Clinical Roundtable Monograph

Gastroenterology & Hepatology July 2014

Clinical Rationale for Confirmation Testing After Treatment of Helicobacter pylori Infection: Implications of Rising Antibiotic Resistance

Moderator

Colin W. Howden, MD
Professor of Medicine
Division of Gastroenterology and Hepatology
Northwestern University Feinberg School of Medicine
Chicago, Illinois

Discussants

William D. Chey, MD
Professor of Medicine
Division of Gastroenterology
Director, GI Physiology Laboratory
Co-Director, Michigan Bowel Control Program
University of Michigan Health System
Ann Arbor, Michigan

Nimish B. Vakil, MD
Clinical Professor of Medicine
University of Wisconsin School of Medicine and Public Health
Madison, Wisconsin

Drs Howden, Chey, and Vakil are paid consultants of Otsuka America Pharmaceutical, Inc.

Supported through funding from Otsuka America Pharmaceutical, Inc., manufacturer and marketer of the BreathTek® UBT for *H pylori*.

Abstract

Helicobacter pylori (H pylori) infection is one of the most common chronic bacterial infections worldwide. International guidelines recommend *H pylori* eradication in several scenarios: patients with peptic ulcer disease, patients who have had endoscopic resection of early gastric cancer, and patients with a gastric mucosa-associated lymphoid tissue lymphoma (MALToma). There is variability among the guidelines for other conditions. Treatment options for *H pylori* infection include triple, quadruple, and sequential therapy. Ideally, patients in whom previous eradication attempts failed and those suspected to have resistant strains should be considered for antimicrobial sensitivity testing, which requires culture of gastric mucosal biopsies; such testing, however, has limited availability in the United States. Resistance rates vary by location depending on local antibiotic usage rates. As such, the success rates associated with different regimens vary throughout the world. Many patients with *H pylori* infection are asymptomatic, whereas others are diagnosed with the infection during evaluation of dyspeptic symptoms or following a diagnosis of peptic ulcer. Symptoms may not be an accurate indicator of treatment success. The American College of Gastroenterology (ACG) endorses the carbon 13-labeled urea breath test (^{13}C-UBT) as the most reliable test to confirm *H pylori* eradication. This clinical roundtable monograph begins with an overview of *H pylori* infection and then discusses treatment, antibiotic resistance, management of patients with antibiotic resistance, and posttreatment testing, with a focus on the ACG guidelines.

GASTROENTEROLOGY & HEPATOLOGY
The Independent Peer-Reviewed Journal

Table of Contents

Indexed through the National Library of Medicine (PubMed/Medline), PubMed Central (PMC), and EMBASE

Disclaimer

This clinical roundtable and its subsequent monograph were entirely funded by Otsuka America Pharmaceutical, Inc., manufacturer and marketer of the BreathTek® UBT for *Helicobacter pylori (H. pylori)*. Drs Howden, Chey, and Vakil were also paid by Otsuka America Pharmaceutical, Inc. for participation in the roundtable and development of this monograph and are promotional speakers for BreathTek® UBT for the *H. pylori* Kit. Editorial support for the monograph was provided by Gastro-Hep Communications, Inc., which also received payment from Otsuka America Pharmaceutical, Inc. Otsuka America Pharmaceutical, Inc. is the distributor of the BreathTek® UBT for *H. pylori* Kit.

Gastro-Hep Communications, Inc.'s support of this monograph does not imply its agreement with the views expressed herein. Every effort has been made to ensure that drug and medical device usage, important safety information, and other information are presented accurately and completely; however, the ultimate responsibility for prescribing and use of any diagnostic test for *H. pylori* rests with the prescribing physician. Gastro-Hep Communications, Inc. and the participants shall not be held responsible for errors or for any consequences arising from the use of information contained herein. Readers are strongly urged to consult any relevant primary literature. No claims or endorsements are made for any drug, compound, or medical device at present under clinical investigation.

July 2014 05US14EBP1226

Overview of *Helicobacter pylori*

William D. Chey, MD
Professor of Medicine
Division of Gastroenterology
Director, GI Physiology Laboratory
Co-Director, Michigan Bowel Control Program
University of Michigan Health System
Ann Arbor, Michigan

Helicobacter pylori (*H pylori*) is a common chronic bacterial infection that may have originated in East Africa approximately 58,000 years ago.[1] The bacterium was originally known as *Campylobacter pyloridis*. In 1984, Marshall and Warren identified a clinical association between infection with *H pylori* and the development of chronic type B gastritis and dyspeptic symptoms.[2] In 1990, investigators identified an association between *H pylori* and peptic ulcer disease by demonstrating that the eradication of *H pylori* infection cures peptic ulcer disease and prevents recurrence.[3]

Epidemiology

H pylori is a spiral-shaped, gram-negative bacteria that infects approximately half of people throughout the world's population.[4,5] This infection tends to be more common in developing countries than in developed countries. The prevalence rate of *H pylori* infection in the United States and Canada is approximately 30%, whereas at least 70% of adults in Asia, Africa, Central America, and South America are infected with *H pylori*.[5] The prevalence of infection can vary within developed countries according to differences in socioeconomic living conditions (Figure 1); an increased prevalence of *H pylori* is associated with low socioeconomic status.[6]

Most people with *H pylori* become infected during childhood.[6] In developed nations, primary acquisition occurs in less than 1% of adults each year.[4,6] Although infection most often occurs in children, seropositivity increases with age. The difference in age-related prevalence observed in many developed countries, such as the United States, has been attributed to a birth cohort effect. In developed countries, the current generation of native-born young people is less likely to become infected than previous generations. In the United States and other developed countries, one of the most abundant reservoirs of *H pylori* are immigrants from less-developed countries, such as those in Eastern Europe, Africa, parts of Latin America, and Southeast Asia.

Survival and Transmission

H pylori has developed a unique ecologic niche. It can survive within the extremely harsh environment of the human stomach, which is highly acidic.[4] Once ingested, the organism's flagella allows it to be motile and to move quickly to the gastric mucus gel overlying the epithelium. *H pylori* bores into the gastric mucus gel and is thereby protected from the harsh acidic environment of the gastric lumen.[4] Another feature of *H pylori* is that it has very strong urease activity, which allows it to manipulate the surrounding microenvironment to increase survival in the human stomach.[4] This urease activity can be leveraged for the purposes of making a diagnosis.

The best documented route of transmission for *H pylori* is fecal-oral, but there are also reports of gastric-oral and oral-oral infection.[6,7] For example, there are several cases of infected infants and children regurgitating gastric contents and infecting other infants and children, giving credence to the gastric-oral transmission route.[7] Evidence for oral-oral transmission comes from several studies demonstrating that *H pylori* has been isolated from saliva, subgingival biofilm, and dental plaque.[7] This route of transmission remains controversial and is unlikely to be the principle source of *H pylori* transmission.

There are a number of risk factors for *H pylori* transmission. The risk of contracting *H pylori* is increased by the presence of infected family members, including siblings.[8] As was previously mentioned, low socioeconomic status is associated with an increased risk for *H pylori* infection.[7] Crowded living conditions, poor sanitation, and poor hygiene are also risk factors for transmission.[7]

Clinical Consequences of Infection

Environmental factors as well as host- and organism-specific characteristics will determine the natural history of the infection and consequent pathologic and clinical sequelae. Most people (>70%) who are infected with *H pylori* are asymptomatic and unaware that they have the

July 2014 05US14EBP1226

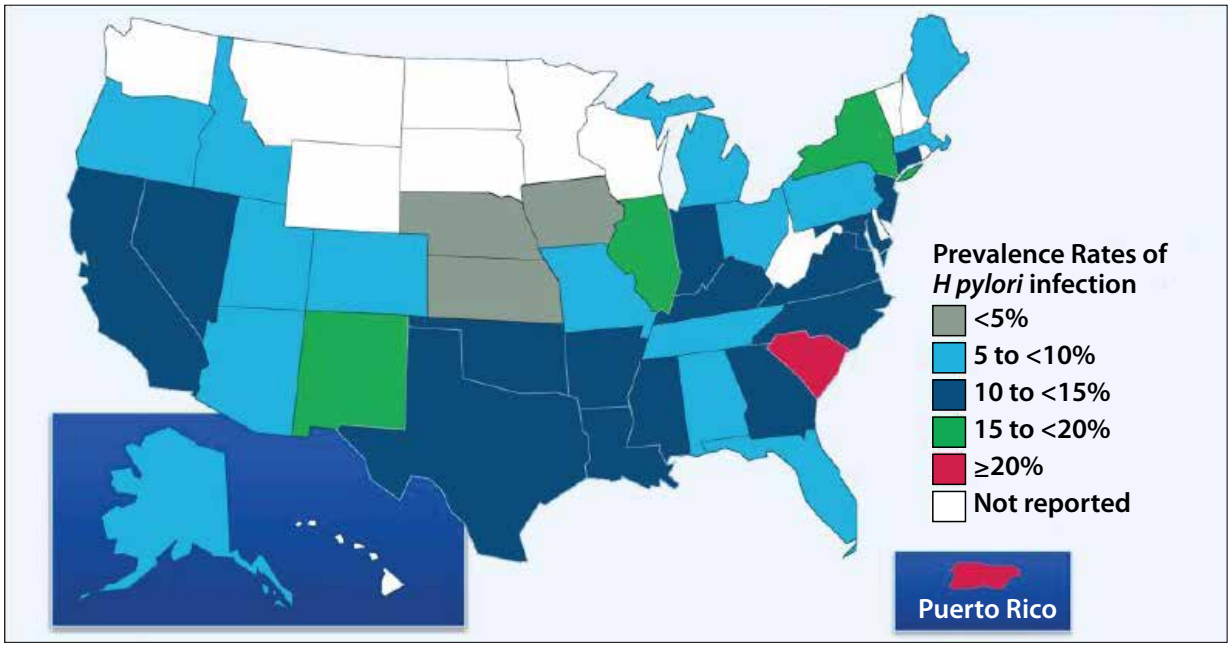


Figure 1. The prevalence rates of *Helicobacter pylori* (*H pylori*) in the United States. Data are based on 78,985 gastric biopsy specimens obtained from private, community-based endoscopic centers or multispecialty surgery centers.

Adapted from Sonnenberg A et al. *Gastroenterology*. 2010;139(6):1894-1901.[37]

infection.[7] Approximately 20% of infected patients will go on to develop any of a number of different diseases. The best characterized manifestations of *H pylori* infection are peptic ulcer disease and gastric neoplasms, including adenocarcinoma and mucosa-associated lymphoid tissue lymphoma (MALToma).[9] It is likely that these diseases develop as a result of the chronic inflammation that occurs from the interaction between the host, virulence factors associated with the particular strain of *H pylori,* and environmental factors, such as medications and diet.

Benefits of Treating H pylori Infection

There are consensus/guideline documents on the management of *H pylori* infection from several parts of the world. The American College of Gastroenterology (ACG) published guidelines in 2007.[9] An Asia-Pacific Consensus document was published in 2009.[10] Recommendations from the Maastricht/Florence Consensus conference were published in 2012.[11] All 3 documents make strong, unequivocal recommendations for treating *H pylori* in patients with peptic ulcer disease or gastric MALToma, and following endoscopic resection of early gastric cancer. The ACG guidelines and the Maastricht/Florence document endorse the eradication of *H pylori* in patients with uninvestigated dyspepsia when the background prevalence of infection exceeds 20%, whereas the Asia-Pacific Consensus does not.[9-11] The guidelines also differ in whether they recommend eradication of *H pylori* in patients with functional dyspepsia or patients taking nonsteroidal anti-inflammatory drugs (NSAIDs) or aspirin, and whether they recognize a potential association between *H pylori* infection and iron-deficiency anemia, idiopathic thrombocytopenic purpura, and B_{12} deficiency.[9-11] Table 1 outlines the recommendations from the ACG, the Asia-Pacific Consensus, and the Maastricht/Florence Consensus.

In the ACG guidelines, *H pylori* treatment is recommended in patients after endoscopic resection of early gastric cancer, with active peptic ulcer disease (gastric or duodenal ulcer), a confirmed history of peptic ulcer disease that was not previously treated for *H pylori*, low-grade gastric MALToma, or uninvestigated dyspepsia (if the prevalence of *H pylori* is >20%).[9] These clinical conditions have a well-established association with *H pylori* infection. In addition, there are several scenarios in which the diagnosis and treatment of *H pylori* are controversial, such as patients with functional dyspepsia, gastroesophageal reflux disease (GERD), or unexplained iron-deficiency anemia; those using NSAIDs; and those at higher risk of gastric cancer.[9]

Peptic Ulcer Disease

In a study of patients admitted to the hospital with upper gastrointestinal bleeding across 22 sites in the United States, approximately half of those with peptic ulcer disease were infected with *H pylori* (45.3%-49.6%) and approximately half were using NSAIDs or aspirin (52.9%-57.2%).[12] By far, *H pylori* and NSAIDs are the 2 most

July 2014 05US14EBP1226

Table 1. Indications for the Treatment of *Helicobacter pylori*

American College of Gastroenterology[9] (2007)	Maastricht/Florence Consensus Conference[11] (2012)	Asia-Pacific Consensus[10] (2009)
Established Indications	PUD	PUD
Active PUD	Gastric MALToma	MALToma
Confirmed history of PUD but not previously treated for *H pylori*	Following endoscopic resection of early gastric cancer	Atrophic gastritis
Gastric MALT lymphoma	Uninvestigated dyspepsia (if *H pylori* prevalence >20%)	Following resection of gastric cancer
Following endoscopic resection of early gastric cancer	Functional dyspepsia	First-degree relative with gastric cancer
Uninvestigated dyspepsia (if *H pylori* prevalence >20%)	Prior to use of NSAIDs in patients with a history of PUD	If desired by the patient (following full consultation with the physician)
Controversial Indications	Chronic NSAID or low-dose aspirin use	Functional dyspepsia
Functional dyspepsia	Chronic PPI use (>1 year)	NSAID-naive users
GERD	Unexplained iron deficiency, idiopathic thrombocytopenic purpura, or B_{12} deficiency	Prior to long-term aspirin use in patients with a high risk of PUD and PUD-related complications
Use of NSAIDs (especially for patients with a history of PUD or who are initiating NSAID therapy)	First-degree relative with gastric cancer	Long-term low-dose aspirin use in patients with a history of upper gastrointestinal bleeding or perforation
Unexplained iron deficiency	Severe pan-gastritis, corpus-predominant gastritis, or severe mucosal atrophy	Screening strategy in communities with a high incidence of gastric cancer
Populations at increased risk for gastric cancer	Chronic gastric inhibition lasting longer than 1 year	Unexplained iron deficiency or idiopathic thrombocytopenic purpura
	Environmental risk factors for gastric cancer (eg, heavy smoking or high exposure to dust, coal, quartz, cement, or quarry work)	

GERD, gastroesophageal reflux disease; MALToma, mucosa-associated lymphoid tissue lymphoma; NSAIDs, nonsteroidal anti-inflammatory drugs; PPI, proton pump inhibitor; PUD, peptic ulcer disease.

common causes of peptic ulcer disease in the United States.[9] In addition, many of the patients with *H pylori* infection are using NSAIDs or aspirin. Up to 25% of ulcers are idiopathic, meaning that patients have no evidence of *H pylori* infection or history of NSAID or aspirin use.[13] In those patients, the cause of ulcers is unclear. However, a subset of idiopathic ulcers are likely related to surreptitious or unwitting use of NSAIDs or aspirin.

Given that many duodenal ulcers and gastric ulcers are caused by *H pylori* infection,[14] eradication of *H pylori* could impact the natural history of *H pylori*–associated ulcers. A systematic review and economic analysis of 52 studies by Ford and colleagues convincingly demonstrated that patients with peptic ulcer disease—either duodenal ulcer or gastric ulcer—who were successfully eradicated of their *H pylori* infection had a substantially reduced risk of ulcer relapse compared with patients who were not treated or were unsuccessfully treated (Figure 2).[15] For duodenal ulcers, the relapse rates were 14% with eradication therapy vs 60% with an ulcer-healing drug (relative risk [RR] of ulcer recurring, 0.73 [95% CI, 0.42-1.25]) or no treatment (RR, 0.19 [95% CI, 0.15-0.26]). The number needed to treat was 2.5 (95% CI, 2-4). For gastric ulcers, the relapse rate was 12% for eradication therapy vs 45% for no treatment (RR, 0.31 [95% CI, 0.19-0.48]), and the number needed to treat was 3 (95% CI, 2.3-5).

A more recent study from Spain prospectively collected data from 1000 patients with peptic ulcers who were followed for at least 12 months.[16] The cohort was 75% male, 41% had a history of NSAID use, 69% had a duodenal ulcer, 27% had a gastric ulcer, and 4% had a pyloric ulcer. The recurrence of bleeding was very low in this study; the cumulative incidence of rebleeding was 0.5% (95% CI, 0.16%-1.16%), and the incidence rate was 0.15% per patient year of follow-up. In this study, *H pylori* eradication virtually eliminated the risk of ulcer rebleeding.

In summary, *H pylori* eradication significantly reduces the likelihood of duodenal and gastric ulcer recurrence and virtually eliminates the risk of ulcer rebleeding. It must be acknowledged, however, that a small proportion of patients develop ulcers even after *H pylori* infection is eradicated.

Gastric MALToma

Gastric MALToma is a clear and unequivocal indication for the eradication of *H pylori* infection. High-level evidence suggests that eradication of *H pylori* alters the natural

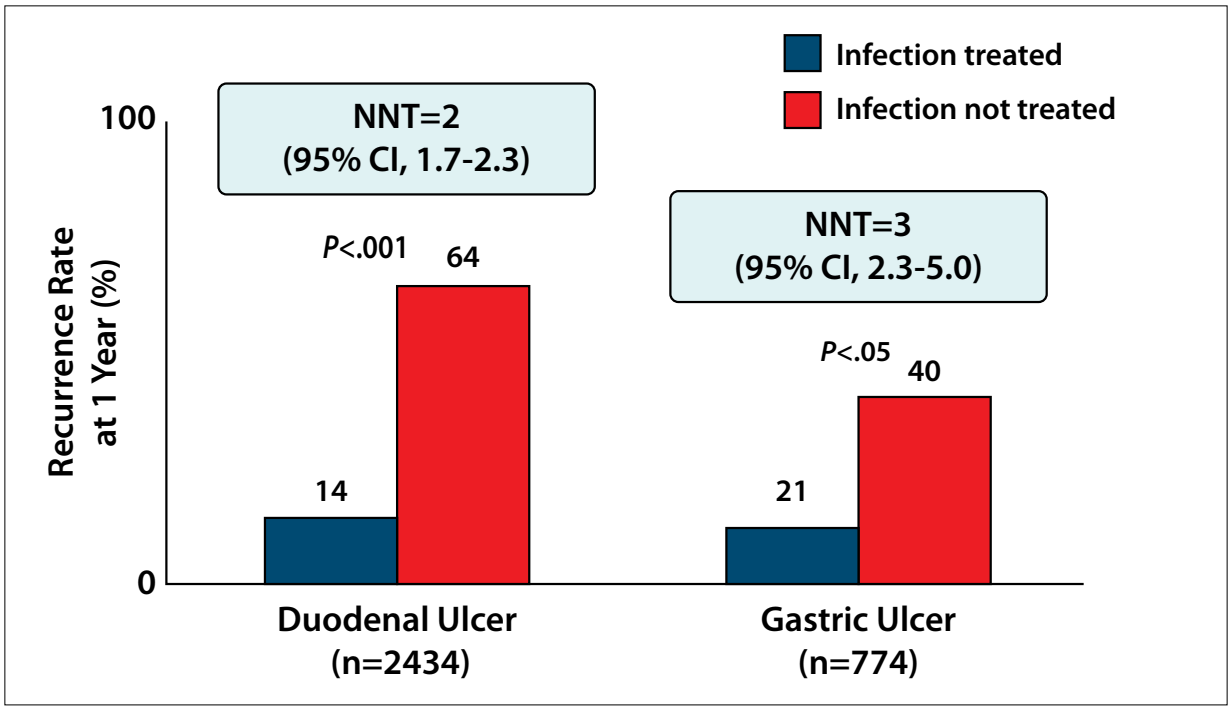


Figure 2. In a meta-analysis, patients with peptic ulcer disease who were successfully eradicated of their *Helicobacter pylori* infection had a substantially reduced risk of ulcer relapse compared with patients who were not treated or were unsuccessfully treated.

NNT, number needed to treat. Adapted from Ford AC et al. *Am J Gastroenterol.* 2004;99(9):1833-1855.[15]

history of gastric MALToma.[9,17] Eradicating *H pylori* in patients with gastric MALToma leads to tumor regression in 60% to 90% of successfully treated patients.[18] Many patients with low-grade MALToma are able to maintain their response for many years; the 5-year recurrence rate for low-grade MALToma is between 3% to 13%.[19] Even for high-grade MALToma, there are now data to suggest that remission rates as high as 64% might be seen, with very low levels of recurrence after successful eradication.[20] Therefore, both low-grade and high-grade MALToma may benefit from eradication of *H pylori* infection. As in patients with peptic ulcers, eradication of *H pylori* dramatically reduces the likelihood of recurrence of MALToma. As such, *H pylori* eradication is recommended in gastric MALToma.[9]

Dyspepsia

Patients with uninvestigated dyspepsia are defined as those with dyspeptic symptoms seen in primary care who have not undergone endoscopic evaluation. For these patients, the ACG guidelines recommend a "test and treat" approach as well as a trial with proton-pump inhibitor (PPI) therapy.[21] There is clear evidence to suggest that *H pylori* eradication is at least as good—and perhaps even better and more cost effective—than a short course of PPI therapy or no therapy at all.[21] The ACG and Maastricht/Florence Consensus guidelines recommend a noninvasive test (urea breath test, stool antigen test, or serology test) for *H pylori* infection.[11,21] If *H pylori* is identified in patients with uninvestigated dyspepsia, the infection should be eradicated with a course of antibiotics.[21]

Functional dyspepsia is a somewhat more controversial topic. A meta-analysis published by Moayyedi and colleagues as part of the Cochrane Collaboration[22] evaluated 17 high-quality randomized controlled trials including more than 3500 patients with functional dyspepsia. The analysis determined that there is a greater likelihood of symptom improvement with *H pylori* eradication compared with placebo. The therapeutic gain was small (7%), but statistically significant. Therefore, when all of the literature was aggregated, *H pylori* eradication was better for functional dyspepsia than doing nothing, but the majority of the patients exposed to this strategy did not improve.

GERD

GERD remains a complicated topic. Several studies suggest that there is an inverse relationship between *H pylori* infection and the prevalence of GERD, erosive esophagitis, and Barrett's esophagus.[9,23] The interplay between *H pylori* infection and GERD is not completely understood.[23] Eradication of *H pylori* can be associated with a spectrum of outcomes, including worsening of reflux-related symptoms.[23] For example, in a patient with *H pylori*–induced gastric atrophy,

treatment to eradicate the infection might allow for the restitution of the normal gastric epithelium which, in turn, could lead to increased gastric acid secretion. As a result, GERD and its potential complications may be unmasked. Conversely, in a small proportion of GERD patients, eradication of *H pylori* might improve symptoms.[23] At present, it is reasonable to conclude that GERD should not be considered a clear indication for testing and treating *H pylori*. However, treatment of *H pylori* for some other accepted indication should not be withheld for fear of worsening GERD.

NSAIDs

A meta-analysis from Vergara and associates[24] examined 5 studies that evaluated *H pylori* eradication in patients using NSAIDs. Interestingly, 2 of the studies were negative, and 3 of the studies were positive. In the aggregate analysis, 34 of 459 patients (7.4%) developed a peptic ulcer in the eradicated group vs 64 of 480 patients (13.3%) in the control group (OR, 0.43 [95% CI, 0.20-0.93]).[24] Overall, there appeared to be a benefit to eradicating *H pylori* infection in patients using NSAIDs.

H pylori and NSAIDs are both independent risk factors for peptic ulcer disease.[9] Patients with a peptic ulcer should undergo a diagnostic evaluation for *H pylori* infection, even if they are using NSAIDs or aspirin.[9] If *H pylori* infection is present, it should be eradicated, regardless of whether the patient is taking NSAIDs or aspirin.[9]

Ulcer risk may be additive, and perhaps synergistic, in patients with *H pylori* infection who are using NSAIDs or aspirin.[9,25] Curing *H pylori* may decrease ulcer risk, particularly in patients starting NSAID therapy for the first time.[25,26] However, *H pylori* eradication is not as effective as PPI maintenance in preventing recurrent ulcer bleeding.[26] Best practice dictates that all patients with an ulcer should be tested for *H pylori,* regardless of their NSAID status.

Gastric Adenocarcinoma

Compelling evidence suggests that *H pylori* prevalence is higher in patients with early gastric cancer.[9] This association was demonstrated in a meta-analysis conducted by Wang and colleagues in 2007.[27] Among the 2722 patients with early gastric cancer, *H pylori* prevalence was 87% vs 61% in the control subjects (OR, 3.4 [95% CI, 2.15-5.33]; *P*<.00001). In addition, 2 studies clearly demonstrated that eradication of *H pylori* decreases the chance that metachronous gastric cancer will develop after endoscopic resection of early gastric cancer.[28,29] In 2008, Fukase and colleagues reported results from a randomized controlled trial showing a significant reduction in the development of recurrent or metachronous gastric cancers in patients who received prophylactic eradication of *H pylori* after endoscopic resection of early gastric cancer (HR, 0.339 [95% CI, 0.157-0.729]; *P*<.003).[28] More recently, Bae and colleagues from Korea[29] published a retrospective analysis of patients who were *H pylori*–negative (n=340), *H pylori*–eradicated (n=485), or *H pylori*–uncured or –untreated (n=182).[29] Overall, *H pylori* cure after endoscopic resection of early gastric cancer reduced metachronous gastric cancer and increased recurrence-free survival. In a univariate analysis, the noneradicated group had a 2.7-fold increased likelihood of developing a metachronous gastric cancer when compared with the *H pylori*–negative group (*P*<.01). This finding held true even after correction for potential confounding factors. In addition, patients in the noneradicated group had a 2.0-fold increased likelihood of developing metachronous gastric cancer than the eradicated group (*P*=.01). This study has convincingly shown that in patients with endoscopically resected early gastric cancer—a fairly common scenario in the Far East—eradication of *H pylori* dramatically reduces the likelihood of developing a metachronous lesion.

Population screening and eradication of *H pylori* as a chemopreventive strategy for gastric cancer is more complicated. Three studies provide some insights.[30-32] The first was a prospective, randomized, placebo-controlled, population-based prevention study in China that enrolled more than 1600 healthy *H pylori* carriers randomized to either *H pylori* eradication or placebo.[30] Throughout the course of the 7.5-year follow-up, 18 new cases of gastric cancer were identified: 7 in the *H pylori* eradication treatment group and 11 in the placebo group (the difference was not statistically significant). In the subgroup analysis of patients with no precancerous lesions on presentation (absence of atrophy or intestinal metaplasia), no patients who received *H pylori* eradication treatment developed gastric cancer as opposed to 6 patients in the placebo group. These data suggest that there may be a point at which eradication of *H pylori* may not lead to benefits in terms of cancer chemoprevention.

The second study prospectively followed 96 patients from Japan who were successfully treated for *H pylori* infection.[31] The patients were grouped according to whether they had chronic gastritis without gastric intestinal metaplasia, chronic gastritis with gastric intestinal metaplasia, or gastric intestinal metaplasia with dysplasia/cancer in a different location of the stomach. Interestingly, intestinal metaplasia scores on histology did not change throughout the 4 years of the study.[31]

The concept that intestinal metaplasia does not appear to regress when *H pylori* infection is eradicated was recently confirmed by a third study of 5000 patients from Taiwan who received *H pylori* therapy to evaluate the impact on reducing gastric premalignant lesions.[32] There was a 77.2% (95% CI, 72.3%-81.2%) reduction in the incidence of gastric atrophy in the patients who were treated for *H pylori*, but no difference in the reduction of intestinal metaplasia. Among patients who received

treatment, there was a 25% reduction in the incidence of gastric cancer (95% CI, 0.372%-1.524%) and a 67.4% reduction (95% CI, 52.2%-77.8%) in the development of peptic ulcer disease. After eradication, the prevalence of endoscopic esophagitis increased from 13.7% to 27.3% (P<.001), which resulted in an annual incidence of 6% (95% CI 5.1%- 6.9%) per person-year. In an earlier study of patients with esophagitis, eradication of *H pylori* led to significant regression of gastric atrophy and intestinal metaplasia during follow-up (P<.05).[33] It is important to keep in mind that, overall, there has been no definitive evidence to support *H pylori* cure as a chemopreventive strategy in the general population.

Iron Deficiency

It has been suggested that *H pylori* infection may lead to alterations in iron absorption and occult blood loss through the development of erosive esophagitis or peptic ulcer disease.[9] It has also been suggested that *H pylori* may utilize iron itself.[34] An epidemiologic study in children suggested that *H pylori* infection may be associated with iron deficiency (OR, 2.6 [95% CI, 1.5-4.6]).[34] However, compelling data from clinical trials to prove cause and effect are lacking. One trial of children with iron deficiency and *H pylori* infection compared treatment with iron supplementation for 6 weeks (control group) vs iron supplementation plus a 2-week course of treatment for *H pylori* infection and another 2-week course of treatment if the infection had not resolved at 2 months after treatment initiation (intervention group).[34] The study identified no differences in the likelihood of iron deficiency at 2 months and 14 months between the groups.[35] It appears that eradication of *H pylori* infection does not necessarily correlate to a correction of the iron deficiency.

Idiopathic Thrombocytopenic Purpura

In 2007, Franchini and colleagues[36] conducted a meta-analysis to determine the effect of *H pylori* cure on idiopathic thrombocytopenic purpura. The investigators analyzed the data in several different ways—all treated vs not treated, cured vs not treated, cured vs treated but not cured—and identified an association between idiopathic thrombocytopenic purpura and *H pylori* infection (P<.0001 for each comparison). Both the Maastricht and the Asia-Pacific guidelines recommend testing for and eradicating *H pylori* in patients diagnosed with idiopathic thrombocytopenic purpura.[10,11]

Conclusion

H pylori infection remains one of the most common worldwide human infections. The prevalence is higher among minorities, immigrants from developing countries, and persons in crowded living conditions. Most people are infected as children via fecal-oral transmission, but there have been suggestions of gastric-oral and oral-oral transmission as well. The infection leads to no clinical sequelae in most cases. Clinical sequelae are a result of the complex interactions between host genetics, environmental factors, and virulence of the infecting organism.

International treatment guidelines universally endorse *H pylori* eradication in patients with peptic ulcer, following resection of early gastric cancer, and in patients with MALToma. There is broadening agreement for the treatment of *H pylori* infection in patients with uninvestigated and perhaps functional dyspepsia. *H pylori* eradication may be beneficial in patients initiating NSAID therapy or chronically using NSAIDs or aspirin. Epidemiologic studies suggest an inverse relationship between *H pylori* infection and erosive esophagitis and Barrett's esophagus. *H pylori* eradication reduces the incidence of gastric atrophy, but it may not influence the regression of intestinal metaplasia or change the natural history for the development of gastric adenocarcinoma. Patients with unexplained iron-deficiency anemia or idiopathic thrombocytopenic purpura might benefit from *H pylori* testing and treatment.

Acknowledgment

Dr Chey was paid by Otsuka America Pharmaceutical, Inc. for participation in this roundtable and development of this monograph. Dr Chey is a consultant for AstraZeneca, Perrigo, and Takeda.

References

1. Linz B, Balloux F, Moodley Y, et al. An African origin for the intimate association between humans and *Helicobacter pylori*. *Nature*. 2007;445(7):915-918.
2. Marshall BJ, Warren JR. Unidentified curved bacilli in the stomach of patients with gastritis and peptic ulceration. *Lancet*. 1984;1(8390):1311-1315.
3. Rauws EA, Tytgat GN. Cure of duodenal ulcer associated with eradication of *Helicobacter pylori*. *Lancet*. 1990;335(8700):1233-1235.
4. Kivi M, Tindberg Y. Helicobacter pylori occurrence and transmission: a family affair? *Scand J Infect Dis*. 2006;38(6-7):407-417.
5. Hunt RH, Xiao SD, Megraud F, et al; WGO-OMGE Global Guidelines Task Force. WGO Practice Guideline—*Helicobacter pylori* in developing countries. World Gastroenterology Organisation. http://www.worldgastroenterology.org/assets/downloads/en/pdf/guidelines/11_helicobacter_pylori_developing_countries_en.pdf. Posted August 2010. Accessed March 27, 2014.
6. Logan RP, Walker MM. ABC of the upper gastrointestinal tract: epidemiology and diagnosis of *Helicobacter pylori* infection. *BMJ*. 2001;323(7318):920-922.
7. Vale FF, Vítor JM. Transmission pathway of *Helicobacter pylori*: does food play a role in rural and urban areas? *Int J Food Microbiol*. 2010;138(1-2):1-12.
8. Garg PK, Perry S, Sanchez L, Parsonnet J. Concordance of *Helicobacter pylori* infection among children in extended-family homes. *Epidemiol Infect*. 2006;134(3):450-459.
9. Chey WD, Wong BC; Practice Parameters Committee of the American College of Gastroenterology. American College of Gastroenterology guideline on the management of *Helicobacter pylori* infection. *Am J Gastroenterol*. 2007;102(8):1808-1825.
10. Fock KM, Katelaris P, Sugano K, et al; Second Asia-Pacific Conference. Second Asia-Pacific Consensus Guidelines for *Helicobacter pylori* infection. *J Gastroenterol Hepatol*. 2009;24(10):1587-1600.
11. Malfertheiner P, Megraud F, O'Morain CA, et al; European Helicobacter Study Group. Management of *Helicobacter pylori* infection—the Maastricht IV/ Florence Consensus Report. *Gut*. 2012;61(5):646-664.

July 2014 05US14EBP1226

12. Jensen DM, Savides T, Sitzer M, et al. Demographics, risk factors, and outcomes of peptic ulcer hemorrhage in the united states: results of a large multicenter study. *Gastroenterology*. 2003;124(4):A17.
13. Iijima K, Kanno T, Koike T, Shimosegawa T. *Helicobacter pylori*-negative, non-steroidal anti-inflammatory drug: negative idiopathic ulcers in Asia. *World J Gastroenterol*. 2014;20:706-713.
14. *Helicobacter pylori*: Fact Sheet for Health Care Providers. Centers for Disease Control and Prevention. http://www.cdc.gov/ulcer/files/hpfacts.pdf. Updated July 1998. Accessed March 27, 2014.
15. Ford AC, Delaney BC, Forman D, Moayyedi P. Eradication therapy in *Helicobacter pylori* positive peptic ulcer disease: systematic review and economic analysis. *Am J Gastroenterol*. 2004;99(9):1833-1855.
16. Gisbert JP, Calvet X, Cosme A, et al; *H. pylori* Study Group of the Asociación Española de Gastroenterología (Spanish Gastroenterology Association). Long-term follow-up of 1,000 patients cured of *Helicobacter pylori* infection following an episode of peptic ulcer bleeding. *Am J Gastroenterol*. 2012;107(8):1197-1204.
17. Farinha P, Gascoyne RD. *Helicobacter pylori* and MALT lymphoma. *Gastroenterology*. 2005;128(6):1579-1605.
18. Montalban C, Norman F. Treatment of gastric mucosa-associated lymphoid tissue lymphoma: *Helicobacter pylori* eradication and beyond. *Expert Rev Anticancer Ther*. 2006;6(3):361-371.
19. Nakamura S, Matsumoto T, Suekane H, et al. Long-term clinical outcome of *Helicobacter pylori* eradication for gastric mucosa-associated lymphoid tissue lymphoma with a reference to second-line treatment. *Cancer*. 2005;104(3):532-540.
20. Chen LT, Lin JT, Tai JJ, et al. Long-term results of anti-Helicobacter pylori therapy in early-stage gastric high-grade transformed MALT lymphoma. *J Natl Cancer Inst*. 2005;97(18):1345-1353.
21. Talley NJ, Vakil NB, Moayyedi P. American Gastroenterological Association technical review on the evaluation of dyspepsia. *Gastroenterology*. 2005;129(5):1756-1780.
22. Moayyedi P, Soo S, Deeks J, et al. Eradication of *Helicobacter pylori* for non-ulcer dyspepsia. *Cochrane Database Syst Rev*. 2006:CD002096.
23. Pandolfino JE, Howden CW, Kahrilas PJ. *H. pylori* and GERD: is less more? *Am J Gastroenterol*. 2004;99(7):1222-1225.
24. Vergara M, Catalán M, Gisbert JP, Calvet X. Meta-analysis: role of *Helicobacter pylori* eradication in the prevention of peptic ulcer in NSAID users. *Aliment Pharmacol Ther*. 2005;21(12):1411-1418.
25. Chan FK, To KF, Wu JC, et al. Eradication of *Helicobacter pylori* and risk of peptic ulcers in patients starting long-term treatment with non-steroidal anti-inflammatory drugs: a randomised trial. *Lancet*. 2002;359(9300):9-13.
26. Lai KC, Lam SK, Chu KM, et al. Lansoprazole reduces ulcer relapse after eradication of *Helicobacter pylori* in nonsteroidal anti-inflammatory drug users—a randomized trial. *Aliment Pharmacol Ther*. 2003;18(8):829-836.
27. Wang C, Yuan Y, Hunt RH. The association between *Helicobacter pylori* infection and early gastric cancer: a meta-analysis. *Am J Gastroenterol*. 2007;102(8):1789-1798.
28. Fukase K, Kato M, Kikuchi S, et al; Japan Gast Study Group. Effect of eradication of *Helicobacter pylori* on incidence of metachronous gastric carcinoma after endoscopic resection of early gastric cancer: an open-label, randomised controlled trial. *Lancet*. 2008;372(9636):392-397.
29. Bae SE, Jung HY, Kang J, et al. Effect of *Helicobacter pylori* eradication on metachronous recurrence after endoscopic resection of gastric neoplasm. *Am J Gastroenterol*. 2014;109(1):60-67.
30. Wong BC, Lam SK, Wong WM, et al. *Helicobacter pylori* eradication to prevent gastric cancer in a high-risk region of China: a randomized controlled trial. *JAMA*. 2004;291(2):187-194.
31. Watari J, Das KK, Amenta PS, et al. Effect of eradication of *Helicobacter pylori* on the histology and cellular phenotype of gastric intestinal metaplasia. *Clin Gastroenterol Hepatol*. 2008;6(4):409-417.
32. Lee YC, Chen TH, Chiu HM, et al. The benefit of mass eradication of *Helicobacter pylori* infection: a community-based study of gastric cancer prevention. *Gut*. 2013;62(5):676-682.
33. Yang HB, Sheu BS, Wang ST, Cheng HC, Chang WL, Chen WY. *H. pylori* eradication prevents the progression of gastric intestinal metaplasia in reflux esophagitis patients using long-term esomeprazole. *Am J Gastroenterol*. 2009;104(7):1642-1649.
34. Cardenas VM, Mulla ZD, Ortiz M, Graham DY. Iron deficiency and *Helicobacter pylori* infection in the United States. *Am J Epidemiol*. 2006;163(2):127-134.
35. Gessner BD, Baggett HC, Muth PT, et al. A controlled, household-randomized, open-label trial of the effect that treatment of *Helicobacter pylori* infection has on iron deficiency in children in rural Alaska. *J Infect Dis*. 2006;193(4):537-546.
36. Franchini M, Cruciani M, Mengoli C, Pizzolo G, Veneri D. Effect of *Helicobacter pylori* eradication on platelet count in idiopathic thrombocytopenic purpura: a systematic review and meta-analysis. *J Antimicrob Chemother*. 2007;60(2):237-246.
37. Sonnenberg A, Lash RH, Genta RM. A national study of *Helicobactor pylori* infection in gastric biopsy specimens. *Gastroenterology*. 2010;139(6):1894-1901.

Antibiotic Resistance in Patients With *Helicobacter pylori* Infection

Nimish B. Vakil, MD
Clinical Professor of Medicine
University of Wisconsin School of Medicine and Public Health
Madison, Wisconsin

Current Use of Antibiotics in Patients With H pylori

Limited data are available on the current use of antibiotics in patients with *H pylori*. In 2004, Sharma and Howden reported the results of a survey of primary care practices in the United States that administered *H pylori* treatment regimens.[1] At that time, the most frequently reported treatment regimens were combinations of a PPI, clarithromycin, and either amoxicillin or metronidazole. Since that time, there has been very little additional information on the use of antibiotics in patients with *H pylori* in primary care practices in the United States.

The primary method of tracking the current use of antibiotics is by prescription drug usage. In the United States, 2 proprietary preparations are available for the treatment of *H pylori* infection: a triple combination consisting of lansoprazole, clarithromycin, and amoxicillin in a single capsule[2] and a quadruple preparation consisting of bismuth subcitrate potassium, metronidazole, and tetracycline in a single capsule taken with omeprazole.[3] Triple therapy is still widely used in the United States, whereas quadruple therapy, at least with the single pill, is prescribed less frequently.[4] Sequential therapy, consisting of a PPI and amoxicillin for 5 days followed by a PPI, clarithromycin, and tinidazole for an additional 5 days,

July 2014 05US14EBP1226

Table 2. Practical Criteria for Aiding in Antibiotic Selection for Treatment of *Helicobacter pylori* Infection

Primary care providers should ask patients about previous antibiotic use • Prior treatment with multiple courses of macrolide therapy for any reason precludes triple therapy
A simple way of assessing resistance rates in the community is to test patients after treatment to determine eradication success • Very high rates of success with a particular therapy is a clear indication that resistance is not significantly affecting the key agent in that treatment • High rates of failure to a particular therapy provide presumptive information that the resistance rates have risen and the key ingredient in that regimen may no longer be effective
If a patient has failed clarithromycin treatment in the past, future treatment regimens should not contain clarithromycin

may provide an alternative to clarithromycin-based triple therapy or bismuth quadruple therapy.[5]

It should be noted that prescriptions for the individual drugs are common because of the lower cost of generic agents as opposed to the proprietary preparations. As a result, it becomes almost impossible to track how many patients are being treated with which drug combination. However, it appears that in the United States, triple therapy with a PPI, amoxicillin, and clarithromycin is still widely preferred by primary care doctors.

Treatment in other parts of the world differs depending on the prevalence of *H pylori* resistance strains and the availability of certain drugs. In Northern Europe, Scandinavia, and the Netherlands, triple therapy is still the preferred treatment of choice and works well.[6] In Germany and Belgium, however, triple therapy is much less effective, so quadruple therapy and sequential therapy are more often utilized.[7-9] In Italy, triple therapy is completely unsuccessful.[7,10] In some countries, sequential therapy is the preferred treatment, and in others, such as Spain, quadruple therapy is preferred.[11,12] In South Korea, rates of resistance are very high; therefore, treatment generally starts with either quadruple or sequential therapy and then proceeds to other therapies.[13,14] Triple therapy and quadruple therapy are used in different parts of Japan.[15] In China, triple therapy is still widely utilized.[16]

There is no single answer to the question: "What is the optimal antibiotic treatment for use in patients with *H pylori*?" Overall, treatment should be dictated by local patterns of resistance. However, the local patterns of resistance are not known in some parts of the world, including the United States. As a result, empiric testing and personal assessments of response rates are used to judge the rates of resistance (Table 2).

Antimicrobial Resistance Rates

In the United States, national monitoring studies have been limited. A national monitoring study for *H pylori* resistance was run by the Centers for Disease Control and Prevention until 2003. The latest data on US prevalence was published in 2004 as part of the *Helicobacter pylori* Antimicrobial Resistance Monitoring Project (HARP), a prospective, longitudinal network that monitored antimicrobial resistance in *H pylori* isolates in the United States.[17] There were 347 *H pylori* isolates collected from 1998 through 2002. At that time, the resistance rates were 25.1% for metronidazole, 12.9% for clarithromycin, and 0.9% for amoxicillin. Similar data were reported in studies from the late 1990s. For example, in a study by Osato and colleagues,[18] resistance rates were 10.6% for clarithromycin, 21.6% for metronidazole, and 0.08% for amoxicillin. In multicenter trials of esomeprazole conducted in the late 1990s, data were collected on *H pylori* resistance.[19] The resistance rates were 12% for clarithromycin and 33% for metronidazole; *H pylori* resistance to amoxicillin was not detected.

There has been a remarkable change in the rates of resistance for *H pylori* throughout the past several years. Systematic studies have been performed primarily in Europe, but also in Asia. Throughout Europe, there is a wide variation in the prevalence rates of clarithromycin resistance, ranging from 23% to 27% in Italy, to 15% to 20% in France, to less than 6% in some parts of Northern Europe, such as Sweden, Norway, and Finland.[7,20] Interestingly, studies have shown that variation in the prevalence rates of resistance was strongly related to the use of long-acting clarithromycin and azithromycin, as well as levofloxacin for the treatment of other infections.[20] For example, the Netherlands and Finland have enacted measures to prevent the use of clarithromycin and azithromycin to treat upper respiratory tract infections; consequently, resistance to clarithromycin is uncommon in these countries. In contrast, clarithromycin and azithromycin are widely used in Italy for various infections, resulting in a very high rate of resistance.

Similar data have been shown for the fluoroquinolones. In Germany, the rate of resistance to levofloxacin/ciprofloxacin rose from 20.9% in 2006 to 29% in 2011, primarily because of the widespread use of levofloxacin to treat infections unrelated to *H pylori*.[21]

Wide variability in the rates of resistance is also reported in Asia. In Japan, resistance rates are 20% to 40% for clarithromycin, 14.9% for levofloxacin, and 14.8% for metronidazole.[7] In contrast, metronidazole resistance is 49% in Korea.[7] The high resistance rate for metronidazole reflects the local utilization of the agent for non–*H pylori* infections; in Korea, metronidazole is widely used for the treatment of gynecologic infections.

These data show that local use of antimicrobials for indications unrelated to *H pylori* infection is strongly related

July 2014 05US14EBP1226

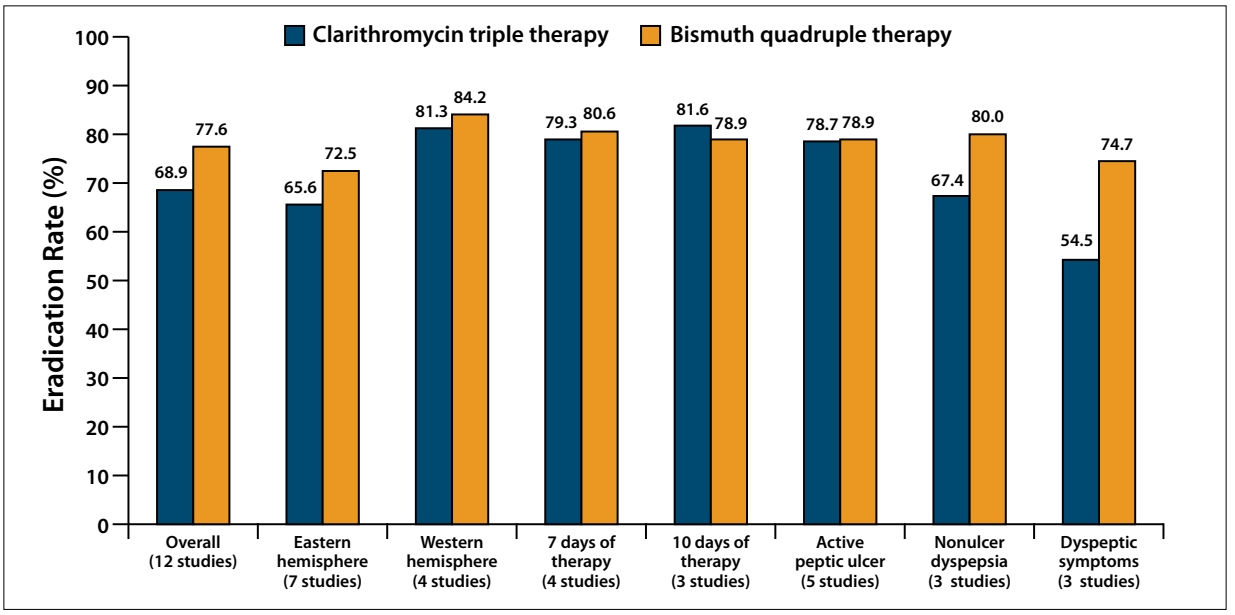


Figure 3. Eradication rates of *Helicobacter pylori* reported with triple and quadruple therapy in a meta-analysis.

Adapted from Venerito M et al. *Digestion*. 2013;88(1):33-45.[29]

to the development of resistance. There are 3 antibiotics that rarely develop resistance—bismuth, amoxicillin, and tetracycline—and that may be options for the treatment *H pylori*. Bismuth is similar to an antiseptic agent, acting topically in the stomach. Bismuth is one of the few drugs for which no resistance to *H pylori* has been described. In a systematic review of studies conducted between 2006 and 2009, resistance to tetracycline was less than 3% in all countries except those in Africa, where resistance was 43.9%.[7] In general, tetracycline resistance is rare because it requires that the organism develop 3 adjacent point mutations at specific locations.[22] Therefore, tetracycline remains an important component of treatment regimens, particularly in populations with higher rates of *H pylori* resistance. Resistance to amoxicillin requires a mutation that prevents binding of the drug to the organism.[22] Because this mutation is rare, amoxicillin remains a key component of many forms of treatment. In the HARP study, resistance to amoxicillin was less than 1%.[17]

Risk Factors for Resistance

The most important factor influencing risk of drug resistance is the use of the antimicrobial agent in a particular community. There are patient characteristics, however, that will also impact risk of resistance. In the SHARP (Surveillance of *H pylori* Antimicrobial Resistance Partnership) study from the late 1990s, clarithromycin resistance was significantly associated with geographic region (with highest rates in the northeastern and mid-Atlantic regions and lowest rates in the southern region; P=.050), older age (P<.001), female sex (P<.001), and inactive ulcer disease (P<.001).[23] Metronidazole resistance was significantly associated with female sex (relative risk, 1.7) and Asian ethnicity (relative risk, 1.9).[23] In a more recent study of untreated symptomatic adults from Bulgaria, younger age (<65 years) was an independent predictor of metronidazole resistance.[24] Respiratory infections were a predictor of clarithromycin resistance, and urinary tract infections were a predictor of ciprofloxacin resistance.[24] In addition, coinfections increased the risk of resistance to clarithromycin, metronidazole, and ciprofloxacin.[24]

In many parts of the world, there are patients who are resistant to 2 or 3 drugs, most often clarithromycin, levofloxacin, and possibly 1 other agent. Patient-specific prognostic indicators of multidrug microbial resistant strains include a history of multiple treatments, older age, and female sex. In the HARP study, black race was the only significant risk factor associated with increased resistance to more than 1 antimicrobial agent (HR, 2.1 [95% CI, 1.1-3.80]).[17] Resistance was not associated with the use of antibiotics 12 months before upper endoscopy (HR, 1.9 [95% CI, 0.9-3.7]) or age (HR, 0.6 [95% CI, 0.3-1.1]).[17]

Management of Patients Resistant to Antibiotics

When *H pylori* is not eradicated in a particular patient, drug resistance is the most important cause for failure after lack of adherence with the treatment regimen has been excluded (Figure 3).[5,25] According to current estimates, if a patient finishes approximately 80% of the treatment regimen, he or she will achieve successful eradication if the organism is susceptible to the key antibiotics in the regimen.[5,25]

Another principle to remember is that every regimen contains a key agent, and if the patient is resistant to this key agent, then the treatment will fail. For example, clarithromycin is the key agent in triple therapies that contain it. In the United States, resistance to clarithromycin is perhaps the most important issue to consider when patients fail a triple therapy that contains it. Patients who fail such triple therapy should proceed to a new regimen that uses a different key agent.[5]

Sequential therapy is another option.[5] Various sequential strategies have been described in the literature, but the original and best-characterized sequential therapy consists of a PPI and amoxicillin for 5 days followed by a PPI, clarithromycin, and tinidazole (metronidazole) for an additional 5 days.[5,25] The ACG specifies that this sequential regimen ". . . may provide an alternative to clarithromycin-based triple or bismuth quadruple therapy but requires validation within the United States before it can be recommended as a first-line therapy."[5] The third lines of treatment consist of levofloxacin-based triple therapy[5] and/or rifabutin-based triple therapy.[26,27] The preference at my institution is to use rifabutin-based triple therapy because of the high emergence of resistance when levofloxacin is widely used in the community, as has been observed in Germany.[21]

Optimal management of patients with suspected resistance involves obtaining cultures and performing antimicrobial sensitivity testing.[25,28] This approach is difficult to implement in the United States because these tests are not widely available at commercial laboratories. When possible, however, follow-up antimicrobial sensitivity testing should be scheduled when the *H pylori* therapy is prescribed.

New technologies developed in Asia and Europe offer polymerase chain reaction (PCR)-based methods for testing antimicrobial resistance. These tests use a biopsy taken from the stomach to determine whether the organism is susceptible to certain antibiotics. Unfortunately, these techniques are not approved for use in the United States and are generally not available.

At the present time, it is difficult to assess antimicrobial resistance in the United States because the epidemiologic data are more than a decade old. It is necessary to rely on inferences from European and Asian studies and antimicrobial use patterns to estimate rates of resistance. It seems likely that rates of resistance to clarithromycin and azithromycin are moderate, given how often these agents are used. Rates of levofloxacin resistance are likely to be moderate to high, and rates of amoxicillin and tetracycline resistance are likely to be extremely low. These factors may need to be considered when a patient fails initial treatment and requires additional rounds of therapy.

Acknowledgment

Dr Vakil was paid by Otsuka America Pharmaceutical, Inc. for participation in this roundtable and development of this monograph. Dr Vakil is a consultant for AstraZeneca and Restech. He has received speaker's fees from Takeda.

References

1. Sharma VK, Howden CW. A national survey of primary care physicians' perceptions and practices related to *Helicobacter pylori* infection. *J Clin Gastroenterol*. 2004;38(4):326-331.
2. PREVPAC (lansoprazole, amoxicillin, and clarithromycin) [prescribing information]. Deerfield, IL: Takeda Pharmaceuticals America, Inc.; October 2013.
3. Pylera (bismuth subcitrate potassium, metronidazole, tetracycline hydrochloride capsules) [prescribing information]. Bridgewater, NJ: Aptalis Pharma US, Inc.; 2006. Revised May 2013.
4. *H. pylori* and peptic ulcers. National Digestive Diseases Information Clearinghouse (NDDIC). http://digestive.niddk.nih.gov/ddiseases/pubs/hpylori/. Updated October 30, 2013. Accessed May 7, 2014.
5. Chey WD, Wong BC; Practice Parameters Committee of the American College of Gastroenterology. American College of Gastroenterology guideline on the management of *Helicobacter pylori* infection. *Am J Gastroenterol*. 2007;102(8):1808-1825.
6. Bytzer P, Dahlerup JF, Eriksen JR, Jarbøl DE, Rosenstock S, Wildt S; Danish Society for Gastroenterology. Diagnosis and treatment of *Helicobacter pylori* infection. *Dan Med Bull*. 2011;58(4):C4271.
7. De Francesco V, Giorgio F, Hassan C, et al. Worldwide *H. pylori* antibiotic resistance: a systematic review. *J Gastrointestin Liver Dis*. 2010;19(4):409-414.
8. Selgrad M, Meissle J, Bornschein J, et al. Antibiotic susceptibility of *Helicobacter pylori* in central Germany and its relationship with the number of eradication therapies. *Eur J Gastroenterol Hepatol*. 2013;25(11):1257-1260.
9. Vekens K, Vandebosch S, De Bel A, Urbain D, Mana F. Primary antimicrobial resistance of *Helicobacter pylori* in Belgium. *Acta Clin Belg*. 2013;68(3):183-187.
10. Tursi A, Elisei W, Giorgetti G, Picchio M, Brandimarte G. Decreasing efficacy of the standard seven-day triple therapy containing amoxycillin and clarithromycin in curing *Helicobacter pylori* infection in clinical setting in Italy: a 10-year follow-up study. *Panminerva Med*. 2014;56(1):57-61.
11. De Francesco V, Hassan C, Ridola L, Giorgio F, Ierardi E, Zullo A. Sequential, concomitant and hybrid first-line therapies for *H. pylori* eradication: a prospective, randomized study. *J Med Microbiol*. 2014;63(Pt 5):748-752.
12. Molina-Infante J, Romano M, Fernandez-Bermejo M, et al. Optimized nonbismuth quadruple therapies cure most patients with *Helicobacter pylori* infection in populations with high rates of antibiotic resistance. *Gastroenterology*. 2013;145(1):121-128.
13. Kim JS, Ji JS, Choi H, Kim JH. Sequential therapy or triple therapy for *Helicobacter pylori* infection in Asians: systematic review and meta-analysis. *Clin Res Hepatol Gastroenterol*. 2014;38(1):118-125.
14. Yoon H, Lee DH, Kim N, et al. Meta-analysis: is sequential therapy superior to standard triple therapy for *Helicobacter pylori* infection in Asian adults? *J Gastroenterol Hepatol*. 2013;28(12):1801-1809.
15. Shiota S, Yamaoka Y. Strategy for the treatment of *Helicobacter pylori* infection. *Curr Pharm Des*. 2013;19:1-12.
16. Fock KM, Katelaris P, Sugano K, et al; Second Asia-Pacific Conference. Second Asia-Pacific Consensus Guidelines for *Helicobacter pylori* infection. *J Gastroenterol Hepatol*. 2009;24(10):1587-1600.
17. Duck WM, Sobel J, Pruckler JM, et al. Antimicrobial resistance incidence and risk factors among *Helicobacter pylori*-infected persons, United States. *Emerg Infect Dis*. 2004;10(6):1088-1094.
18. Osato MS, Reddy R, Reddy SG, Penland RL, Malaty HM, Graham DY. Pattern of primary resistance of *Helicobacter pylori* to metronidazole or clarithromycin in the United States. *Arch Intern Med*. 2001;161(9):1217-1220.
19. Laine L, Fennerty MB, Osato M, et al. Esomeprazole-based *Helicobacter pylori* eradication therapy and the effect of antibiotic resistance: results of three US multicenter, double-blind trials. *Am J Gastroenterol*. 2000;95(12):3393-3398.
20. Megraud F, Coenen S, Versporten A, et al. *Helicobacter pylori* resistance to antibiotics in Europe and its relationship to antibiotic consumption. *Gut*. 2013;62(1):34-42.
21. Wueppenhorst N, Stueger HP, Kist M, Glocker EO. High secondary resistance to quinolones in German *Helicobacter pylori* clinical isolates. *J Antimicrob Chemother*. 2013;68(7):1562-1566.
22. Wu W, Yang Y, Sun G. Recent insights into antibiotic resistance in *Helicobacter pylori* eradication. *Gastroenterol Res Pract*. 2012;2012:723183.
23. Meyer JM, Silliman NP, Wang W, et al. Risk factors for *Helicobacter pylori* resistance in the United States: the surveillance of *H. pylori* antimicrobial resistance partnership (SHARP) study, 1993-1999. *Ann Intern Med*. 2002;136(1):13-24.

July 2014 05US14EBP1226

24. Boyanova L, Ilieva J, Gergova G, et al. Numerous risk factors for *Helicobacter pylori* antibiotic resistance revealed by extended anamnesis: a Bulgarian study. *J Med Microbiol*. 2012;61(Pt 1):85-93.
25. Malfertheiner P, Megraud F, O'Morain CA, et al; European Helicobacter Study Group. Management of *Helicobacter pylori* infection—the Maastricht IV/ Florence Consensus Report. *Gut*. 2012;61(5):646-664.
26. Gisbert JP, Calvet X. Review article: rifabutin in the treatment of refractory *Helicobacter pylori* infection. *Aliment Pharmacol Ther*. 2012;35(2):209-221.
27. Gisbert JP, Calvet X, Bujanda L, Marcos S, Gisbert JL, Pajares JM. "Rescue" therapy with rifabutin after multiple *Helicobacter pylori* treatment failures. *Helicobacter*. 2003;8(2):90-94.
28. Manfredi M, Bizzarri B, Manzali E, Fugazza A, Gismondi P, de'Angelis GL. Which treatment in *Helicobacter pylori* infection? *Clin Exp Pharmacol*. 2013;3(4):1-3.
29. Venerito M, Krieger T, Ecker T, Leandro G, Malfertheiner P. Meta-analysis of bismuth quadruple therapy versus clarithromycin triple therapy for empiric primary treatment of *Helicobacter pylori* infection. *Digestion*. 2013;88(1):33-45.

Management of Patients With *Helicobacter pylori* Infection

Colin W. Howden, MD
Professor of Medicine
Division of Gastroenterology and Hepatology
Northwestern University Feinberg School of Medicine
Chicago, Illinois

Symptoms Are Not a Good Indicator for Testing After Treatment

H pylori is a complicated chronic bacterial infection whose symptoms are not a reliable indicator of the success or failure of treatment. This characteristic is in contrast to bacterial infections of the urinary tract or the sinopulmonary tract; for these infections, once antibiotic treatment is prescribed, symptomatic improvement usually correlates very closely with bacterial cure. After treatment for *H pylori* infection, symptoms are not a reliable sign of the presence or absence of the infection. In a study by Fendrick and colleagues, symptoms persisted after confirmed eradication in more than half of patients with *H pylori*–associated peptic ulcer disease.[1] Regular use of H_2 blockers and/or PPIs was reported in 56% of patients with confirmed eradication. Many people with *H pylori* infection have essentially no symptoms or very trivial symptoms. It is therefore important to know which patients to test for the infection and which tests to use.

Treatments for *H pylori* have limited success. After a course of therapy is completed, the question arises of whether the patient should undergo re-testing to determine whether treatment was successful. In my opinion, posttreatment testing should be routine. *H pylori* infection has potential serious long-term sequelae, and patients are interested in knowing whether the infection has been cured or not.

Methods of Testing

Several tests are available to check for *H pylori* infection, including noninvasive and invasive approaches.[2] It is important to remember that the sensitivity of tests for active *H pylori* infection may be impaired by the recent use of PPIs, bismuth, or antibiotics.[2]

Apart from endoscopic testing and serology, the 2 noninvasive tests of active infection are the fecal antigen test and the urea breath test. Both are appropriate and approved for detecting the infection and also for assessing treatment success or failure.[3,4]

Fecal Antigen Test

The fecal antigen test can be used to diagnose the infection and also to determine the success or failure of treatment. A systematic review reported pretreatment and posttreatment sensitivity and specificity values exceeding 90% when using the monoclonal fecal antigen test.[4]

The fecal antigen test is fairly widely applied, although patient compliance is imperfect because of the nature of the test. In a mail-in study of fecal occult blood testing that included 1940 patients, the overall compliance rate was only 17.9%.[5]

The fecal antigen test has high sensitivity and specificity.[4] However, like the urea breath test, its accuracy is impaired by the recent or current use of PPIs or antibiotics.[6-9] There is a misperception that PPIs and antibiotics negatively influence the urea breath test but not the fecal antigen test. In fact, that is not the case. Recent use of PPIs or antibiotics can produce a false-negative result with both the fecal antigen test and the urea breath test.[6-9] PPIs should be discontinued for at least 2 weeks before the fecal antigen test.[3] If the patient complies with the recommendation to defer use of PPIs or antibiotics for the appropriate period of time before the test and collects the specimen in the appropriate manner, the fecal antigen test is accurate and reliable for detecting *H pylori* infection and for determining posttreatment status.

July 2014 05US14EBP1226

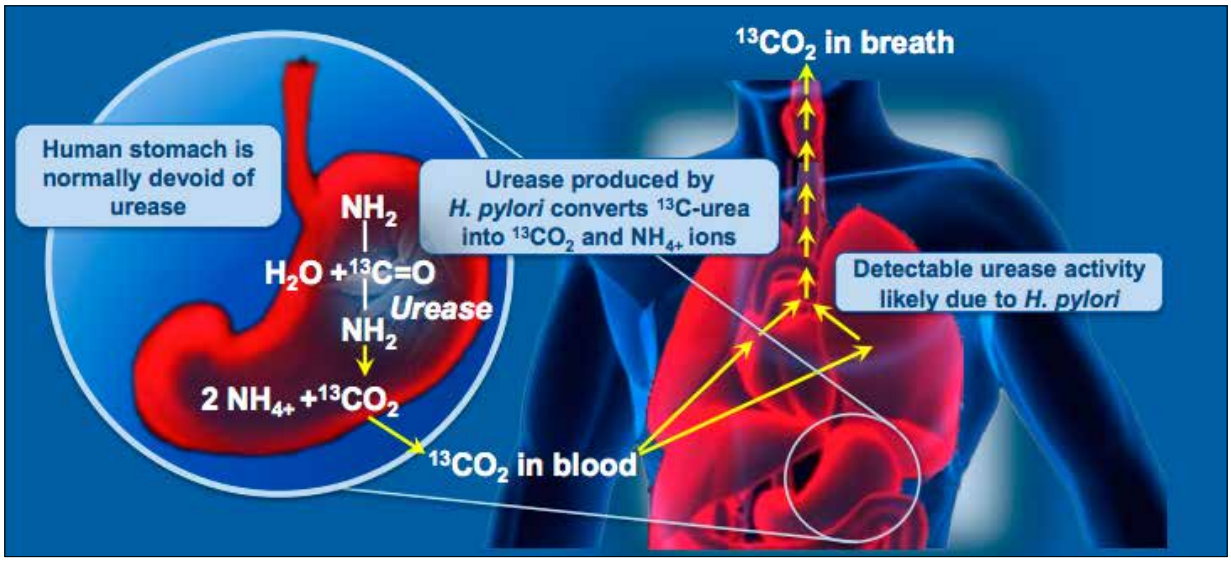


Figure 4. The urea breath test detects urease activity, a marker of *Helicobacter pylori* (*H pylori*) infection, through the oral administration of carbon 13–labeled urea. If the stomach is infected with *H pylori*, its urease splits the carbon 13–labeled urea to produce ammonia and carbon 13-labeled CO_2 ($^{13}CO_2$), which is expired in the breath.

Urea Breath Test

The other noninvasive, accurate testing option for *H pylori* infection is the urea breath test, which is also approved for use before and after treatment.[2,3] The urea breath test and the fecal antigen test have excellent positive and negative predictive values regardless of *H pylori* prevalence.[2] The Maastricht IV/Florence Consensus considers the ^{13}C urea breath test to be the best noninvasive test for *H pylori* infection.[3] According to the ACG guidelines, the urea breath test and the fecal antigen test are both reliable methods of identifying active *H pylori* infection before the use of antibiotic therapy.[2] The ACG guidelines state that the urea breath test is the most reliable nonendoscopic test to document eradication of *H pylori* infection.[2]

Urease is important to the *H pylori* organism. Normally, the human stomach has no urease activity in it. Therefore, detection of urease activity implies the presence of *H pylori*. The urea breath test involves the oral administration of carbon 13-labeled urea (Figure 4).[2,10] If the stomach is infected with *H pylori*, its urease splits the carbon 13-labeled urea to produce ammonia and carbon 13-labeled CO_2 ($^{13}CO_2$), which is expired in the breath.[2,10]

The urea breath test is simple to perform and can be administered in the office setting or at regional or national laboratories. The test has high levels of sensitivity and specificity, typically greater than 90%.[2,3,10]

Similar to the fecal antigen test, the urea breath test should be administered after the patient has discontinued PPIs for 2 weeks.[2,3,11-15] In a study of 13 patients with active *H pylori* infection, lansoprazole treatment led to equivocal or false-negative urea breath test results in 61%.[11] Similar results were observed in studies of esomeprazole, pantoprazole, omeprazole, and ranitidine, with equivocal or false results occurring in 2% to 40% of patients, depending on the study parameters.[12-14] In addition, concomitant administration of antibiotics or bismuth can also contribute to false-negative results.[2,6] In a study that included 20 patients with *H pylori* infection, treatment with 2 weeks of bismuth subsalicylate resulted in 45% to 55% false-negative results.[6] The ACG recommends that bismuth and antibiotics be withheld for at least 28 days before the urea breath test.[2]

The US Food and Drug Administration recently approved updated labeling for BreathTek UBT.[16] If the test result is positive in a patient receiving a PPI, then the result can be considered a true positive, and appropriate treatment for the infection should be offered. If the test result is negative in a patient receiving a PPI, it should be considered a possible false-negative result. The test should be repeated once the patient has stopped using PPIs for 2 weeks.

Serology

In the United States, the most common means of testing is serology because of its simplicity, widespread availability, and perceived low cost.[2] However, serology is the least reliable means of testing for *H pylori* infection because of its relatively low specificity, particularly in areas where there is a low background prevalence of the infection, as is the case in much of the continental United States.[2] Most importantly, serology should not be used after the patient has been treated for *H pylori* infection because antibodies to *H pylori* may remain detectable indefinitely despite cure of the infection.[2,17,18] Serologic tests cannot distinguish active *H pylori* infection from past infection. Table

July 2014 05US14EBP1226

Table 3. Noninvasive Tests for *Helicobacter pylori*

Test	Advantages	Disadvantages
Serology	Widely available Least expensive of available tests	Positive results may reflect previous rather than current infection Not recommended for confirming eradication
Urea breath test	High negative and positive predictive values Useful before and after treatment	False-negative results possible in the presence of proton pump inhibitors or with recent use of antibiotics or bismuth preparations Considerable resources and personnel required to perform test
Stool antigen test	High negative and positive predictive values with monoclonal antibody test Useful before and after treatment	Process of stool collection may be distasteful to patient False-negative results possible in the presence of proton-pump inhibitors or with recent use of antibiotics or bismuth preparation

Data from McColl KE. *N Engl J Med.* 2010;362:1597-1604.[19]

3 summarizes the strengths and limitations of currently available noninvasive tests for *H pylori* infection.

Gastric Biopsy

Invasive testing involves upper endoscopy with biopsy.[2,3] This approach adds to the cost of overall management,[2] but testing for *H pylori* infection can be incorporated into an upper endoscopy if a patient is undergoing the procedure for another clinical indication. Biopsy-based tests include histology, rapid urease testing, culture, and PCR, all of which have excellent specificity.[2] Like the fecal antigen test and the urea breath test, the upper endoscopy tests are negatively impacted by recent use of PPIs, bismuth, or antibiotics.[2]

Culture allows for the determination of *H pylori* antibiotic sensitivities. However, as noted above, it is not widely available and therefore not often recommended.[2] Histology is more expensive than rapid urease testing. For patients who have not received a PPI within 2 weeks or an antibiotic or bismuth within 4 weeks, the rapid urease test is a good option for detection of *H pylori*.[2]

ACG Guideline Recommendations

The ACG has suggested a move toward tests of active infection.[2] At the present time, the ACG endorses the carbon 13-labeled urea breath test and the fecal antigen test as reliable tests for identifying *H pylori* infection before treatment.[2] The carbon 13-labeled urea breath test is considered the most reliable nonendoscopic test to confirm *H pylori* eradication.[2] The fecal antigen test may be an alternative to the urea breath test, although this assay has not been as well validated in the posttreatment setting.[2] As was previously discussed, serology should be avoided posttreatment owing to persistence of *H pylori*–specific antibodies after the infection has been cleared.[2,17,18] The ACG recommends a delay in posttreatment testing for *H pylori* eradication until 4 weeks after the completion of therapy to minimize the potential of false-negative results.[2]

Table 4. ACG Recommendations for Posttreatment Testing for Eradication of *Helicobacter pylori*

Test of active infection is recommended when endoscopic follow-up is unnecessary
Urea breath test is the most reliable nonendoscopic test to document eradication
Testing should be performed at least 4 weeks after treatment completion
Serologic testing in the posttreatment setting should be avoided
Results can remain positive for years after successful eradication

ACG, American College of Gastroenterology.

Data from Chey WD, Wong BC; Practice Parameters Committee of the American College of Gastroenterology. *Am J Gastroenterol.* 2007;102(8):1808-1825.[2]

Currently, the ACG practice guidelines indicate that posttreatment testing for all patients is "neither practical nor cost-effective."[2] Instead, the ACG recommends that posttreatment testing be restricted to patients with persistent dyspeptic symptoms or a history of peptic ulcer, MALToma, or endoscopic resection of early gastric cancer.[2] Although the most recent version of the ACG guidelines stop short of recommending routine posttreatment testing, this approach provides valuable information for both the patient and the physician. Without this information, there is little comprehension of local treatment success rates. Table 4 summarizes the current practice recommendations from the ACG regarding posttreatment testing.

Test Selection

The noninvasive tests of active infection—the urea breath test and the fecal antigen test—are the most appropriate tests in most situations. These tests are simple to perform and provide highly reliable results when performed under optimal circumstances.[2,3]

Serologic testing may have a limited role in urban environments with a large proportion of immigrants.[3] In settings with a low prevalence of *H pylori* infection, serology is potentially useful because of its high negative predictive value; in such a setting, a negative serologic test result is of some benefit for excluding *H pylori* infection. There may also be a limited role for serologic testing in hospitalized patients with bleeding peptic ulcer since, in that situation, the pretest probability of infection is much higher than in the outpatient setting. Some clinicians are reluctant to perform

biopsy-based tests on patients with recent ulcer bleeding, and there may be some practical difficulties in ordering the urea breath test or fecal antigen test in the inpatient setting. In patients from areas of low background prevalence of *H pylori* infection, a positive serologic test might be appropriately followed by a urea breath test or fecal antigen test once the acute bleeding episode has been controlled.[2]

Incorporating Testing into the Management Plan

There has been some reluctance on the part of primary care physicians to incorporate tests of active infection because of perceptions that these tests are too difficult, too complicated, not routinely available, or not covered by various insurance plans. However, there is a good case for moving away from serology toward tests of active infection. In addition, post-treatment testing is important, and I offer it routinely to patients whom I have treated for *H pylori* infection.

Acknowledgment

Dr Howden was paid by Otsuka America Pharmaceutical, Inc. for participation in this roundtable and development of this monograph. Dr Howden is a consultant for Takeda, Otsuka, Ironwood, and Salix. He has received speaking honoraria from Takeda, Otsuka, Ironwood, Forest, and GlaxoSmithKline International.

References

1. Fendrick AM, Chey WD, Margaret N, Palaniappan J, Fennerty MB. Symptom status and the desire for *Helicobacter pylori* confirmatory testing after eradication therapy in patients with peptic ulcer disease. *Am J Med*. 1999;107(2):133-136.
2. Chey WD, Wong BC; Practice Parameters Committee of the American College of Gastroenterology. American College of Gastroenterology guideline on the management of *Helicobacter pylori* infection. *Am J Gastroenterol*. 2007;102(8):1808-1825.
3. Malfertheiner P, Megraud F, O'Morain CA, et al; European Helicobacter Study Group. Management of *Helicobacter pylori* infection—the Maastricht IV/ Florence Consensus Report. *Gut*. 2012;61(5):646-664.
4. Ahmed F, Murthy UK, Chey WD, Toskes PP, Wagner DA. Evaluation of the Ez-HBT *Helicobacter* blood test to establish *Helicobacter pylori* eradication. *Aliment Pharmacol Ther*. 2005;22(9):875-880.
5. Ore L, Hagoel L, Lavi I, Rennert G. Screening with faecal occult blood test (FOBT) for colorectal cancer: assessment of two methods that attempt to improve compliance. *Eur J Cancer Prev*. 2001;10(3):251-256.
6. Bravo LE, Realpe JL, Campo C, Mera R, Correa P. Effects of acid suppression and bismuth medications on the performance of diagnostic tests for *Helicobacter pylori* infection. *Am J Gastroenterol*. 1999;94(9):2380-2383.
7. Manes G, Balzano A, Iaquinto G, et al. Accuracy of the stool antigen test in the diagnosis of *Helicobacter pylori* infection before treatment and in patients on omeprazole therapy. *Aliment Pharmacol Ther*. 2001;15(1):73-79.
8. Erzin Y, Altun S, Dobrucali A, et al. Evaluation of two enzyme immunoassays for detecting *Helicobacter pylori* in stool specimens of dyspeptic patients after eradication therapy. *J Med Microbiol*. 2005;54(Pt 9):863-866.
9. Asfeldt AM, Lochen ML, Straume B, et al. Accuracy of a monoclonal antibody-based stool antigen test in the diagnosis of *Helicobacter pylori* infection. *Scand J Gastroenterol*. 2004;39(11):1073-1077.
10. Gisbert JP, Pajares JM. Review article: ^{13}C-urea breath test in the diagnosis of *Helicobacter pylori* infection—a critical review. *Aliment Pharmacol Ther*. 2004;20(10):1001-1017.
11. Chey WD, Woods M, Scheiman JM, et al. Lansoprazole and ranitidine affect the accuracy of the 14 C-urea breath test by a pH-dependent mechanism. *Am J Gastroenterol*. 1997;92(3):446-450.
12. Levine A, Shevah O, Shabat-Sehayek V, et al. Masking of ^{13}C urea breath test by proton pump inhibitors is dependent on type of medication: comparison between omeprazole, pantoprazole, lansoprazole and esomeprazole. *Aliment Pharmacol Ther*. 2004;20(1):117-122.
13. Ozturk E, Yesilova Z, Ilgan S, et al. Performance of acidified ^{14}C-urea capsule breath test during pantoprazole and ranitidine treatment. *J Gastroenterol Hepatol*. 2009;24(7):1248-1251.
14. Graham DY, Opekun AR, Hammoud F, et al. Studies regarding the mechanism of false negative urea breath tests with proton pump inhibitors. *Am J Gastroenterol*. 2003;98(5):1005-1009.
15. Laine L, Estrada R, Trujillo M, et al. Effect of proton-pump inhibitor therapy on diagnostic testing for *Helicobacter pylori*. *Ann Intern Med*. 1998;129(7):547-550.
16. BreathTek (urea breath test *H. pylori* kit) [package insert]. Rockville, MD: Otsuka America Pharmaceutical Inc.; Revised May 2013.
17. Ho B, Marshall BJ. Accurate diagnosis of *Helicobacter pylori*. Serologic testing. *Gastroenterol Clin N Am*. 2000;29(4):853-862.
18. Ekström AM, Held M, Hansson LE, Engstrand L, Nyrén O. *Helicobacter pylori* in gastric cancer established by CagA immunoblot as a marker of past infection. *Gastroenterology*. 2001;121(4):784-791.
19. McColl KE. Clinical practice. *Helicobacter pylori* infection. *N Engl J Med*. 2010;362:1597-1604.

Clinical Rationale for Confirmation Testing After Treatment of *Helicobacter pylori* Infection: Discussion

Q&A

Colin W. Howden, MD Dr Chey, you mentioned a number of definite and possible indications for testing and treating *H pylori* infection. An area of confusion that I see in clinical practice, particularly among my primary care colleagues, centers around the difficult term *gastritis*. How do you explain the phenomenon of gastritis to your primary care colleagues, residents, and medical students?

William D. Chey, MD I convey the distinction between the histologic diagnosis of gastritis, in which all patients who develop chronic infection develop gastritis, vs the symptom-based diagnosis of dyspepsia, which is entirely different. Importantly, the presence of *H pylori* infection does not necessarily indicate that *H pylori* is the cause of the patient's dyspeptic symptoms.

Colin W. Howden, MD Dr Vakil, I share your level of frustration in trying to obtain cultures and sensitivity

July 2014 05US14EBP1226

testing. It surprises me that so many microbiology labs in academic medical centers have not developed this type of testing. Has that been your experience also?

Nimish B. Vakil, MD Yes. For a while, we offered this service through our Veterans Affairs (VA) hospital in Milwaukee to people in other parts of the country. Currently, we are not able to offer this as a service to the general community. There are many obstacles to obtaining culture and sensitivity testing, and there are no institutions in the United States that offer it as a clinical service.

Colin W. Howden, MD Dr Chey, has that been your experience?

William D. Chey, MD We are performing *H pylori* cultures at the University of Michigan on a selected basis. We had to start doing these tests ourselves because we could not get them done anywhere else. It is a constant source of frustration because reports in the literature indicate the necessity of selecting therapy on the basis of antimicrobial resistance testing,[25,28] and yet we cannot obtain that information in the United States.

Colin W. Howden, MD It is a big issue.

Nimish B. Vakil, MD The lack of funding at the national level has played a contributing role. For example, since the HARP study was terminated in 2003 owing to budgetary cuts, we lack a recent snapshot of *H pylori* infection and resistance rates in the United States. If there were large, epidemiologic studies ongoing in the United States, we could at least make some educated guesses as to how we should proceed with regard to antimicrobial resistance.

William D. Chey, MD It is important to keep in mind that follow-up testing can get lost in the transition from the inpatient to the outpatient setting.

Colin W. Howden, MD I agree. Before the patient leaves the hospital, a clear plan should be in place for determining *H pylori* status. However, such plans are not always made. I have seen patients fall through the cracks.

Nimish B. Vakil, MD We have started scheduling the *H pylori* test the day treatment is prescribed. We count a month from the end of treatment, and then the discharge instructions include an appointment for the urea breath test or the fecal antigen test.

Colin W. Howden, MD The urea breath test is used in our clinic because of its simplicity and availability. There are some data to suggest that patients prefer the urea breath test over the fecal antigen test. These data suggest that patients do not always follow through with the fecal antigen test or complete it properly. However, I have no personal experience in using the test. Do either of you have experience with the fecal antigen test?

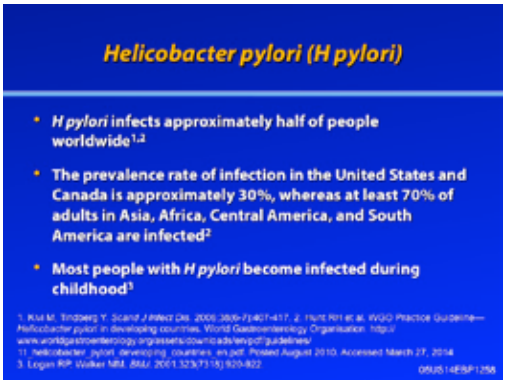
Nimish B. Vakil, MD The fecal antigen test is used at my institution because we have some patients with insurance that does not cover the urea breath test. We have not seen the difficulties with compliance that were originally reported when the fecal antigen test became available. Although some patients may be reluctant to obtain stool samples, they will do so if they believe the results are important and the test is covered by their insurance.

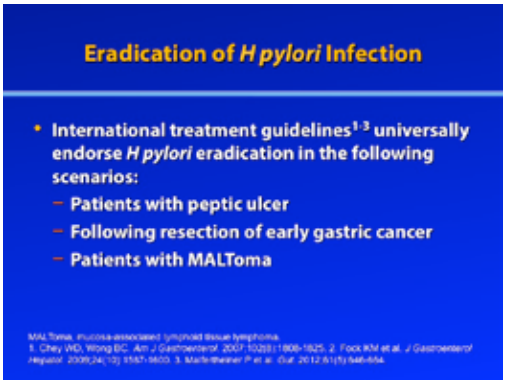
William D. Chey, MD I have not had much trouble with the fecal antigen test either. At my institution, we perform both tests, although the urea breath test is more frequently used. There are some patients who are squeamish about collecting their stool, but when we express the importance of the test, they will usually agree to collect the sample. If the patient remains squeamish, then we order the urea breath test.

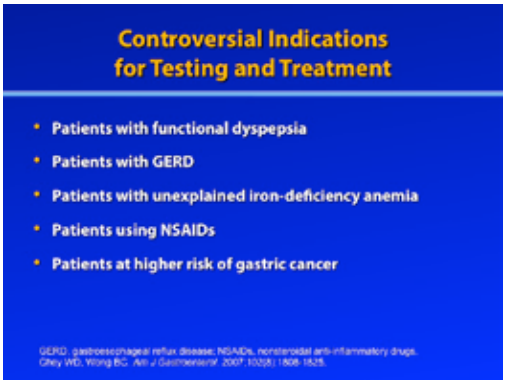
Acknowledgment

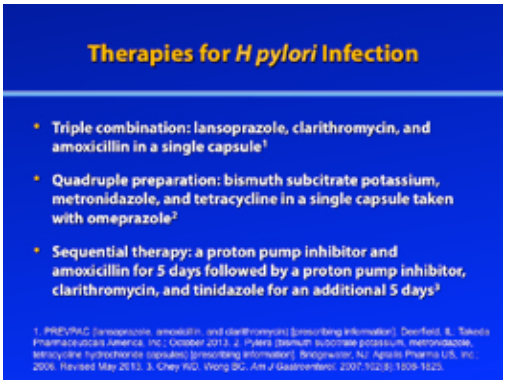
Drs Howden, Chey, and Vakil were paid by Otsuka America Pharmaceutical, Inc. for participation in this roundtable and development of this monograph. Dr Chey is a consultant for AstraZeneca, Perrigo, and Takeda. Dr Howden is a consultant for Takeda, Otsuka, Ironwood, and Salix. He has received speaking honoraria from Takeda, Otsuka, Ironwood, Forest, and GlaxoSmithKline International. Dr Vakil is a consultant for AstraZeneca and Restech. He has received speaker's fees from Takeda.

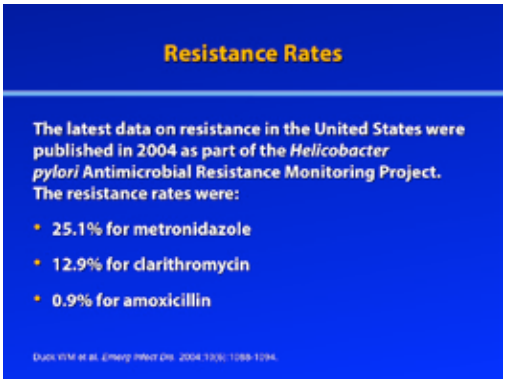
Slide Library











July 2014 05US14EBP1226

Management of Patients Resistant to Antibiotics

- Every regimen contains a key agent, and if the patient is resistant to this key agent, then the treatment will fail. Patients who fail such triple therapy should proceed to a new regimen that uses a different key agent
- Sequential therapy is an option after failure of triple therapy
- Optimal management of patients with suspected resistance involves obtaining cultures and performing antimicrobial sensitivity testing

Information is based on the personal experience of Dr. Nimish B. Vakil.

Serology Testing for *H pylori* Infection

- Serology is the most common means of testing for *H pylori* in the United States[1]
- Serology is the least reliable means of testing for *H pylori* infection because of its relatively low specificity[1]
- Serologic tests cannot distinguish active *H pylori* infection from past infection[1-3]

1. Chey WD, Wong BC. Am J Gastroenterol. 2007;102(8):1808-1825. 2. Ho B, Marshall BJ. Gastroenterol Clin N Am. 2000;29(4):853-862. 3. Epstein AM et al. Gastroenterology. 2001;121(4):784-791.

Noninvasive Testing for *H pylori* Infection

Test	Advantages	Disadvantages
Urea breath tests (^{13}C and ^{14}C)	Identifies active *H pylori* infection Excellent PPV and NPV regardless of *H pylori* prevalence Useful before and after *H pylori* therapy	Reimbursement and availability are inconsistent
Fecal antigen test	Identifies active *H pylori* infection Excellent PPV and NPV regardless of *H pylori* prevalence Useful before and after *H pylori* therapy	Polyclonal test is less well validated than the urea breath test in the post-treatment setting Monoclonal test appears reliable before and after antibiotic therapy Unpleasantness associated with collecting stool

NPV, negative predictive value; PPV, positive predictive value
Adapted from Chey WD, Wong BC. Am J Gastroenterol. 2007;102(8):1808-1825.

Post-treatment Testing for *H pylori*

- The urea breath test is considered the most reliable nonendoscopic test to confirm *H pylori* eradication
- The fecal antigen test may be an alternative to the urea breath test, but this assay has not been as well validated in the post-treatment setting
- Serology should be avoided post-treatment owing to persistence of *H pylori*–specific antibodies after the infection has been cleared

Chey WD, Wong BC. Am J Gastroenterol. 2007;102(8):1808-1825.

05US14EBP1226

Brief Summary about BreathTek UBT

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 and pediatric patients 3 to 17 years old. 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 $^{13}CO_2$ to $^{12}CO_2$ in breath samples, in clinical laboratories or point-of-care settings. The Pediatric Urea Hydrolysis Rate Calculation Application (*p*UHR-CA), provided as a web-based calculation program, is required to obtain pediatric test results.

The BreathTek UBT Kit is for administration by a health care professional, as ordered by a licensed health care practitioner.

Warnings and Precautions

- For in vitro diagnostic use only. The Pranactin®-Citric solution is taken orally as part of the diagnostic procedure and contains Phenylalanine (one of the protein components of Aspartame), 84 mg per dosage unit, and should be used with caution in diabetic patients. (For reference, 12 ounces of typical diet cola soft drinks contain approximately 80 mg of Phenylalanine.)
- 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 alternate method.
- False negative test results may be caused by:
  - — Ingestion of proton pump inhibitors (PPIs) within 2 weeks prior to performing the BreathTek UBT. If a negative result is obtained from a patient ingesting a PPI within 2 weeks prior to the BreathTek UBT, it may be a false-negative result and the test should be repeated 2 weeks after discontinuing the PPI treatment. A positive result for a patient on a PPI could be considered positive and be acted upon.
  - — Ingestion of antimicrobials, or 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*.
- False positive test results may be caused by urease associated with other gastric spiral organisms observed in humans such as *Helicobacter heilmannii* or achlorhydria.
- If particulate matter is visible in the reconstituted Pranactin-Citric solution after thorough mixing, the solution should not be used.
- Patients who are hypersensitive to mannitol, citric acid or Aspartame should avoid taking the drug solution as this drug solution contains these ingredients. Use with caution in patients with difficulty swallowing or who may be at high risk of aspiration due to medical or physical conditions.
- No information is available on use of the Pranactin-Citric solution during pregnancy.
- For pediatric test results, the Urea Hydrolysis Rate (UHR) results must be calculated. The Delta over Baseline (DOB) results are only used to calculate the UHR metrics to determine *H. pylori* infection in pediatric patients. DOB results **cannot** be used to determine the infection status of pediatric patients. Use the web-based *p*UHR-CA (https://BreathTekKids.com) to calculate the UHR.
- Safety and effectiveness has not been established in children below the age of 3 years.

Adverse Events

During post-approval use of the BreathTek UBT in adults, 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.

In two clinical studies conducted in 176 (analyzed) pediatric patients ages 3 to 17 years to determine the initial diagnosis and post treatment monitoring of *H. pylori*, the following adverse events experienced by ≥1% of these patients were: vomiting (5.1%), oropharyngeal pain (4.5% to include throat irritation, sore throat, throat burning), nausea (2.3%), restlessness (2.3%), stomach ache/belly pain (1.1%), and diarrhea (1.1%). Most of the adverse events were experienced by patients within minutes to hours of ingestion of the Pranactin-Citric solution.

In another clinical study comparing the UBiT®-IR300 and POCone® in pediatric patients ages 3 to 17 years, the following adverse events were observed among the 99 subjects enrolled: 2 incidences of headache, and 1 incidence each of cough, dry mouth and acute upper respiratory infection.

May 2014 05US14EBP1200

Otsuka
Medical Device Division of
Otsuka America Pharmaceutical, Inc.

Urea Breath Test for H. pylori
BreathTek

June 2014 05US14EBP1226