Houston Consensus Conference on Testing for *Helicobacter pylori* Infection in the United States

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Abstract

Despite guidelines for detection and treatment of *Helicobacter pylori* infection, recommendations to test patients before and after therapy are commonly not followed in the United States. At the Houston Consensus Conference, 11 experts on management of adult and pediatric patients with *H pylori*, from different geographic regions of the United States, met to discuss key factors in diagnosis of *H pylori* infection, including identification of appropriate patients for testing, effects of antibiotic susceptibility on testing and treatment, appropriate methods for confirmation of infection and eradication, and relevant health system considerations. The experts divided into groups that used a modified Delphi panel approach to assess appropriate patients for testing, testing for antibiotic susceptibility and treatment, and test methods and confirmation of eradication. The quality of evidence and strength of recommendations were evaluated using the GRADE system. The results of the individual workshops were presented for a final consensus vote by all panel members. After the Expert Consensus Development meeting, the conclusions were validated by a separate panel of gastroenterologists, who assessed their level of agreement with each of the 29 statements developed at the Expert Consensus Development. The final

recommendations are provided, on the basis of the best available evidence, and provide consensus statements with supporting literature to implement testing for *H pylori* infection at health care systems across the United States.

Keywords

Bacterial Infection; Urea Breath Test; Stool Antigen Test; Resistance

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Since 2015, 4 major *Helicobacter pylori* consensus documents have been published.[1–4] The stimulus for this consensus conference was that, despite previous guidelines, recommendations regarding appropriate testing before therapy were commonly not followed, and testing after therapy was also not recommended for practitioners in the United States.[5] For example, a large 2007 retrospective study of US pharmacy claims involving 1.9 million health plan members showed serology to be the most common *H pylori* test used.[6] A more recent study, performed between 2010 and 2013, analyzed first-time *H pylori* diagnostic tests among more than 100 million individuals and reported that serology was used in ~70% of 515,700 tests, of which 4.2% were positive.[7] Serology was used in ~70%; 15,495 tests (4.2%) were positive.[7] Despite the need to confirm the results of serologic tests in low prevalence populations,[8] only a minority of patients with positive serology had confirmatory testing (ie, urea breath test [UBT] in ~16% and stool antigen immunoassay [HpSAg] testing in 11%) within the 14-day window allowed by the study. Although reimbursement potentially influences practice patterns, the Centers for Medicare and Medicaid Services reimburses all methods of *H pylori* testing and at that time reimbursed $19.80 for serology, $91.89 for UBT, and $19.62 HpSAg. Since that time, several commercial insurance companies have designated serology as not medically necessary and no longer reim-burse for that test.[7]

A 2017 study among practicing gastroenterologists reported gastric biopsy as the most common diagnostic method (59%) followed by HpSAg (20%)[9]; the pre-dominance of biopsy likely reflected the fact that specialist practice often consists of referrals. The most common therapy prescribed was standard triple therapy, and among these 53% were for 14 days and 30% were for 7 or 10 days. This regimen has continued to be used despite data that the cure rates with standard triple therapy had fallen below 80% by 2000.[10–13] The issue of falling cure rates was not incorporated into the guidelines until 2012[14] and not explicitly until 2017.[1] Moreover, despite declining eradication rates with standard triple therapy, gastrointestinal physicians report confirming *H pylori* eradication in only 58% of cases.[9]

Clearly, a knowledge gap regarding best practices for *H pylori* diagnosis and therapy exists even among physicians most likely to be considered experts by their colleagues, and despite regularly updated guidelines, many gaps persist in practice. The guidelines developed by this consensus group focused on identifying the target populations for diagnosis and therapy with the aim of providing practical advice for US practitioners and recommendations for guidelines and to be adopted by US health care systems.

Clearly, performance gaps exists in the practice of *H pylori* diagnosis and therapy even among expert physicians, and despite regularly updated guidelines. We convened a

consensus conference to develop a set of recommendations for appropriate diagnostic testing and treatment strategies focusing on eradication of active *H pylori* infections. These recommendations would provide practical advice for US practitioners, and also guidelines to be adopted by US health care systems.

Methods

The first step was to identify areas that would potentially be discussed at the meeting and to develop a set of draft consensus statements. This was done by the meeting leaders, Drs Graham and El-Serag, who compiled a list of important unresolved issues that included: (1) the impact of *H pylori* on gastric pathology if left untreated; (2) the amount of unnecessary hospitalizations due to *H pylori*–related gastric pathology; (3) the ability to reduce antibiotic overuse (or misuse) through active infection testing; and (4) the role of a test-treat-test strategy for *H pylori* diagnosis and eradication confirmation in the outpatient setting. We prepared draft consensus statements for the following 4 key topics related to *H pylori* management: (1) Who are the appropriate patient groups for testing?; (2) What is the impact of antibiotic susceptibility on testing and treatment of *H pylori* infection; (3) What are the appropriate testing methods for confirmation of eradication?; and (4) What are the health system considerations that are relevant to *H pylori* testing?

We used a modified Delphi panel approach, which is an iterative, evidence-based process that combines the best available scientific data with the collective judgment of experts to develop the consensus statements. For each of the draft consensus statements, key references were identified, and with the assistance of a commercial vendor (Hospicom, Cold Spring, NY) draft consensus statements were developed.

We identified an 11-member, multidisciplinary, expert panel consisting of opinion leaders in *H pylori* management from different geographic regions of the United States to assess the appropriateness of the candidate statements. Participants included adult and pediatric gastroenterologists, family and internal medicine practitioners, and experts in laboratory medicine. The group was sufficiently large to provide geographic, practice setting, and knowledge/attitude/belief diversity, and small enough to allow the dynamic exchange in a group discussion.[15] The panel members met in a 1-day face-to-face meeting.

Before the meeting, copies of the draft statements were sent to the invited panel members and the invitees were instructed to review, revise, and modify the draft consensus statements. Invitees were also instructed to review the available evidence and to be able to present the evidence and debate the issues at the face-to-face meeting designed to result in a consensus among the group for each statement. Each invitee was directed to prepare their point of view on each statement they were assigned and to state whether they agreed with the statement as written or to propose revisions and to provide the evidence in both cases. All invitees were asked to vote on all the statements for group consensus results.

The Expert Consensus Development Meeting was held in Houston, Texas, on October 28, 2016, to refine and vote on the statements. The quality of evidence and strength of recommendations were evaluated using the GRADE system (Table 1).[16,17] Voting was done

using ballots which were immediately tabulated and the levels of agreement were shown on the screen using a 5-point Likert-type scale with responses ranging from 1 (*strongly disagree*) to 5 (*strongly agree*).

The attendees were divided into 3 work groups: (1) identification of appropriate patients for testing; (2) antibiotic susceptibility testing and treatment of *H pylori* infection; and (3) testing methods and confirmation of eradication. The teams refined and revised the statements and either agreed with the statement as written or provided a revised statement. Additionally, they were also asked to provide key references and to assign a grade and level of evidence for each statement. The statements and rationale were then presented to the full meeting participants and all statements were assigned a score using the 5-point Likert-type scale regarding the level of agreement. The statements either achieved consensus, when 80% or more indicated they strongly agreed or agreed with the statement, or achieved no consensus. Those statements failing to achieve consensus underwent postvote revision with full group discussion followed by a second and final vote to attempt to reach consensus.

External Validation

After the Expert Consensus Development meeting at which the statements were refined or revised, and the consensus was reached, an external validation was done where the statements were posed to a separate panel of gastroenterologists to assess their level of agreement with statements designed by the expert panel. Validation was tested using an online survey that assessed the level of agreement with each of the 29 statements previously developed at the Expert Consensus Development Meeting was assessed using a 5-point Likert-type scale with responses ranging from 1 (*strongly disagree*) to 5 (*strongly agree*).

The validation group was identified by an expert contract group (SERMO, New York, NY) who identified 100 respondents who met all the criteria listed in Supplementary Tables 1 and 2 from a panel of 4100 U.S.-based gastroenterologists. Each respondent received a nominal incentive of $15 to complete the survey. The results of their responses were then tabulated and compared with those of the expert panel.

Role of the Sponsor

The consensus conference was sponsored by Otsuka America Pharmaceutical, Inc (OAPI). Each conference participant received an honorarium from OAPI. Members of OAPI's Medical Device Division were present and made brief introductions, but were not involved in substantive discussions or drafting of the manuscript. The final draft of the manuscript was reviewed by OAPI.

Meeting Logistics and Coordination

Planning for the meeting including meeting logistics and coordination of travel was done by Hospicom. Additionally, Hospicom helped to identify the appropriate references, provided a scribe for each working group, managed the details of blinded voting, and assisted in preparing the slides used to present the drafts of the statements.

Results

The 11 members of the working group met in Houston, Texas, for an all-day meeting to discuss, debate, and revise the statements drafted in advance of the meeting. The original topics were: (1) identification of appropriate patients for testing (14 statements); (2) antibiotic susceptibility testing and treatment of *H pylori* infection (5 statements); and (3) testing methods and confirmation of eradication (11 statements; 1 statement was duplicated and in 2 groups). The group achieved consensus (defined as 80% or more agreed or strongly agreed) for 27 of the 29 statements. All 29 statements were submitted to the external review panel, and 6 statements, including the 2 not agreed upon by the expert panel, did not achieve consensus when reviewed by the external panel. All 6 of the statements that did not achieve consensus were within the "Identification of Appropriate Patients for Testing" topic. Finally, the statements were reformatted as recommendations using published guidelines.[18]

Statements

Identification of appropriate patients for testing approved by both the panel and the external group

- *Statement 1:* We recommend that all patients with active *H pylori* infection be treated (100% agree/strongly agree, Grade 1A).

- *Statement 2:* All patients with current or past gastric or duodenal ulcers should be tested for *H pylori* infection (100% agree/strongly agree; Grade 1A).

- *Statement 3:* We recommend that all patients with uninvestigated dyspepsia be tested for *H pylori* infection (100% agree/strongly agree, Grade 1A).

- *Statement 4:* We recommend routine testing for *H pylori* infection in patients with reflux symptoms only if they are at high risk for *H pylori*-related disease (91% agree/strongly agree, Grade 1C).

- *Statement 5:* We recommend that patients with gastric mucosa-associated lymphoid tissue (MALT) lymphoma be tested for *H pylori* infection (100% agree/strongly agree, Grade 1B).

- *Statement 6:* We recommend that individuals with family history of gastric cancer be tested for *H pylori* infection (100% agree/strongly agree, Grade 1B).

- *Statement 7:* We recommend that patients who are first-generation immigrants from high prevalence areas be tested for *H pylori* infection (82% agree/strongly agree, Grade 1B).

- *Statement 8:* We suggest that patients of Latino and African American racial or ethnic groups may be considered for *H pylori* testing due to their high risk of infection (91% agree/strongly agree, Grade 2C).

The underlying principles regarding testing for *H pylori* are that *H pylori* infection is associated with a significant risk of important clinical outcomes, and that risk is not predictable for a given individual. The infection causes chronic progressive damage to the gastric mucosa that in 20%–25% of individuals will result in life-threatening clinical

outcomes such as peptic ulcer or gastric cancer.[19–22] *H pylori* infection differs from other chronic infections with long latent periods and clinically important outcomes such as tuberculosis and syphilis in that *H pylori* remains transmissible (Statement 1).[19] Therefore, the Kyoto consensus guideline defined H pylori as an infectious disease that when diagnosed should be cured unless there are extenuating circumstances.[4] While in the United States the prevalence of *H pylori* infection is relatively low in the overall general population, there are large sub-populations (eg, African Americans, Hispanics, Korean Americans, Chinese Americans) with high *H pylori* prevalence and increased risk of important clinical outcomes such as peptic ulcer or gastric cancer.[21,23,24]

H pylori is etiologically related to gastric and duodenal ulcers, gastric cancer, and MALT lymphoma.[25] Peptic ulcer disease is one of the most common and important clinical manifestations of *H pylori* infection. Patients with a current or past history of a gastroduodenal ulcer should be considered to be at risk of peptic ulcer disease until the cause of the disease is eliminated (Statement 2). The natural history of peptic ulcers in patients with uncured *H pylori* ulcer disease is complicated with potentially life-threatening complication, most often bleeding in approximately 25% of the infected individuals.[19,20] Cure of the infection results in healing of peptic ulcers and prevention of recurrence and ulcer complications such as bleeding or rebleeding.[26]

Dyspepsia has been defined as predominant epigastric pain lasting at least 1 month.[27] Patients with uninvestigated dyspepsia represent a special problem because their clinical presentation overlaps with the presenting symptoms of *H pylori*–related peptic ulcer disease (Statement 3). *H pylori* is one of the causes of dyspepsia in the absence of peptic ulcer. However, the number needed to treat for *H pylori* to achieve 1 symptomatic response has been estimated at 8,[28] perhaps due to the delayed or exaggerated response of the functional components of the patient's symptomatology. The recommendation to test and treat those with dyspepsia and *H pylori* infection has been included in the Kyoto, Maastricht, American College of Gastroenterology, and Canadian consensuses.[1,2,4,27] Although *H pylori* eradication may not resolve the clinical problem of dyspepsia in most patients, successful *H pylori* eradication therapy will reduce significantly the long-term risk of developing either peptic ulcer or gastric cancer.[29] While many infected patients remain asymptomatic and may never develop complications, there are no predictors to determine which patients with non-atrophic *H pylori*-associated gastritis that, if left un-treated, will not progress.[4]

Gastroesophageal reflux disease (GERD) is typically a manifestation of robust acid secretion and an abnormal esophagogastric antireflux barrier. In the US population, where *H pylori* is infrequent, there is an inverse correlation between the prevalence of *H pylori* and erosive esophagitis or Barrett's esophagus.[30] Thus, the recommendation not to routinely use noninvasive testing for *H pylori* in patients with GERD unless they are at high risk for *H pylori* disease (eg, on the basis of ethnic group; Statement 4). While this may seem to conflict with the recommendation that *H pylori* eradication be considered for patients who use proton pump inhibitors (PPIs), that recommendation is limited to the subset of GERD patients in whom longer term PPI use is planned (Statement 10). High acid output is also associated with antral predominant *H pylori* gastritis and with duodenal ulcer disease. If endoscopy is done for any reason such as to evaluate heartburn symptoms, it would be

prudent to include gastric biopsy to exclude *H pylori* infection. Treatment of *H pylori* in patients with GERD does not alter the course or treatment of that disease.[1,31]

Gastric B cell lymphoma (also known as MALT lymphoma) and gastric cancer are both etiologically related to *H pylori* infection.[32] Because MALT lymphoma is often responsive to *H pylori* eradication, it is recommended that all patients with gastric MALT lymphoma be tested for *H pylori* with the idea that treatment will usually produce a remission or even a cure (Statement 5).[33]

First-degree relatives of those with symptomatic *H pylori* disease such as peptic ulcer or gastric cancer are usually raised in the same environment and household as the affected patient (Statements 2 and 11).[34] Because *H pylori* is primarily acquired in childhood and transmitted within families, first-degree relatives are at increased risk of *H pylori* infection and disease outcomes, leading to the recommendation that these individuals are candidates for an *H pylori* test and treat strategy (Statement 2 and 6).[35] Whether it is cost effective to extend this recommendation to all family members, particularly those in close contact with an *H pylori*–infected individual, is unknown but seems reasonable.

In many areas of the world, *H pylori* infections are still common as reflected by gastric cancer still being the fourth most common cause of cancer deaths.[36] Japan, Korea, China, and Taiwan all have particularly high gastric cancer rates and have either begun or are considering, countrywide *H pylori* screening and eradication for gastric cancer prevention.[4,29,37] The prevalence of *H pylori* infection is high among people born in those areas, and they retain the infection and the associated high risk of gastric cancer despite immigration to low gastric cancer countries such as the United States.[38] These individuals become part of the US population at increased risk of gastric cancer, and should be considered for an *H pylori* test and treat program (Statements 7 and 8). Latino and African American racial-ethnic groups in the United States also have an increased prevalence of *H pylori* and an increased risk of gastric cancer (Statement 8).[23] Those with extensive atrophy should also be considered for cancer surveillance if such a program and expertise is available locally.[29]

Achieving consensus by the expert panel but not by the external reviewers

In most instances, the expert panel and external validation panel were in high agreement. The reasons offered for disagreement are shown in Supplementary Figures 1–6 for each question where the 2 groups differed. These generally related to the less well-known associations of *H pylori* with diseases or conditions, and in which there were relatively few large and high quality clinical trials on which to base judgement.

- *Statement 9:* We recommend that patients with idiopathic thrombocytopenia be tested for *H pylori* infection (experts vs survey: 100% vs 68% agree/strongly agree, Expert Grade 1B) (Supplementary Figure 1).

This statement is based on observational data showing that antimicrobial therapy may be associated with improved platelet counts in idiopathic thrombocytopenia.[39] Those infected with a CagA-positive *H pylori* infection are most likely to show increased platelet count following successful H pylori eradication therapy.[39–42] Much of the positive literature comes from Japan, where most infections are CagA positive. The American Society of Hematology

2011 guidelines (which are at this time under revision) have recommended *H pylori* testing and eradication of *H pylori* infection in adults with idiopathic thrombocytopenia (ie, "Screening for *H pylori* should be considered in adults for whom eradication therapy would be undertaken if testing were positive. Eradication therapy for *H pylori* should be administered to patients who are found to have an infection").[43] In the United States, CagA-positive strains are less prevalent than in Asian countries and thus one should expect a lower response rate than in Asian countries.

- *Statement 10:* We suggest that patients receiving long-term PPIs (>1 month) be tested for *H pylori* infection (experts vs survey: 82% vs 68% agree/strongly agree, Expert Grade 2C) (Supplementary Figure 2)

This statement is based on studies suggesting an association between PPI use and increased risk of developing atrophic gastritis, the acknowledged primary risk factor (or predisposing lesion) for gastric cancer.[44–48] Their observation of an acceleration in the development and severity of corpus gastritis, including enhanced development of intestinal metaplasia, has been supported by a number of other studies.[49–52] Detailed studies have shown that by reducing acid secretion in the gastric corpus, PPI therapy alters the *H pylori* corpus mucosa interaction, allowing the infection to extend into the gastric pits, where it elicits an inflammatory response that involves the proliferative zone.[53] However, long-term clinical data to substantiate clinically adverse outcomes with PPI use in such cases are still lacking.

- *Statement 11:* We recommend that family members residing in the same household of patients with proven active *H pylori* infections undergo *H pylori* testing (experts vs survey: 91% vs 78% agree/strongly agree, Expert Grade 1B) (Supplementary Figure 3).

- *Statement 12:* We recommend that individuals with a family history of peptic ulcer disease be tested for *H pylori* infection (experts vs survey: 91% vs (73% agree/strongly agree, Expert Grade 1B) (Supplementary Figure 4).

These statements are based on the concept that it is reasonable to search and, if present, eradicate *H pylori* in high-risk groups. *H pylori* infections are usually acquired during childhood and spread among families.[54–57] Thus, first-degree relatives of those with *H pylori* are also likely to be at higher risk of H pylori acquisition and of *H pylori*–related diseases (peptic ulcer and gastric cancer) than the general US population.[34,58–61]

Failed to achieve consensus by the panel and external group

- *Statement 13:* We suggest that patients taking daily nonsteroidal anti-inflammatory drugs for more than short periods (eg, >1 month) be tested for *H pylori* infection (experts vs survey: 73% vs 68% agree/strongly agree, Expert Grade 2C) (Supplementary Figure 5).

This statement is based on observational data showing that the presence of an *H pylori* infection is associated with approximately double the risk of bleeding as a nonsteroidal anti-inflammatory drugs complication, and clinical trials data showing that *H pylori* eradication markedly reduces the risk of bleeding among those using aspirin daily.[62,63]

- *Statement 14:* We suggest that *H pylori* testing be considered in patients treated with medications whose absorption is known to be impacted by infection (eg, L-DOPA, thyroxin; experts vs survey 63% vs 68% agree/strongly agree, Expert Grade 2C) (Supplementary Figure 6).

This statement was based on limited evidence that *H pylori* infection reduces the bioavailability of a number of drugs, possibly by reducing intragastric pH. There are data regarding the effectiveness of bioavailability of iron, thyroxin, L-DOPA, possibly delavirdine, and ketoconazole.[64–66]

Antibiotic susceptibility testing and treatment of H pylori infection approved by both the panel and the external group

- *Statement 15:* We recommend that empiric eradication therapy for *H pylori* be based on region or population-specific antibiotic susceptibility data (91% agree/ strongly agree, Grade 1B).

- *Statement 16:* We recommend consulting an expert following 2 proven unsuccessful treatment attempts with different antibiotics suggesting multidrug resistance (82% agree/strongly agree, Grade 1B).

- *Statement 17:* We recommend that validated diagnostic testing of stool or gastric mucosal biopsy by culture and susceptibility, or molecular analysis be universally available (100% agree/strongly agree, Grade 1).

- *Statement 18:* We suggest that antibiotics that may be routinely evaluated for susceptibility include amoxicillin, clarithromycin, levofloxacin, metronidazole, and tetracycline (100% agree/strongly agree, Grade 2C).

- *Statement 19:* We recommend that professional societies provide the research needed to support evidence-based reimbursement decisions for antibiotic susceptibility testing for *H pylori* (100% agree/strongly agree, Grade 1).

Discussion of Statements Regarding Antibiotic Susceptibility Testing and Treatment of H pylori *Infection*

H pylori is an infectious disease caused by a Gram-negative spiral bacterium. Since the introduction of antibiotics, the basis of choice of therapy has been to use a susceptibility-based approach.[67] Traditionally, antimicrobial treatment regimens are first optimized in terms of treatment parameters such as drugs, doses, formulations, methods of administration, and the frequency and duration of administration to reliably achieve the highest cure rates obtainable. For most common infectious dis-eases, there may be more than 1 choice (Table 2). New acceptable regimens are those confirmed to be non-inferior to the best current regimens.[10,68,69] Choice of the best regimen for the individual patient is then based on secondary parameters such as availability, cost, methods of administration, the presence of allergy, and patient tolerance and compliance. The timing of initial therapy should be guided by the urgency of the situation.[67] As *H pylori* infections are typically acquired in childhood and present in adulthood, there are few, if any, situations where urgent therapy is needed.

H pylori is susceptible to a variety of widely available antibiotics. Because community, region, and countrywide antimicrobial surveillance for *H pylori* are not yet available, providers are generally required to choose a therapy empirically.[68] One definition of empiric antibiotic therapy is drug selection based on experience and relevant indirect information including current resistance patterns (http://amrls.cvm.msu.edu/integrated/principles/pharmacology). The lack of knowledge of current *H pylori* resistance patterns places a requirement on the provider to obtain history of prior antimicrobial use by the patient, and to have knowledge of the local or regional success with different antimicrobial regimens. Because antimicrobial susceptibility testing is available locally for essentially all other important pathogens, it seems reasonable that it should also be offered for *H pylori* and that *H pylori* should be included in local, regional, and national antimicrobial surveillance programs. The main issues preventing this from being realized include lack of a demand for the services and reimbursement for testing. As molecular testing becomes more feasible and practical, it seems likely that it should become available at least for clarithromycin and fluoroquinolones.[70] However, the problem of securing appropriate reimbursement remains to be solved.

Antimicrobial resistance is generally related to antibiotic use in the community (ie, increasing antibiotic use leads to an increasing prevalence of resistance). Over the last 3 decades, macrolide and fluoroquinolone use have markedly increased with a concomitant increase in their resistance in *H pylori*. Most clinical trials of antimicrobials for *H pylori* therapy have generally not featured susceptibility testing. Recommendations by professional societies have generally focused on the results of comparisons of trials done in populations where antimicrobial resistance has greatly affected outcomes.[71] As such, a recommendation that regimen A is superior to B is often based on results of meta-analysis in which both regimens achieved unacceptable low cure rates due to resistance. However, these results are population-specific and not generalizable.[71] For example, the results in the comparison may show an average cure rate of 76% for a regimen such as bismuth quadruple therapy, which reliably achieves 95% or greater cure rates with adherent patients with susceptible infections. It has also resulted in the pragmatic misuse of antibiotics such that all or most subjects receive an antibiotic that will have no beneficial effect on the outcome of their infection. Examples include the recommendation to use a 4-drug therapy such as concomitant therapy which consists of a PPI, amoxicillin, metronidazole, and clarithromycin.[68,71] The rationale is that while clarithromycin and metronidazole resistance may have individually undermined clarithromycin or metronidazole triple therapies, as long as the prevalence of combined metronidazole-clarithromycin resistance is low the therapy will likely be successful. However, all patients will receive at least 1 antibiotic that is not needed (eg, metronidazole for those with clarithromycin susceptible infections) and contribute to worldwide resistance. In Japan, about 1 million patients each year receive vonoprazan-clarithromycin triple therapy.[72] Approximately 80% of patients would be cured by the vonoprazan-amoxicillin components and receive clarithromycin unnecessarily.[71] As clarithromycin resistance has increased to approximately 50% in Japan the cure rates overall have now fallen to below 90% on average.

There are a number of *H pylori* treatment regimens that reliably cure at least 95% of infections in adherent patients with susceptible organisms.[10] The goal should be to reliably

identify which regimen is best for an individual patient. All statements below relate to that objective, requiring that the clinician have the data needed to choose a patient-specific regimen. In the United States, *H pylori* resistance patterns are not generally known and there has been only 1 relevant study published in the last decade from a single center.[73] From that one publication, it appears that resistance to clarithromycin, metronidazole, and fluoroquinolones has increased to the point that they should not be used as empiric triple therapies.[73] Resistance to amoxicillin, tetracycline, and rifabutin remain rare.

Testing methods and confirmation of eradication approved by both the panel and the external groups

- *Statement 20:* We recommend the use of tests for active *H pylori* infection (ie, UBT, HpSAg testing) for the initial diagnosis (100% agree/strongly agree, Grade 1A).

- *Statement 21:* We recommend that, if endoscopy is being performed, biopsies (2 each) from the antrum and corpus (± the incisura) should be obtained (100% agree/strongly agree, Grade 1A).

- *Statement 22:* We recommend that serology not be utilized for detection of active *H pylori* infection (100% agree/strongly agree, Grade 1A).

- *Statement 23:* We recommend that bismuth and antibiotics be stopped at least 4 weeks before *H pylori* testing with tests for active infection (ie, UBT, and HpSAg testing and histology; 100% agree/strongly agree, Grade 1C).

- *Statement 24:* We recommend that PPIs should be discontinued at least 4 weeks before UBT and HpSAg testing (100% agree/strongly agree, Grade 1B).

- *Statement 25:* H2 blockers and antacids may be utilized without affecting the accuracy of UBT and HpSAg testing (100% agree/strongly agree, Grade 1A).

- *Statement 26:* When PPIs are not discontinued before testing, we recommend that a positive test for active infection still be considered a positive result. However, when PPIs are not discontinued before testing and there is a negative test result, we recommend repeat testing for diagnosis after an appropriate interval due to the possibility of a false-negative test (100% agree/strongly agree, Grade 1C).

- *Statement 27:* We recommend that all patients receiving treatment for *H pylori* receive posttreatment confirmation of eradication. We recommend that only tests that evaluate for active infection, such as UBT, HpSAg test, or histology (if endoscopy is required for other reasons), are utilized for this purpose (100% agree/strongly agree, Grade 1A).

- *Statement 28:* Once appropriate testing has confirmed eradication, we recommend against further *H pylori* testing, (100% agree/strongly agree, Grade 1C).

Testing methods and confirmation of eradication

We recommend post-treatment confirmation of eradication in part because failure to eradicate leaves the patient at risk for clinical outcomes associated with the infection, and also because current therapies fail in at least 20% of cases. For most patients, noninvasive testing is preferred. The UBT relies on the fact that *H pylori* contain the non-human enzyme urease which will hydrolyze ingested urea into ammonia and carbon dioxide. The simplest tests measure the appearance of labeled carbon dioxide in the breath after oral administration of 13C- or 14C-labeled urea. The most widely used UBT administers both 13C-urea and citric acid, which serves to acidify the stomach and enhance urease activity. Citric acid results in a higher positive signal by inhibiting urease activity caused by the presence of other urease-containing organisms in the stomach. HpSAg testing is based on the presence of *H pylori* antigens in stool. A number of HpSAg tests have been developed with those using monoclonal antibodies are most reliable. Whichever test is chosen it is important to use a well-validated test and to be aware of the factors that predispose to false positive and false negative results.

The most common factor causing false negative tests is a low density of *H pylori* in the stomach translating into low urease activity and a low antigen load in the stool.[74] The most common cause of a low antigen load is the use of antimicrobials including bismuth or PPIs. This will also affect the diagnostic accuracy of all invasive tests (histology, culture, and rapid urease) as well as some noninvasive tests (UBT and HpSAg), but not serology testing.[74] After antimicrobial therapy, bismuth, or PPI use, any residual *H pylori* will repopulate the stomach. Generally, the longer one waits after completing therapy, the more accurate the result. Clinical trials have shown that 4 weeks post-therapy or PPI use provides the most accurate ability to separate infected from uninfected subjects.[75] H2 receptor antagonists do not inhibit *H pylori* so if an antisecretory drug is needed they can be substituted for a PPI. H2 receptor antagonists may reduce urease activity, so they should not be administered the same day as the UBT, which ideally would also contain citric acid. Serology-based tests are not recommended for diagnosis of an active *H pylori* infection because the antibodies may remain positive for decades after *H pylori* eradication.[76]

H pylori can be visualized by histology and cultured from gastric biopsies, mucus, and even fluid. The density of *H pylori* may vary, and it is, therefore, important to obtain both antral and corpus biopsies when using histology to detect *H pylori*.[77–79] The presence of gastric mucosal inflammation, particularly polymorphonuclear leukocytes (eg, chronic active gastritis) is highly suggestive of *H pylori* infection, and should prompt a more detailed examination. If the patient was recently taking antimicrobials or PPIs, the bacterial load may be low, and there may be an overgrowth of other bacteria that may confuse some pathologists. However, chronic active gastritis will not be present in these cases. When in doubt, immunohistochemistry is the preferred method of confirming the presence of *H pylori* in biopsy material.[80]

With any test, interpretation depends on the sensitivity and specificity as well as pretest probability. A discussion of the importance of pretest probability is presented in the supplemental material.

General Statements

- *Statement 29:* The absence of gastric atrophy, intestinal metaplasia or dysplasia at the time of initial biopsy does not preclude development of subsequent serious pathology (eg, ulcer, malignancy) if *H pylori* infection persists (100% agree/ strongly agree, Grade 1A).

Although the natural history of *H pylori* gastritis is for progressive gastric mucosal damage, the outcome of an individual infection is unpredictable.[78,79] Once atrophic gastritis is present the risk of gastric cancer is elevated, and while *H pylori* eradication may stop the progress of gastritis and thus reduce or limit the risk, the current thought is that the clock cannot be reset completely. Infected individuals are at risk of transmitting the infection, developing a peptic ulcer with or without complications, and developing gastric cancer. The lack of a history of symptoms suggestive of extensive damage provides no predictive value of future complications. This provides further support for Statement 1. "We recommend that all patients with active *H pylori* infection be treated."

Concluding Statements

The guidelines developed by this consensus group focused on identifying the target populations for diagnosis and therapy with the aim of providing practical advice for US practitioners. Both the Expert Consensus Panel and the validation panel agreed on the majority of statements. The lack of widespread availability of susceptibility testing was seen as a major barrier to effective and reliable therapy. These guidelines provide a basis for guidelines to be adopted by US health care systems.

Potential Issues With Serology and the Problem of False Positive Tests

With any test, interpretation depends on the sensitivity and specificity as well as pretest probability. For example, when used in screening in asymptomatic individuals, or in low *H pylori* prevalence areas, many positive tests will be false positive results. Consider a population of 1000 asymptomatic US individuals in which the prevalence of *H pylori* is 15%. Available tests vary in sensitivity and specificity ranging from a high of approximately 95% for the urea breath test or a second-generation monoclonal-based stool antigen immunoassay to a low of 70% or less for some in-house serologic tests. Supplementary Table 3 shows the results of testing depending on the sensitivity and specificity of the available tests. The table shows the positive and negative likelihood ratios, the number of positive and negative test results, and the proportion that are true positive and true negative. Even with the most sensitive and specific tests (eg, 95%) only 77% of positive tests are correct and this proportion rapidly falls as the specificity and sensitivity decrease. For example, a serologic test that is 75% sensitive and specific would produce 324 positive results, of which only 150 were true positives (http://araw.mede.uic.edu/cgi-bin/testcalc.pl). Supplementary Figure 7 shows the marked effect of disease prevalence on the positive and negative predictive values, which is reflected in most negative tests being correct in low disease prevalence situations. If the true prevalence rate were only 4%, only 20% of positives would be true positives. In populations with a high pretest probability such as a population of duodenal ulcer patients, the results would be reversed and we would need to

question whether negative tests were correct. For example, in 1000 patients with a pretest probability of *H pylori* duodenal ulcer of 85%, we would have 744 positive tests, of which 97% would be true positives, and 256 negative tests, of which 50% would be false negatives (95% confidence interval, 46%–54%). The marked effect of disease prevalence on positive and negative predictive values results in the recommendation to confirm all positive tests in conditions of low pretest probability and all negative tests when the pretest probability is high. In the study mentioned above only 4.2% of the serologic tests were positive.[7] Confirmation requires that the second test differ in mechanism from the original one,[8] such that serology would be confirmed with a urea breath test, stool antigen immunoassay, or histology. This problem is not restricted to serology and extends to all diagnostic testing.

To continue with the example above where the disease prevalence is 15%, treating all the positives would result in treatment of an additional group of false positive cases which would increase the number treated by 33% with the 95% specific or sensitive test, 50% with the 85% specific or sensitive test and 65% specific or sensitive with the 75% test. In theory, to prevent this antibiotic misuse, all positive tests should be confirmed before treatment except in populations with a high pretest probability. Retesting of any positive result has been suggested.[8] However, this provides a poor solution. For example, with a 75% sensitive or specific test and 15% *H pylori* prevalence among 1000 patients would yield 334 positive tests and only 150 *H pylori*–infected (Supplementary Table 1). The positive tests would include only 112 of the 150 with *H pylori* infections, as 38 (25%) would have been scored as false negative and never retested. Although confirmation retesting the group with positive tests (pretest probability 34%) with a 95% sensitive or specific test would identify the majority of the 112 with *H pylori* infection, the overall treatment rate for the 150 infected would be <75%. Overall, even tests with high sensitivity and specificity perform relatively poorly in low pretest probability conditions, while tests with a sensitivity and specificity below 90% should be avoided.

In the United States, large commercial testing laboratories may utilize "in-house" developed tests that are not Food and Drug Administration (FDA) approved.[7] Therefore, in the United States one should always demand that diagnostic laboratories use only FDA-approved tests. One clue to identifying unapproved tests is a report showing results for *H pylori* IgG, IgA, and IgM. IgA and IgM *H pylori* diagnostic tests are rarely FDA approved; generally only IgG tests provide reliable results.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Dr Crowe noted being an author of several topics for UpToDate. Dr. Graham is a consultant for RedHill Biopharma regarding novel *Helicobacter pylori* therapies and has received research support for culture of *H pylori* and is the PI of an international study of the use of antimycobacterial therapy for Crohn's disease. He is also a consultant for BioGaia in relation to probiotic therapy for *H pylori* infection and for Takeda in relation to *H pylori* therapies.

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Table 1.

GRADE: Quality of Evidence and Strength of Recommendations

Quality of evidence	
A. High quality	Further research is very unlikely to change our confidence in the estimate of effect
B. Moderate quality	Further research is very unlikely to have an important impact on our confidence in the estimate of effect and may change the estimate
C. Low quality	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
D. Very low quality	Any estimate of effect is very uncertain
Strength of recommendation	
1. Strong Recommendation:	Strong recommendation for using an intervention/strong recommendation against using an intervention
2. Weak recommendation	Weak recommendation for using an intervention/weak recommendation against using an intervention

Table 2.

General Principles of Antimicrobial Therapy

- Obtaining an accurate diagnosis

- Understanding the difference between empiric and definitive therapy

- Understanding drug characteristics that are peculiar to antimicrobial agents (eg, pharmacodynamics and efficacy at the site of infection)

- Accounting for host characteristics that influence antimicrobial activity

- Recognizing the adverse effects of antimicrobial agents on the host

- Knowing when to consult specialists for guidance

NOTE. Adapted from Leekha et al.[67]