revealed a significant reduction among patients with no precancerous lesions at presentation.

The bottom line is that while *H pylori* is likely an important factor in gastric carcinogenesis, eradication of the organism after many decades of infection and promotion of carcinogenesis is not likely to prevent most cases of gastric cancer.

### MALT lymphoma

A connection between *H pylori* and mucosa-associated lymphoid tissue (MALT) lymphoma is well established, as *H pylori* infection has been documented in up to 90% of patients with low-grade MALT lymphoma.[18–20] In contrast to gastric adenocarcinoma, clinical trials have more clearly indicated an interventional role for *H pylori* eradication in MALT lymphoma, with as many as three quarters of patients with low-grade MALT lymphoma experiencing complete or partial tumor remission following *H pylori* eradication.[21–24] The completeness and durability of this treatment effect remain unknown, however.

### Uninvestigated dyspepsia

There are many mechanisms by which *H pylori* may produce dyspeptic symptoms (eg, upper abdominal pain or discomfort, bloating, nausea, early satiety). These include the effect of *H pylori*–related inflammation on receptors, perturbations of motility, and acid sensitivity. Epidemiologic studies have suggested a higher prevalence of *H pylori* in dyspeptic patients, but confirmatory randomized controlled interventional trials are lacking.

**Diverse epidemiologies of *H pylori* infection within the United States**

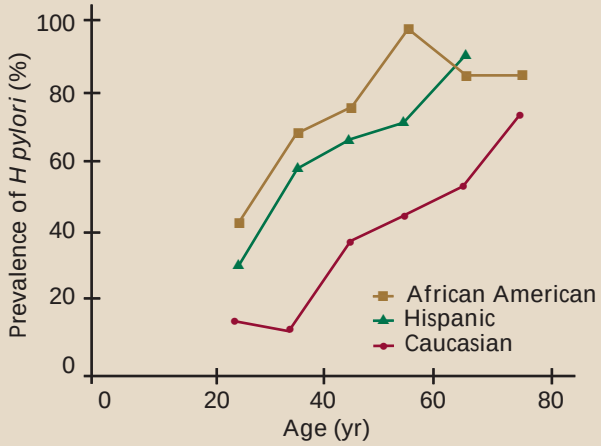


**FIGURE 2.** The prevalence of *Helicobacter pylori* infection within the United States differs dramatically by race, with racial and ethnic minorities showing prevalence curves more typical of developing nations (see Figure 1). Adapted from *H pylori and Peptic Ulcer*, NIH Publication 97-4225. Bethesda, MD: National Digestive Diseases Information Clearinghouse; 1997.

Because of this lack of data from interventional studies, decision analytic models have been developed to investigate the value of a "test-and-treat" strategy for *H pylori* in patients with *uninvestigated* dyspepsia (ie, dyspepsia not evaluated via endoscopy or imaging of the upper gastrointestinal tract).[25–29] The *H pylori* test-and-treat strategy was dominant over strategies involving early endoscopy in each of these economic models, showing similar outcomes at lower cost.

Thus, despite a lack of randomized trial data supporting a test-and-treat strategy for *H pylori*, this strategy has increasingly been adopted for appropriate patients with uninvestigated dyspepsia—ie, those younger than 50 years of age with no "alarm features" (weight loss, evidence of bleeding, vomiting, dysphagia, anemia, or family history of gastric malignancy). A test-and-treat strategy for *H pylori* in such patients has been endorsed by the United Kingdom's

**Clinicians should stratify patients for *H pylori* risk according to the variable epidemiology of the infection**

National Institute for Clinical Excellence[30] and will soon be recommended in upcoming guidelines on dyspepsia from the American Gastroenterological Association and the American College of Gastroenterology.[31]

## CONDITIONS IN WHICH A ROLE FOR *H PYLORI* IS UNCERTAIN OR UNLIKELY

### Nonulcer dyspepsia

In contrast to uninvestigated dyspepsia, *nonulcer* dyspepsia refers to dyspepsia in which the patient has undergone upper gastrointestinal evaluation via endoscopy and an ulcer has been ruled out.

Some epidemiologic studies have suggested an increased prevalence of *H pylori* in patients with nonulcer dyspepsia. However, numerous large interventional trials of *H pylori* eradication therapy in patients with nonulcer dyspepsia have yielded conflicting results, failing to confirm a cause-and-effect relationship.[32–36] The differences in trial results can be explained by differences in the settings, definitions, and instruments used.[36] The preponderance of evidence suggests that there is little, if any, effect of *H pylori* eradication in patients with nonulcer dyspepsia.[36]

**Eradication of *H pylori* markedly reduces peptic ulcer recurrence**

### NSAID-induced ulcer

Although synergism in the development of peptic ulcer between NSAID use and *H pylori* infection has been suggested, NSAIDs and *H pylori* cause ulcers via different pathophysiologic mechanisms. Because *H pylori* infection induces local prostaglandin production, it is biologically plausible that *H pylori* could even be protective against NSAID-induced ulcer. A number of prevalence and incidence studies have investigated proposed ulcer-inducing interactions between *H pylori* and NSAIDs, yielding conflicting results.

Generally, the results appear to differ according to whether the subjects were naïve or chronic NSAID users. In short-term and long-term studies in NSAID-naïve Asian patients infected with *H pylori*, Chan et al[37,38] demonstrated significant reductions in ulcer rates in patients who received *H pylori* eradication therapy prior to naproxen therapy compared with those who received no eradication therapy. These results, together with findings from other studies, have fairly well established the notion that *H pylori* eradication prior to NSAID therapy will reduce ulcer incidence in NSAID-naïve Asian patients.

There is currently no evidence, however, that this is true in US populations or in chronic NSAID users, because similar studies in chronic NSAID users have found no benefit from *H pylori* eradication. In fact, Hawkey et al[39] found that *H pylori* eradication in long-term NSAID users with past or current ulcer was associated with impaired ulcer healing, suggesting that prostaglandin-related protection was perhaps at work. Similarly, *H pylori* infection was associated with higher rates of maintenance of NSAID ulcer healing in two other large studies in chronic NSAID users.[40,41]

The risks of ulcer bleeding in NSAID users infected with *H pylori* have likewise been variable, precluding clear conclusions.

At this time, it appears that *H pylori* infection may increase the rate of NSAID ulcer complications[42] and that *H pylori* eradication may reduce the incidence of ulcers in new NSAID users, particularly among Asians. However, it also appears that *H pylori* could possibly be protective against NSAID-induced ulceration in chronic NSAID users. Further research is needed in all of these areas.

### Gastroesophageal reflux disease

The existence and nature of any association between *H pylori* and gastroesophageal reflux disease (GERD) is one of the most complicated questions concerning *H pylori*.

It has been hypothesized that the loss of acid secretory capacity (gastric atrophy) over time that is related to chronic *H pylori* infection might reduce the incidence of GERD. Proponents of this hypothesis point to the opposing time trends of peptic ulcer disease and reflux disease, suggesting that the decline in *H pylori* prevalence could be associated with an increase in GERD and its complications.[43] They also point to evidence of an inverse relationship between corpus gastritis and esophagitis.[44] Additionally, some clinical trial evidence has suggested that *H pylori* eradication may increase the risk of reflux esophagitis[45] and that certain strains of *H pylori* may be protective against serious complications of GERD.[46]

More recent clinical trials have suggested,

**TABLE 2**

**The role of *H pylori* in various diseases: What we know today**

| | CAUSATIVE/CONTRIBUTORY ROLE FOR *H PYLORI*? | EFFECT OF *H PYLORI* ERADICATION |
|---|---|---|
| Peptic ulcer disease | Yes | Reduces ulcer recurrence rate |
| Gastric adenocarcinoma | Yes | Uncertain |
| MALT lymphoma | Yes | Partial or complete remission in more than half of patients |
| Uninvestigated dyspepsia | Yes, in some patients | Symptom improvement in some patients |
| Iron-deficiency anemia | Likely | May lead to anemia resolution when *H pylori* is the cause |
| Idiopathic thrombocytopenic purpura | Yes, in some patients | Platelet counts improve after eradication |
| Nonulcer dyspepsia | Controversial | Little effect, if any |
| NSAID-induced ulcer | Controversial; perhaps only in naïve NSAID users | May reduce ulcer incidence in Asian naïve NSAID users |
| GERD | Unlikely, at least for most patients; *H pylori* may protect against GERD | Uncertain |
| Pancreatic cancer | Uncertain | Unknown |
| Coronary artery disease | Unlikely | Probably none |

MALT = mucosa-associated lymphoid tissue; NSAID = nonsteroidal anti-inflammatory drug; GERD = gastroesophageal reflux disease

however, that a subset of patients with GERD may benefit from *H pylori* eradication[47] or that *H pylori* eradication has no effect on GERD relapse rates.[48]

More research is clearly needed before firm conclusions can be made. In the meantime, clinical practice should be guided by the premise that there is no clear relation between *H pylori* infection and GERD.

### Chronic inflammation in coronary disease

Chronic inflammation appears to be an integral pathophysiologic mechanism for plaque disruption and the precipitation of coronary symptoms and events. Several early epidemiologic and clinical reports suggested an increased prevalence of *H pylori* in patients with coronary artery disease, but subsequent case-control investigations have largely dismissed such an association.[49–51]

### Pancreatic cancer

Several case-control studies have indicated a possible modest association between *H pylori* infection and pancreatic cancer,[52,53] although the biologic plausibility of such an association has not been clearly elucidated. Prospective studies are needed to further examine this question.

## CONDITIONS IN WHICH EMERGING DATA SUGGEST A ROLE FOR *H PYLORI*

**A test-and-treat strategy for *H pylori* is increasingly supported for patients with uninvestigated dyspepsia**

### Iron-deficiency anemia

An association between *H pylori* and iron-deficiency anemia was first observed in the late 1990s in a group of Native Americans in Alaska with widespread iron deficiency attributable to occult gastrointestinal bleeding.[6] Potential mechanisms for this association include iron sequestration by the *H pylori*–infected antrum, altered iron absorption related to the degree of gastritis and pH elevation, and increased microscopic blood loss from the mucosa.

The findings from Alaska were followed by similar findings from a case-control study in a Danish population showing an odds ratio of 1.4 (95% CI, 1.1 to 1.8) for reduced serum iron levels in *H pylori*–infected individuals.[54] Since then, interventional trials have shown successful resolution of iron-deficiency anemia following *H pylori* eradication.[55,56]

While additional studies are encouraged, *H pylori* appears to be a risk factor for iron-deficiency anemia. For patients in whom there is no other explanation for iron-deficiency anemia, *H pylori* testing and eradication may be an effective management approach.

### Idiopathic thrombocytopenic purpura

*H pylori* causes an inflammatory response and provokes an immunologic reaction. It has been proposed that other chronic immune disorders may be caused by an immunologic reaction to *H pylori* antigens, resulting in antibodies that cross-react with human tissues. Uncontrolled studies have suggested a role for *H pylori* in chronic idiopathic thrombocytopenia,[57,58] and recent controlled trials confirm that some patients with this disorder may benefit from therapy to eradicate *H pylori*.[59,60]

## SUMMARY

Despite falling prevalence rates in the developed world, *H pylori* is still present in the United States and is particularly prevalent among racial minorities and recent immigrants. *H pylori* infection is clearly associated with an increased risk of peptic ulcer disease, gastric cancer, and MALT lymphoma, and it is associated with some cases of uninvestigated dyspepsia. Identification and eradication of *H pylori* improves outcomes in patients with peptic ulcer disease and causes tumor regression in patients with MALT lymphoma. It is uncertain whether *H pylori* eradication will improve outcomes in patients with gastric cancer. Decision analytic models suggest that a test-and-treat strategy for *H pylori* is rational and cost-effective for patients with uninvestigated dyspepsia.

**_H pylori_ cure has little, if any, effect in patients with nonulcer dyspepsia**

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**Practice should be guided by the premise that there is no clear relation between *H pylori* and GERD**

REVIEW

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# How to test for *Helicobacter pylori* in 2005

Infection with *Helicobacter pylori* can be diagnosed either by invasive techniques requiring endoscopy and biopsy (histologic examination, rapid urease test, culture, polymerase chain reaction) or by one of several noninvasive testing methods—serologic tests, the urea breath test, and the stool antigen test. Guidelines for managing dyspeptic patients in primary care settings recommend the use of noninvasive tests for *H pylori* detection at the outset,[1–3] as this approach has been demonstrated to be clinically effective and less costly than invasive testing,[4,5] along with being more convenient.

This article briefly reviews the available noninvasive tests for *H pylori* detection and discusses factors that should inform the choice of an individual test.

**The major disadvantage of serologic tests is that they cannot distinguish between active and past infection with *H pylori***

## ACTIVE VS PASSIVE TESTING

A fundamental distinction among tests for *H pylori* is whether they provide direct evidence that *H pylori* infection is currently present (ie, active tests) or indirect evidence, by detecting the presence of antibodies to *H pylori* (ie, passive tests). Because they only detect antibodies to *H pylori*, passive tests do not distinguish between currently active infection and infection that has resolved or been cured.

All serologic tests for *H pylori* are passive tests, whereas the urea breath test and the stool antigen test are both active tests. Recently introduced *H pylori* tests that evaluate saliva or urine also work by detecting antibodies to *H pylori* and thus share with serologic tests the limitations of passive testing. Because antibody concentrations are lower in saliva and urine than in blood, antibody detection is even more difficult with these tests than with serologic tests, so they will not be discussed further here.

*DISCLOSURES: Dr. Vakil has received grant/research support from AstraZeneca Pharmaceuticals, Medtronic, Novartis, and Pfizer; has served as a consultant to AstraZeneca, Medtronic, Meridian Bioscience, and Novartis; and is on the speakers' bureaus of AstraZeneca, Novartis, and TAP Pharmaceutical Products. Dr. Fendrick has served as a consultant to Meridian Bioscience.*

## THE NONINVASIVE TESTS AT A GLANCE

### Serologic tests

Serologic testing detects the presence of specific IgG antibodies to *H pylori* in a patient's serum. These antibodies are present in serum about 21 days after infection and can remain present long after the organism is eradicated. They can be assessed quantitatively using enzyme-linked immunosorbent assay (ELISA) and latex agglutination techniques or qualitatively using office-based kits. Dozens of different serologic tests are commercially available.

Advantages of the serologic tests are their wide availability, their rapid results, the fact that they require no specialized equipment or techniques, and their low cost relative to active tests. For these reasons, serologic tests were the mainstay of *H pylori* diagnosis for a number of years.

The major disadvantage of serologic tests is that they cannot distinguish between active infection and previous exposure to *H pylori*. Because serologic testing detects only antibodies, a positive serology result can occur in three very different patient groups[6]:

1. Those with detectable antibody and active *H pylori* infection (true-positive for antibody, infected).
2. Those with detectable antibody but not actively infected (true-positive for antibody, not infected).
3. Those never infected and with no antibody detectable (false-positive result).

This distinction is critical because eradication therapy is of no clinical value in the second and third groups. As more and more people are successfully treated for *H pylori* in a population, the ranks of the "true-positive for antibody, not infected" group (group 2) will grow. Of course, the inability to distinguish between active and past infection also renders serologic testing useless for confirmatory testing to ensure *H pylori* eradication following treatment to cure the infection.

This inability to distinguish between current and past infection contributes to the other major

shortcoming of serologic testing—that it is less sensitive and specific than the active noninvasive tests for *H pylori* (Table 1).[7] A meta-analysis of 21 clinical trials using commercially available ELISA serology kits found an overall sensitivity and specificity of 85% and 79%, respectively, for active infection with these serologic tests and revealed no significant differences among the various kits.[8] The authors concluded that the overall accuracy of serologic tests may not be adequate for clinical decision-making. A similar analysis by the London Department of Health of 16 serologic tests arrived at similar sensitivity and specificity rates,[9] as did studies from 2001 and 2002 of the more advanced "third-generation" ELISA tests.[10–14]

### Urea breath test

The urea breath test identifies active *H pylori* infection through the organism's urease production. The patient ingests urea labeled with either the nonradioactive isotope carbon 13 ($^{13}C$) (BreathTek UBT for *H pylori*, Meretek Diagnostics, Inc, Lafayette, CO) or the radioactive isotope carbon 14 ($^{14}C$) (PYtest, Kimberly-Clark Corp, Draper, UT). If *H pylori* is present in the stomach, hydrolysis occurs and produces labeled carbon dioxide, which is detectable within a few minutes in the patient's breath. The labeled urea is typically given to the patient with a test meal to delay gastric emptying and increase contact time with the mucosa. After urea ingestion, breath samples are collected for up to 20 minutes by exhaling into a carbon dioxide–trapping agent. Though the amount of radiation in the $^{14}C$ urea breath test is less than daily background radiation exposure,[15] the $^{13}C$ test is preferred in children and pregnant women.[16]

Recently, a new card test for $^{14}C$ urea has been described that uses a flat breath card that is read by a small analyzer, providing a near-patient testing option in primary care settings.

The urea breath test detects active *H pylori* infection and is highly accurate, with a weighted mean sensitivity and specificity from published trials of 94.7% and 95.7%, respectively (Table 1).[7]

### Stool antigen test

The stool antigen test is an enzymatic immunoassay (ELISA) that identifies *H pylori* antigen in stool specimens through a polyclonal anti–*H pylori* antibody (Premier Platinum HpSA, Meridian Bioscience, Inc, Cincinnati, OH). In addition, a rapid stool antigen test (Immuno*Card* STAT! HpSA, Meridian Bioscience, Inc, Cincinnati, OH) is available. Using the rapid assay, a diluted stool sample from the patient is dispensed into the sample port of the test device; after 5 minutes of incubation at room temperature, the device indicates a positive or negative result, providing a near-patient testing option in primary care settings.

**TABLE 1**

**Accuracy of noninvasive tests for *H pylori* infection**

| | SENSITIVITY FOR ACTIVE INFECTION | SPECIFICITY FOR ACTIVE INFECTION |
|---|---|---|
| Urea breath test | 94.7% | 95.7% |
| Stool antigen test | 93.1% | 92.8% |
| Serum IgG antibody (serology) | 85.0% | 79.0% |

Data are weighted mean values compiled from multiple published clinical trials as detailed in reference 7.

The ELISA stool antigen test detects active *H pylori* infection and is highly accurate, with a weighted mean sensitivity and specificity from published trials of 93.1% and 92.8%, respectively,[7] rates that are virtually the same as those for the urea breath test (Table 1). Similar performance has been demonstrated in the rapid format.

## CHANGING PREVALENCE PROFOUNDLY AFFECTS TEST PERFORMANCE

As Table 1 illustrates, the two tests for active infection, the urea breath test and the stool antigen test, are about 8 to 10 percentage points more sensitive and about 14 to 16 percentage points more specific than antibody testing with serology. How important are these differences in clinical practice? The changing prevalence of *H pylori* infection makes them far more significant than they first appear to be.

**There is little point in sequential testing with serology followed by an active test for confirmation**

As the prevalence of *H pylori* infection declines in the United States,[17] the pretest probability that *H pylori* is present in a given patient with dyspepsia also declines. This has implications for the clinical performance of a diagnostic test even though the test's sensitivity and specificity for active infection remain constant.

Figure 1 shows how four hypothetical tests with sensitivities and specificities for active infection of 100%, 97%, 90%, and 80%, respectively, perform in two different populations—one with a 28% prevalence of *H pylori* and one with a 10%

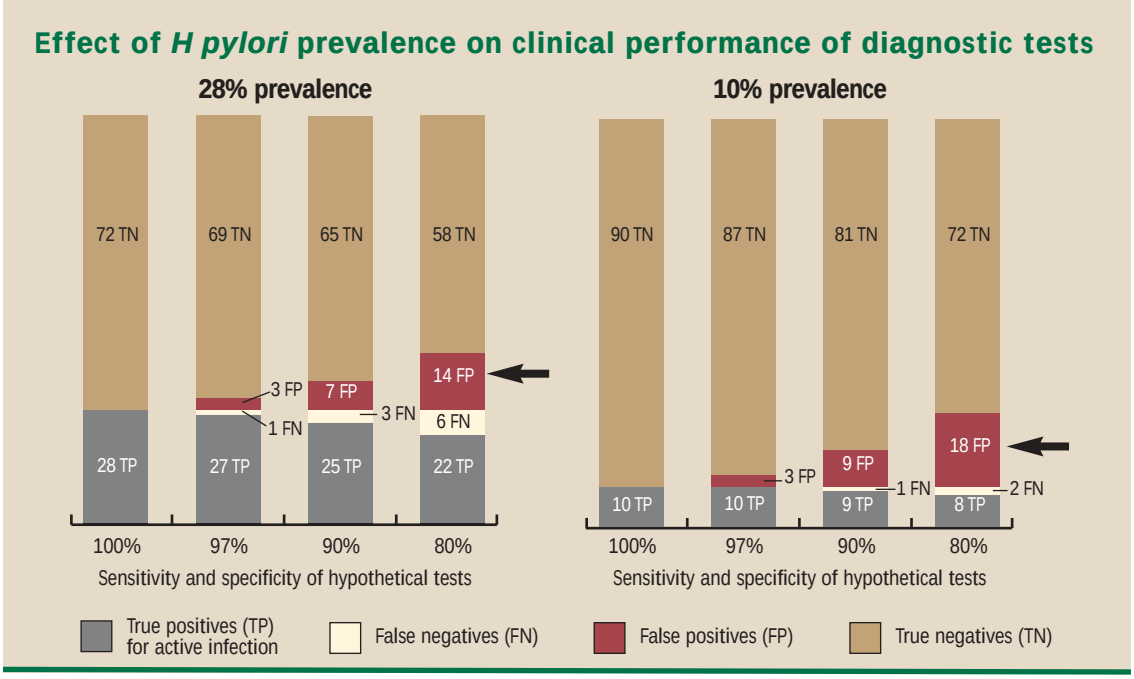


**FIGURE 1.** Performance of four hypothetical diagnostic tests for *H pylori* with sensitivities and specificities for active infection of (a) 100%, (b) 97%, (c) 90%, and (d) 80% in two different populations—one with a 28% prevalence of *H pylori* infection and one with a 10% prevalence. The tests' clinical performance varies substantially even though their differences in sensitivity and specificity seem modest. In the 28% prevalence setting (left), the test with 80% sensitivity and specificity produces a high number of false positives (14 out of 100 patients; arrow)—twice as many as the test with 90% sensitivity and specificity. As the prevalence of *H pylori* falls to 10% (right), the number of additional false positives (arrow) climbs much more quickly with the test with 80% sensitivity and specificity than with the other tests. Adapted from reference 18.

**A test-and-treat strategy is advantageous for patients with a high likelihood of peptic ulcer disease**

prevalence. As the figure illustrates, the clinical performance of the tests varies substantially even though their differences in sensitivity and specificity seem modest. In the population with 28% prevalence, the test with 80% sensitivity and specificity produces twice as many false positives as the test with 90% sensitivity and specificity and nearly five times as many as the test with 97% sensitivity and specificity.[18] As the prevalence of *H pylori* falls (in this case, down to 10% in the right-hand panel of Figure 1), the number of additional false positives climbs much more quickly with the test with 80% sensitivity and specificity than with the other tests.

Of course, an *H pylori* prevalence of 28% or lower is present in many primary care settings in the United States today, which means that a test method with a sensitivity and specificity for active infection of approximately 80%, such as serologic testing, will yield many false positives. This will lead to inappropriate treatment in numerous patients and a host of unwanted outcomes—lack of treatment response, encouragement of antibiotic resistance, patient inconvenience and disappointment, a need for further testing, and additional costs and resource use. This effect will only grow as the prevalence of *H pylori* continues to fall in the United States.

For this reason, the 2000 Maastricht 2 Consensus Report[1] concluded that serologic testing is not accurate enough for use in routine clinical practice.

## WHAT ABOUT COST?

Even in light of data showing the clinical inferiority of serologic testing, the question sometimes arises of whether it is justified to first test with a low-cost serologic test and then follow up with a more accurate active test if deemed necessary.

This type of sequential testing strategy was assessed in an economic model evaluating noninvasive testing strategies in primary care settings.[19] The analysis compared the costs per number of correct diagnoses achieved with various sequential testing strategies and with single tests across three *H pylori* prevalence scenarios: low (30%), intermediate (60%), and high (90%). Estimates of prevalence and test characteristics were derived from a systematic literature review, and cost estimates were derived from the 2000 Medicare fee schedule.

Although serologic testing had the lowest cost per correct diagnosis ($90 to $95) at all three prevalence levels, its diagnostic accuracy was low (80% to 84%). At low and intermediate prevalence, use of an active test alone was substantial-

ly more accurate at a modest additional cost; the stool antigen test had a diagnostic accuracy of 93% at an average cost of $126 to $127 per correct diagnosis and an incremental cost of $336 to $381 per additional correct diagnosis (specific data were not reported for the urea breath test used alone). Only at high prevalence (90%) did a sequential strategy using serologic testing begin to justify itself; in this scenario, serologic testing with ELISA followed by confirmatory urea breath testing for negative ELISA results produced diagnostic accuracy of 96% at a cost of only $112 per correct diagnosis.[19]

The authors concluded that active testing with the stool antigen test or urea breath test is clearly preferable at low and intermediate *H pylori* prevalence (60% or lower), given these tests' high level of accuracy at modest incremental cost over serologic testing. In high-prevalence settings, which are highly unusual in the developed world, serologic testing becomes competitive, but its relative accuracy is still poor. The authors recommended that, given the modest cost of the stool antigen and urea breath tests, there is little point in sequential testing with a low-cost test followed by an active test for confirmation. Because of the highly comparable accuracy of the stool antigen and urea breath tests, any differences between them in cost per correct diagnosis were due almost wholly to differences in the costs of the tests used in this analysis ($50 for the stool antigen test and $104 for the urea breath test, based on their Medicare reimbursement levels at the time).[19]

## IS 'TEST AND TREAT' STILL RECOMMENDED?

The "test-and-treat" strategy for *H pylori* in patients with uninvestigated dyspepsia was developed a number of years ago, when serologic testing was a still a recommended method of noninvasive testing and when the prevalences of both *H pylori* and peptic ulcer disease in the United States were higher than they are today. Recent decision analyses have reappraised the utility of the test-and-treat strategy in the context of (1) the changing epidemiology of *H pylori* and peptic ulcer disease[20,21] and (2) the newer options in noninvasive testing.[6]

### 'Test and treat' remains useful, but empiric PPI therapy may also have a role

Spiegel et al[20] performed a decision analysis that incorporated 6 weeks of empiric proton pump inhibitor (PPI) therapy into several management strategies for patients with uninvestigated dyspepsia. Of four strategies, initial PPI therapy followed by endoscopy for nonresponders was found to be the least costly strategy per patient treated, but it left fewer patients symptom-free at 1 year than did two hybrid strategies that combined a test-and-treat approach for *H pylori* with empiric PPI therapy; these hybrid strategies were slightly more costly. The most costly and least effective strategy was a test-and-treat approach followed by endoscopy for nonresponders. (The strategies that included testing and treating assumed use of an ELISA serologic test, not a test for active *H pylori* infection.) The authors concluded that sequential use of a test-and-treat approach with PPI therapy may be more cost-effective than PPI therapy alone, especially when peptic ulcer disease is highly likely or symptoms are severe, but that PPI therapy alone may be more cost-effective when underlying erosive esophagitis is likely, *H pylori* infection is unlikely, or dyspeptic symptoms are not severe.[20,22]

Ladabaum et al[21] reached similar conclusions from a symptom-driven decision analysis that compared a test-and-treat strategy and empiric PPI therapy for patients with uninvestigated dyspepsia. (Again, the test-and-treat strategy assumed testing with an ELISA serologic test.) Under most epidemiologic conditions, costs per patient treated and clinical outcomes differed little between the two strategies. At the individual patient level, the prevalence of *H pylori* infection, the likelihood that a given patient had peptic ulcer disease, and the proportion of ulcers attributable to *H pylori* strongly influenced which strategy carried the lowest cost per patient treated. At the population level, empiric PPI therapy was consistently less costly if the *H pylori* prevalence was less than 20%.

Both of these decision analyses suggest that a test-and-treat strategy offers an advantage for patients who have a high likelihood of peptic ulcer disease. In light of this, as the prevalence of *H pylori* infection and peptic ulcer disease declines, clinicians should increasingly be attuned to their individual patients' likelihood of *H pylori* infection, based on demographic factors (Table

**TABLE 2**

**US populations with increased probability of *H pylori* infection**

| | |
|---|---|
| African Americans | Persons with poor socioeconomic status |
| Hispanics/Latinos | Native Americans from Alaska |
| Immigrants from developing nations | Persons older than 50 years of age |

**Because of its lower specificity, serologic testing leads to more treatment of patients without active infection, more antibiotic resistance, and wasting of resources**

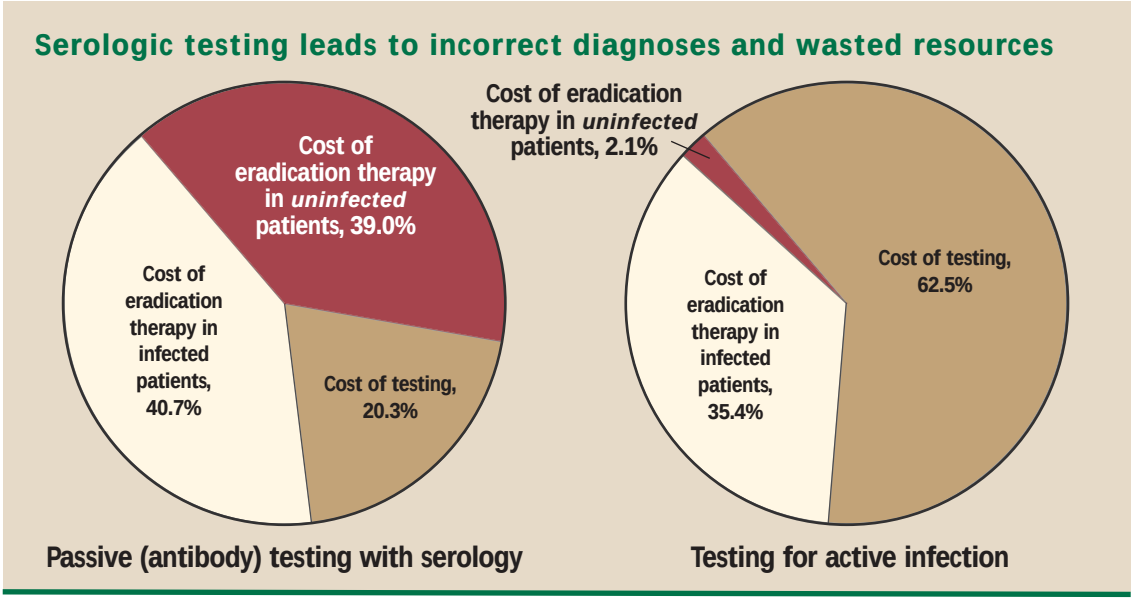


**FIGURE 2.** Breakdown of overall management costs per 100 patients tested with either serologic testing or testing for active infection (with urea breath test) in a test-and-treat strategy for *H pylori* in uninvestigated dyspepsia, assuming 30% prevalence of active *H pylori* infection (see text for details). Because it cannot distinguish between past and current infection, serologic testing leads to many more false-positive results and, in turn, to many incorrect diagnoses of *H pylori* infection and a high level of inappropriate treatment. As a result, 39% of overall spending with the serologic testing strategy is wasted on inappropriate therapy in uninfected patients, vs only 2% of overall spending with active testing. Data are from a decision analysis by Chey and Fendrick.[6]

2), and their likelihood of having peptic ulcer disease, based on symptoms (ie, epigastric pain).

**At least 1 in 4 patients remains infected after treatment to cure *H pylori*, so all patients should be retested following therapy**

### 'Test and treat' now requires an active test

When the suspicion of both *H pylori* and ulcer is reasonable and testing is indicated, physicians clearly should use a test for active infection. That is the conclusion of a decision analysis by Chey and Fendrick[6] that estimated the clinical and economic outcomes associated with either serologic testing for *H pylori* antibody (assumed sensitivity and specificity for active infection of 85% and 79%, respectively, and assumed cost of $25 per test) or active testing with the urea breath test (assumed sensitivity and specificity for active infection of 95% and 98%, respectively, and assumed cost of $100 per test). The model assumed an *H pylori* prevalence of 30%; of the 70% of individuals without active infection, 20% were assumed to have been infected at some time in the past, meaning that 14% of the overall population would have true-positive results for *H pylori* antibody but not have active infection. Patients who tested positive were to be treated with a 14-day regimen of lansoprazole, clarithromycin, and amoxicillin at a cost of $200.[6]

The analysis showed that active testing dramatically reduced the number of patients inappropriately treated (ie, treated despite not having active *H pylori* infection), from 23.7 per 100 patients with serologic testing to only 1.4 per 100 patients with active testing. Moreover, when compared with serologic testing, active testing identified 3 additional patients with current infection per 100 patients tested.

To achieve these clinical advantages, active testing cost an additional $37 per patient tested compared with serologic testing. However, on a population basis, a full 39% of the overall cost of a serology-based management strategy represents wasted resources in the form of inappropriate eradication therapy in incorrectly diagnosed patients (without current infection). With active testing, the corresponding proportion is just 2% (Figure 2). The authors concluded that the modest incremental cost of active testing is well worth it for the additional accuracy achieved and for the avoidance of inappropriate treatment, misuse of antibiotics, patient inconvenience, and wasted resources.

## RETEST TREATED PATIENTS TO CONFIRM CURE

As recommended in the Maastricht 2 Consensus Report,[1] repeat testing after *H pylori* eradication therapy should be offered to all patients to confirm that the infection has been cured.

There are several reasons for this recommendation. First, intention-to-treat analyses of US randomized trials show that successful eradication was achieved in only about three quarters of patients receiving optimal treatment regimens for *H pylori* eradication. Thus, at least one in

four patients will remain infected after therapy and need to be identified for further management. Second, because treatment for *H pylori* involves taking multiple pills over 1 to 2 weeks, patients often fail to adhere to their full regimen. Third, antibiotic resistance is rising among *H pylori* organisms. Finally, confirmatory retesting is good medicine, and most patients who have the organism want to know that it has been eradicated. A study among US patients with peptic ulcer disease in the late 1990s found that most desired retesting to confirm *H pylori* cure at their own expense, and more than half said they were willing to pay more than $50 for it.[23]

Because they detect only antibody to *H pylori*, serologic tests and other passive tests should *not* be used for retesting to confirm eradication. Both the urea breath test and the stool antigen test are appropriate for confirmatory retesting, and a recent trial found that they are equally accurate in confirming *H pylori* eradication after therapy.[24]

Current or recent PPI use can lead to false-negative results with either the urea breath test or the stool antigen test.[18] For this reason, PPIs should be withheld for 2 weeks prior to administration of either test, and post-treatment testing should not be done until 4 weeks after the patient has completed eradication therapy with a PPI and antibiotics.

**TABLE 3**

**Why do confirmatory post-treatment testing?**

- Eradication therapy fails in at least one quarter of patients
- Patients often do not adhere to full treatment regimens
- Antibiotic resistance is rising
- Patients want to know if their infection is cured, and most are willing to pay for this knowledge
- It's good medicine

## CONCLUSIONS AND RECOMMENDATIONS

Testing for *H pylori* infection in primary care settings should be limited to noninvasive testing methods. Active testing with the urea breath test or the stool antigen test is recommended for patients with suspected infection, both for initial detection of the organism and for retesting after therapy to confirm eradication. These two tests for active infection are virtually identical in accuracy, so the choice between them should take into account other factors, such as cost, availability, and patient and physician preference.

Because it cannot distinguish between current and past infection, serologic testing has poor accuracy in settings of low and intermediate *H pylori* prevalence and should no longer be used in the United States.

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# Pitfalls, pearls, and practicalities in the diagnosis of *Helicobacter pylori* infection

**Dr. Gary Falk:** In light of the overviews that Drs. Fennerty, Vakil, and Fendrick have presented on the clinical relevance of *Helicobacter pylori* and the noninvasive testing options for *H pylori* in 2005, let's start our roundtable by considering a case study that touches on additional issues that primary care physicians might grapple with when considering *H pylori* infection in their daily practice.

## CASE STUDY

**Dr. Falk:** A 39-year-old otherwise healthy male patient that you have been seeing for several years comes to your office and reports epigastric burning discomfort without heartburn or acid regurgitation. It is the first time he has reported these symptoms. He has no weight loss, nausea, vomiting, or other alarm symptoms. David, as a community family practitioner, would *H pylori* be on your radar with a patient like this?

**A positive result with serologic testing still leaves me with no idea whether to treat or not.**
***—Dr. David Wyatt***

**Dr. David Wyatt:** Definitely. For a patient with dyspepsia symptoms like these, *H pylori* would certainly be among the things I'd consider, and this type of presentation is very common in my practice.

**Dr. Falk:** How would you approach this patient from a diagnostic perspective?

**Dr. Wyatt:** I would begin by assessing the likelihood that his symptoms, which are dyspeptic symptoms, are due to peptic ulcer. Since peptic ulcer seems like a possibility, I would assess his risk of *H pylori* infection by considering his race and ethnicity, whether he is an immigrant and his country of origin, where he lives—questions that get at the epidemiologic risk factors for *H pylori* infection. If his symptoms did not suggest peptic ulcer disease and he was not a member of a demographic group with an elevated risk for *H pylori* (see **Table 2** on page S11)—say, a middle-class white male whose family had been in the United States for generations—I might be less likely to test for *H pylori* right away, particularly if there were no family history of gastric cancer.

**Dr. Falk:** Let's say his symptoms are consistent with uncomplicated dyspepsia and the probability of *H pylori* infection seems reasonable, so that testing is indicated. Which testing method are you going to use?

**Dr. Wyatt:** I would go straight for one of the tests for active infection, either the urea breath test or the stool antigen test, for all the reasons spelled out in the overview presentations that preceded this. A serologic test would not be an option because it tests only for antibody to *H pylori*. A positive result with serology does not tell me whether the patient has current infection or had a past infection that is now cured; I would still be left with no idea whether to treat or not.

With one of the active tests, a positive result would give me a high level of confidence that treatment to eradicate *H pylori* was appropriate. Because the urea breath test and the stool antigen test are essentially equal in performance, my decision between them would be based on their availability in my area, their availability and cost under the patient's health plan, and, if both were available, the patient's preference after hearing about each test and how it is performed.

**Dr. Falk:** Mark, you also see patients in the primary care setting. Let's say you've tested this patient with an active test, got a positive result, and prescribed treatment for *H pylori* eradication. How do you manage him from that point?

**Dr. Mark Fendrick:** I like to say that the active tests should be sold in pairs—one for making

DISCLOSURES: ***Gary Falk, MD,*** *has served as a consultant to AstraZeneca Pharmaceuticals and Meridian Bioscience.* ***Brian Fennerty, MD,*** *has served as a consultant to AstraZeneca Pharmaceuticals, Eisai, Meridian Bioscience, Santarus, and TAP Pharmaceutical Products.* ***Ben Gold, MD,*** *has served as a consultant to AstraZeneca Pharmaceuticals, Meridian Bioscience, Meretek Diagnostics, and TAP Pharmaceutical Products.* ***Nimish Vakil, MD,*** *has received grant/research support from AstraZeneca Pharmaceuticals, Medtronic, Novartis, and Pfizer; has served as a consultant to AstraZeneca, Medtronic, Meridian Bioscience, and Novartis; and is on the speakers' bureaus of AstraZeneca, Novartis, and TAP Pharmaceutical Products.* ***Leonard Ehrlich, MD, A. Mark Fendrick, MD, Derek van Amerongen, MD,*** *and* ***David Wyatt, MD,*** *have served as consultants to Meridian Bioscience.*

the initial diagnosis and, if positive, the other for testing to confirm eradication after treatment. That way retesting wouldn't even be left to choice. Seriously, though, this patient should be retested after treatment to verify whether the infection has been cured. We've seen from studies that patients demand confirmation of eradication and are willing to pay for it,[1] and there is real clinical value to retesting because of the lack of a guaranteed cure even with optimal therapy. And of course there are some patients in whom retesting is a no-brainer, like those with a family history of gastric cancer or a prior symptomatic documented ulcer.

**Dr. Falk:** Or patients with a bleeding ulcer. Yet post-treatment testing is still often not done. Nimish, what do practice guidelines say on this score?

**Dr. Nimish Vakil:** The Maastricht 2 Consensus Report from 2000[2] recommends that retesting should be offered to all patients after *H pylori* eradication therapy, and the updated Maastricht report that will be issued in 2005 is likely to recommend post-treatment testing for all patients even more strongly. At the time you prescribe therapy, you should tell the patient, "We will bring you back after the treatment is completed and test you again to make sure the infection is gone," and you should schedule the patient's post-treatment test at that time.

**Dr. Falk:** And it goes without saying that the post-treatment test should not be serology. At what point should you do the post-treatment test?

**Dr. Vakil:** It should be done 4 weeks out from the completion of therapy, and when the patient has been off proton pump inhibitor (PPI) therapy for at least 2 weeks, since recent PPI use can cause false-negative results with either active test. Histamine$_2$-receptor blockers can be used as antisecretory salvage therapy during this time if necessary, but ideally you should have the patient off all acid suppressants.

**Dr. Brian Fennerty:** The beauty of that approach is that taking them off all acid suppressants might address the question of whether you are really treating reflux disease.

**Dr. Fendrick:** One more key point is that there is no guarantee that this patient's symptoms will go away even if his infection is cured. *H pylori* eradication does not necessarily equal symptom resolution. Patients must clearly understand that up front and understand that there is value in eradicating the bacterium even without symptom resolution. Eradication with persistence of symptoms is not a failed outcome.

## WHY CARE ABOUT FALSE POSITIVES?

**Dr. Falk:** Let me back up and focus on David's rationale for choosing active testing over serology. The rationale was essentially that serology is inferior to active testing in sensitivity and especially specificity, which produces a lot of false positives in a low-prevalence setting. If I'm the average clinician, how much is that going to resonate with me? After all, if I have a test with 80% sensitivity and 80% specificity, I'm apt to think that's not too bad, especially if the biggest concern is getting false positives. My biggest worry is about missing a diagnosis—getting a false negative—so why should I care about false positives?

**Dr. Fendrick:** On the false-negative question, the specter of false negatives should loom somewhat less large as *H pylori* prevalence declines, and most US physicians now practice in fairly low-prevalence settings.

But the real reason to care about false positives is because of the patients whom I call TPNI—"true positive for antibody, not infected." With an antibody test like serology, the "false-positive" results include both actual false positives for active infection and these TPNI results. When people hear "false positive," they think a test is not doing what it is supposed to do. But in actuality, when serology produces TPNI results it is doing exactly what it is supposed to do—detect antibodies. So even when serology is doing its job well, it is not doing well for the patient.

The result, as we've discussed, is that you end up treating a lot of people who aren't actively infected, which wastes a lot of resources, inconveniences a lot of patients, and contributes to antibiotic resistance.

**Dr. Fennerty:** I think a helpful analogy is to hepatitis B—we would never get a hepatitis B surface antibody and assume that it is an active hepatitis infection. Physicians understand that.

**Schedule the post-treatment test to confirm *H pylori* cure at the same time you prescribe eradication therapy.**
***—Dr. Nimish Vakil***

## INDIVIDUAL PATIENTS TRANSCEND PREVALENCE

**Dr. Vakil:** When we speak of low-prevalence settings, as we have just now, it's important not to give the impression that *H pylori* prevalence is a yes/no phenomenon. Given the melting pot that we have in the United States, there are very few physicians who have a truly low-prevalence situation in all patients at all times.

In Wisconsin, where I practice, we have a low-prevalence population overall, and for our white middle-class patients born in suburban or rural parts of the state, you can argue that *H pylori* is a low-prevalence matter to the point of being almost a nonissue. But no physician in Wisconsin sees only patients like this, except in remote areas. In all of Wisconsin's cities we have large Hmong populations, we have immigrants from Mexico and South America, we have immigrants from Eastern Europe and Russia. The *H pylori* prevalence in these groups is 80% to 90%. So while there are some portions of the community for whom *H pylori* is almost a nonissue, there are other portions for whom it is a huge issue and whose needs are not being met. If a patient who moved here from Mexico walks into your office, you cannot apply the dynamics of a low-prevalence population to him.

**Patients must be told that *H pylori* eradication does not necessarily mean symptom resolution.**
***—Dr. Mark Fendrick***

**Dr. Falk:** You are absolutely right—everyone is being lumped together when the risk is quite different in different populations. Physicians need to realize how much their assessment of the likelihood of infection must be individualized (see **Table 2** on page S11).

**Dr. Vakil:** Many physicians recognize that Hispanics are at increased risk, but they don't realize the degree of risk for many other groups of recent immigrants. For example, the older epidemiologic studies wouldn't suggest elevated risk for Eastern Europeans, but recent immigrants from Eastern Europe have quite a high prevalence, and they are the largest group of immigrants coming to certain parts of the United States.

**Dr. Ben Gold:** That type of demography-based risk information can be a valuable tool for a primary care physician who is evaluating a particular patient, especially as it relates to disease phenotype. I consistently see children adopted from Eastern Europe who have 90% infection rates by 5 years of age and typically have multi–drug-resistant strains of *H pylori*. The infection is associated with a lot of morbidity in these children. It's important for primary care physicians to realize that there are these epidemiologic pockets.

**Dr. Vakil:** Yes, and this idea applies generally to gastric cancer as well. For instance, South Americans who are infected with *H pylori* have about five to ten times the risk of developing gastric cancer as an *H pylori*–infected native white Wisconsinite does. And while I do not disagree with the point in your presentation, Brian, about the gaps in the current data on the *H pylori*/gastric cancer connection, if I were a South American who was infected with *H pylori*, I'd be a bit worried. So I think it's reasonable to test for the organism in patients with a family history of gastric cancer, particularly if they belong to a high-risk population like this or they request testing.

**Dr. Fennerty:** I agree. The problem is that in an adult population there is no evidence that we can change the risk of gastric cancer even if *H pylori* is detected and treated. We just need to be careful not to encourage widespread testing to look for gastric cancer risk in patients without these high-risk factors.

## IMPLICATIONS OF INCORRECT DIAGNOSTIC STRATEGIES

**Dr. Falk:** Before we go into some more focused areas of discussion, let's wrap up this discussion of *H pylori* testing in general by reviewing the specific implications of an incorrect diagnostic strategy. David, would you comment on the clinical implications of an incorrect strategy?

**Dr. Wyatt:** The most fundamental one is that you will inappropriately treat more patients who are not infected, which means putting patients through needless regimens of PPIs or histamine$_2$ blockers plus antibiotics. Because there is no infection for these treatments to address, the patient won't get symptom resolution, which will likely lead you to throw additional treatments at them or to order additional, and probably costly, diagnostic studies. Additional office visits will undoubtedly result. The cost inefficiencies of all of this are obvious. But there are also big costs in terms of patient inconvenience, patient dissatisfaction, and lost time—the wasting of all parties'

time and also a delay during which the patients' symptoms are not being properly addressed.

**Dr. Derek van Amerongen:** The effects on the patient are key. It seems clear to me, from a managed care perspective, that *H pylori* is not going to have a large cost impact on health care systems as a whole, but we need to be sensitive to the cost impact on the individual patient, in terms of out-of-pocket costs. As the patient works his or her way through the unnecessary treatment and then the additional testing to clarify what's really going on, the cost impact can be significant for a family trying to stretch its health care dollar. There also are emotional impacts for patients from being treated and not getting better, which undermines the credibility of the medical system, and we know that's already shaky these days.

**Dr. Falk:** Ben, would you summarize the biologic implications of an inappropriate diagnostic strategy and the resulting inappropriate therapy?

**Dr. Gold:** The most obvious implication is a burgeoning of antibiotic resistance, including multi–drug-resistant organisms, from the inappropriate and nonjudicious use of antibiotics. And it's not just among *H pylori*—other pathogens are being affected. We are seeing an increase over time in multi–drug-resistant and monotherapy-resistant strains of organisms in the United States, Canada, and Europe. Clarithromycin resistance has almost doubled in the last 7 years. Amoxicillin resistance is now being described. Tetracycline resistance, which 5 years ago was unreported, is now being described. Of course, there has been a strong push lately among many medical specialty groups to reduce inappropriate antibiotic use for these reasons.

The second implication is reduced efficacy of our treatments for *H pylori* infection, which is obviously related to the first. Eradication rates following therapy are no longer the proverbial 90%+ rates first reported but have fallen to around 75% or lower, owing to the increase in antibiotic resistance. This has implications on disease outcome as well as on transmission of the organism to yet-uninfected people.

**Dr. Vakil:** Plus, remember that most of the treatment studies are at least 5 or 6 years old, and resistance rates have risen since then. So the rates you mentioned are probably overoptimistic.

**Dr. Leonard Ehrlich:** From my experience in community office settings, I think there is a disconnect on the outpatient side, where there are many physicians who think that the treatment is still very effective and do not retest to check for cure. Despite our earlier discussion of this issue, the message about the need to retest and the high rate of therapeutic failure has not been well disseminated.

## SHOULD WE TEST FOR *H PYLORI* PRIOR TO NSAID THERAPY?

**Dr. Falk:** Let's change gears and consider a controversy that comes up a lot—whether we should test patients for *H pylori* prior to therapy with a nonsteroidal anti-inflammatory drug (NSAID). This question appears to involve two different settings—the NSAID-naïve patient and the chronic NSAID user. You touched on this in your presentation, Brian, but let's explore it a little more in this forum. Can you get us started?

**Dr. Fennerty:** There are three main issues. First, there are no conclusions to be drawn from US data, and the Asian and European data do not always correlate with US outcomes. Second, many of the global societies' recommendations that will be coming out soon will recommend testing and treating for *H pylori* in the naïve NSAID user who is starting therapy, based on the Asian and European data. That is not, however, the position of the American College of Gastroenterology or the American Gastroenterological Association. Third, there is no evidence that testing for *H pylori* is justified in chronic NSAID users, which raises the specter of inevitable confusion if you advocate testing for naïve NSAID users but not for chronic users. Moreover, few patients are actually starting NSAIDs for the first time but are rather switching from one NSAID to another or from a COX-2 inhibitor to an NSAID, which breeds further confusion.

**You cannot apply the dynamics of a low-prevalence population to a patient who moved here from Mexico.**
***—Dr. Nimish Vakil***

**Dr. Fendrick:** *H pylori* and NSAID use are clearly independent risk factors for ulcer. One can argue that, as in other diseases, you should intervene on as many levels, via as many mechanisms, as you can, at least in patients who are at highest risk for ulcer. From that standpoint, testing for *H pylori* before starting NSAID therapy in such patients would probably be good practice, but I agree with Brian

that the evidence is simply not conclusive.

**Dr. Vakil:** This is a difficult question because if you make a blanket recommendation for it, then you are looking at mass testing of all the geriatric patients in their 80s and 90s who are taking NSAIDs, and the data are too weak to recommend that. At the same time, I agree with Mark that it would seem to be a no-brainer in patients at high risk for ulcer, although that tends to be geriatric patients. Further clarification is awaited, and eradication should be considered on a case-by-case basis.

**Dr. Falk:** The life of a primary care physician is complicated enough, and since we all agree that data are currently insufficient to make a clear, evidence-based recommendation, I don't think anyone should be hunting for *H pylori* before they give an NSAID or before they suggest prophylaxis with aspirin. Exceptions would be if the patient has a history of ulcer disease or any other clear-cut risk for *H pylori* infection, such as family history of gastric cancer.

**Dr. Fennerty:** One thing that we can separate out is that there are no data suggesting that testing for *H pylori* is an effective strategy in the aspirin user. That is not even controversial at this point.

**Dr. Falk:** I agree, but for NSAID users I think it is safe to say that right now we just don't know what to do in these patients. This is an evolving area, however, and clearer data are sure to emerge.

**Treating patients without active infection promotes antibiotic resistance among both *H pylori* and other pathogens.**
***—Dr. Ben Gold***

## *H PYLORI* IN PEDIATRIC PATIENTS

**Dr. Falk:** Ben, you specialize in pediatric gastroenterology. Can you give us an overview of considerations for the diagnosis of *H pylori* infection in pediatric patients?

**Dr. Gold:** The epidemiology of *H pylori* infection and the diseases with which it seems to be associated are broadly similar in children and adults. Because most people acquire the organism in childhood, the epidemiology in children is especially important. It's notable that the prevalence of the organism in US children 6 to 19 years of age fell from 25% in the 1988–1991 National Health and Nutrition Examination Survey (NHANES) to 11% in the 1999–2000 NHANES. The prevalence among non-Hispanic white children in the 1999–2000 survey was a mere 5%.[3]

Three consensus guidelines have been published on *H pylori* infection in children and adolescents,[4–6] and the conclusions I will share are drawn from these guidelines along with the Maastricht 2 Consensus Report.[2] There currently are no recommended indications for noninvasive testing for *H pylori* infection in pediatric patients in the primary care setting, at least in the United States (in Europe, the recommended approach may differ). Specifically, testing is not recommended in asymptomatic children or in children without documented ulcer. Testing should be reserved for children with endoscopically documented duodenal or gastric ulcers and therefore can be done with an invasive test in conjunction with endoscopy. Recurrent abdominal pain or nonulcer dyspepsia is not a sufficient indication for screening children at this time.

**Dr. Fendrick:** So you're saying that primary care physicians shouldn't test for *H pylori* in children, that testing shouldn't be considered until the child has reached a point where he or she will have been referred to a gastroenterologist?

**Dr. Gold:** Based on the best available evidence, that's correct. At the specialist level, there are other indications for testing in children, such as following treatment of documented infection or if there is pathologic evidence of mucosa-associated lymphoid tissue (MALT) lymphoma. Screening also can be considered in children with a family history of gastric cancer in a first-degree relative or in children with recurrent peptic ulcer disease, although these uses are not yet endorsed by guidelines. The noninvasive tests for active infection (urea breath test and stool antigen test) may be considered in these settings and for confirmatory testing after treatment, as their characteristics are similar in children and adults. However, use of these noninvasive tests is not universally recommended by current pediatric guidelines. As in adults, current serologic tests are unreliable and not recommended for use in children.

## THE ECONOMICS OF INCORRECT DIAGNOSTIC STRATEGIES: DO PAYERS GET IT?

**Dr. Falk:** We've touched on some of the economic implications of doing things right versus doing things wrong. I'd like to explore the economic implications of testing strategies a

little more fully. Derek, from your vantage point as chief medical officer of a large health plan, how do payers look at testing for a condition like *H pylori* infection?

**Dr. van Amerongen:** Payers see the costs of testing as far more than the cost of the test itself. There's the cost at the site of service—is the test done in the primary care physician's office, as noninvasive tests can be, or in a specialist's office? There's also the cost of false negatives, which is tremendously important because it means missing the disease, which can lead down false diagnostic paths, carries additional costs, and represents a missed opportunity for avoiding worse disease later. From an employer perspective, false negatives represent a missed opportunity to improve the patient's functionality and productivity.

Then there is the cost of false positives, which in the case of *H pylori* includes the cost of unneeded and inappropriate antisecretory and antibiotic therapy, as well as the cost of repeat testing to confirm eradication of an organism that wasn't there to begin with. The payer is also sensitive to out-of-pocket costs to the patient, which can be substantial in the case of false-positive or false-negative results, as I said earlier.

**Dr. Falk:** What are some general principles by which payers evaluate testing strategies?

**Dr. van Amerongen:** First, testing should adhere strictly to guidelines and reflect the best science. Second, the test should be readily accessible; it does no good to endorse a test that no one can get. Third, the implications of the test must stand up to the increasing patient scrutiny that comes with growing patient cost-sharing. Patients are increasingly going to ask, "What is the cost of this test?" and "What will we do next after this test is done?" The latter question leads to the final principle, which is that the test must be clearly integrated with effective therapy. If a test is not going to potentially change what you do, you should never use it.

Based on our discussion today, active testing for *H pylori* satisfies all of these principles rather well, with the possible exception of ready accessibility, which I assume we will be discussing later.

**Dr. Vakil:** Derek, you represent one health plan. How do you respond to concerns that, despite all we have discussed, some managed care organizations might still look at $10 for serology and $100 for an active test and say, "We're going to use the $10 test, at least up front"? I've encountered managed care plans that still put out algorithms on test and treat that recommend a sequential testing strategy that calls for low-cost serologic testing up front.

**Dr. van Amerongen:** That represents a misunderstanding of what managed care is all about. From day one, managed care has promoted adherence to national expert protocols and a rational approach to care. Payers need to focus on the ultimate goal, which is to diagnose people accurately and get them the test or therapy that is most effective for their problem. It's short-sighted to say, "Let's use the cheapest test even though it doesn't work." The smartest thing is to cut to the chase, go to the first-line approach first, which is why they call it first-line, and use the test or therapy that is most likely to get the best outcome. If you tell employers or consumers or payers that this test costs X but it leads to the best outcomes, the response typically will be, "Then that's what it costs."

**Dr. Fendrick:** The most expensive test is the one that doesn't work.

**Dr. Ehrlich:** I agree, and my experience is consistent with Derek's. In the managed care companies where I worked, it was always "the most appropriate test, the most appropriate setting," and so on. When we did continuous quality improvement initiatives at those companies, we would bring in experts to present to us, and then we would develop a guideline based on that expert opinion and disseminate it to our providers.

I think that's the approach that's needed now for *H pylori* testing. Wherever sequential testing with serology first is still being done, it has to be abandoned once and for all. For companies that manage active testing under prior authorization, they need to be reeducated to buy into active testing more fully. Based on what I've heard today, I think the evidence is solid and the message is pretty simple—specificity is not good enough with serology, patients are being misdiagnosed, drug resistance is rising. These messages will resonate with the employers Derek mentioned who are asking about both value and quality.

**We don't yet know what to recommend about testing for *H pylori* in NSAID users, but clearer data will emerge.**
***—Dr. Gary Falk***

**Dr. Vakil:** I agree that you can build a clear case that managed care organizations should reevaluate their dyspepsia management strategies. The timing is good, because an updated dyspepsia guideline from the American Gastroenterological Association is coming out later in 2005, and it can serve to bolster efforts to convince health plans and educate their providers.

**Dr. Fennerty:** Before we leave this economic discussion, I'd like to say that I'm glad it didn't get too caught up in the issue of cost-effectiveness or cost savings. Ultimately, active testing for *H pylori* is not an issue of cost; it's an issue of best medicine. It's a matter of the accurate diagnosis of an infectious disease so that you can employ a specific treatment for that disease. And testing for active infection blows away serologic testing—that's the real issue.

## HOW DO WE BREAK THE SEROLOGY REFLEX?

**Dr. Falk:** Nimish, you've been writing and speaking on this subject for years. Why is it such a huge challenge to break physicians, be they primary care doctors or gastroenterologists, of the serologic testing reflex? It seems like it shouldn't be so hard, since we are not talking about huge expenses here or a highly controversial or emotion-laden clinical issue.

**Any health plans that manage active testing under prior authorization need to rethink that practice.**
***—Dr. Leonard Ehrlich***

**Dr. Vakil:** Two things happened at the same time. Just as we began to change our thinking about testing and treatment, general interest in the whole *H pylori* issue started to ebb and the number of conferences, meetings, and discussions suddenly dropped off. And so the last message that primary care physicians were left with was test and treat, based on Mark's original work, which correctly told them that this is what you should be doing. And at that time, which was about 10 years ago, serology was *the* noninvasive testing option. That was before the noninvasive active tests were marketed and before the prevalence had changed so much.

**Dr. Falk:** So what can be done now to break the serology habit?

**Dr. Vakil:** I think there are two simultaneous components. One is education, and the second is access, and they are interwoven because when you educate physicians about this, if they don't have immediate access to one of the active tests, they can't implement what they have learned. And neither the urea breath test nor the stool antigen test is readily available right now to the average physician in most parts of the country.

The reason physicians tend to incorporate new drugs into their practice is that as soon as they get educated about a drug, they get samples of the drug that they can try. If a physician hears some expert speak at a conference about these highly accurate active tests for *H pylori*, she is likely to go back home, call her lab, and inquire about the active tests. If she's told that they don't have the tests, her interest and openness is likely to end there.

Of course, this is the responsibility of the manufacturers of the tests for active infection. There have been different roadblocks to access in the past, including contracting issues with health plans, reimbursement rates, and diagnostic coding and paperwork issues. In different regions of the country there are different access hurdles. For example, in Wisconsin, where I practice, it is very difficult to get reimbursed for the urea breath test. But by increasing the availability of both tests, you solve that problem. There are signs that the manufacturers' efforts to do this may be increasing. We can hope so, because without good access, education is really undermined.

**Dr. Falk:** Let's just suppose access is no longer a problem. How do you educate physicians in today's climate of declining educational dollars and the lack of a therapeutic interest that's pushing this issue? Let's go around the table with this.

**Dr. Vakil:** No single event ever changes physicians' practices. The education needs to be a repetitive, iterative process in which physicians are reached by different modalities saying the same thing.

**Dr. Gold:** I agree, and the education needs to be data-driven to make them rethink their process, and ideally supported by guidelines in which a medical society's imprimatur provides further validation that this is the way to go.

**Dr. Vakil:** Fortunately, that will be coming later in 2005 in the form of the updated American Gastroenterological Association guideline on dyspepsia and an American College of Gastroenterology guideline on the same subject.

**Dr. Wyatt:** And physicians should be hearing the same thing from their managed care organizations and health networks as well,

telling them, "Look, we no longer support the serologic testing strategy." It's absolutely got to be a multiphase, repetitive effort.

**Dr. van Amerongen:** Disseminating guidelines is important, but the literature on their success is disheartening. I think one way to get change to happen more quickly is to empower consumers, to get them to engage in a much more meaningful discussion with their physicians about their health and about testing and treatment that they may or may not need. When a physician has even a handful of patients come and ask about a particular issue, that physician will begin to change his or her practice. And studies show that when patients actively engage their physicians, care decisions change—invariably for the better.

**Dr. Ehrlich:** I think the key points have been covered. I would add that I'd like to see what the gastroenterologists are doing about this issue nationally. Frankly, in the hospitals with which I have been associated I have not seen active testing being done by gastroenterologists, let alone by primary care physicians. Also, I think it would be interesting to try to convince managed care organizations to require prior authorization before blood serology could be ordered for *H pylori* testing, and to make the tests for active infection available without prior authorization.

**Dr. Fennerty:** While I love that idea, Len, it would cost more to implement that plan than you'd gain from any cost savings, so this will always fall below the radar screen of managed care decision-makers.

**Dr. Falk:** Mark, you get the last word.

**Dr. Fendrick:** Actually, the way to get managed care organizations and primary care physicians to adopt a practice is to make it a HEDIS (Health Plan Employer Data and Information Set) measure for National Committee for Quality Assurance accreditation. Unfortunately, given the smaller scale of this issue and the declining prevalence of *H pylori*, I'm not sure we'll ever get managed care medical directors to devote attention to manipulating the utilization of these tests in an important way. If physicians want active tests enough, they'll find a way to get them to be more available and accepted.

On the question of the serology reflex, I am somewhat optimistic that if the suggetions that have been offered here come to pass, we can break this thing. The literature on the "disadoption" of bad practices is unbelievably poor with the rare exception of when you have something that's better to take the place of the practice you want to disadopt. In this case we clearly do. But this is where the question of access comes in, because Nimish's point about physicians' ability to try out the active tests soon after learning about them is crucial. Let's hope for the best on the access front, because I am optimistic that we will build on this effort and do the right things on the education front.

**Ultimately, active testing for *H pylori* is not an issue of cost but an issue of best medicine.**
***—Dr. Brian Fennerty***

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