ANNUAL REVIEWS

Annual Review of Medicine

Diagnosis and Treatment of *Helicobacter pylori* Infection

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Annu. Rev. Med. 2022. 73:183–95

The *Annual Review of Medicine* is online at med.annualreviews.org

https://doi.org/10.1146/annurev-med-042220-020814

Keywords

Helicobacter pylori, testing, antimicrobial therapy, gastric cancer, antimicrobial stewardship, antibiotic resistance, molecular techniques, guidelines

Abstract

The last 5 years have seen major shifts in defining whom to test and how to treat *Helicobacter pylori* infection. Peptic ulcer has changed from a chronic disease to a one-off condition, and countries with a high incidence of gastric cancer have begun implementing population-wide screening and treatment. A proactive approach to testing and treatment of *H. pylori* is now recommended, including outreach to family members of individuals diagnosed with active infection as well as high-risk local populations such as immigrants from high-risk countries. Increasing antimicrobial resistance has resulted in an overall decline in treatment success, causing a rethinking of the approach to development of treatment guidelines as well as the need to adopt the principles of antibiotic usage and antimicrobial stewardship. Required changes include abandoning empiric use of clarithromycin, metronidazole, and levofloxacin triple therapies. Here, we discuss these transformations and give guidance regarding testing and use of therapies that are effective when given empirically.

INTRODUCTION

Helicobacter pylori gastritis is etiologically related to peptic ulcer and gastric cancer. The infection is generally acquired in childhood especially via transmission within families. This tendency to cluster within families is in part responsible for the clinical observation that the risk of peptic ulcer disease and gastric cancer is increased within families. Among those with *H. pylori* infection, the lifetime risk of peptic ulcer is approximately 1 in 6 (~17%). In 1900, gastric cancer was the most common cancer worldwide. In the United States, it held that distinction until 1975 (1), when it was surpassed by lung cancer. Gastric cancer is the sixth most common cancer worldwide and the third most common cause of cancer death, with 1,089,103 new cases diagnosed in 2020, and was responsible for more than 768,793 deaths in that year (2). Worldwide, the lifetime risk of developing gastric cancer varies from approximately 0.6% to 22% (see below). The rapid decline in *H. pylori* related gastric cancer in the United States and other Western countries was associated with improvements in food preservation (e.g., refrigeration replacing salt) and food transportation. Together, these improvements resulted in a change from a seasonal diet, with a paucity of ascorbic acid–containing foods during the winter, to one where fresh vegetables and fruits were available year-round. This change, and fortification of food with vitamin C, resulted in a marked decrease in the rate of progression from superficial gastritis to atrophic gastritis and a progressive decline in the prevalence of gastric cancer. Improvement in stomach health and the resulting increase in acid secretion resulted in an increase in duodenal ulcers (3). In the 1970s, it was estimated that there were 500,000 new cases of peptic ulcer each year, with more than 400,000 hospitalizations and more than 4,000,000 hospital days devoted to the treatment of peptic ulcers (4). Peptic ulcers were also responsible for 140,000 operations and 9,000 hospital deaths per year (4). Because peptic ulcer remained a major health problem, the National Institutes of Health targeted support and introduced the Centers for Ulcer Research and Education (CURE) in 1974 (3, 5).

Clinically, peptic ulcer disease was a chronic disease; its course has been described using the adage "once an ulcer, always an ulcer." The discovery of *H. pylori* in the early 1980s and subsequent proof that a bacterial infection caused peptic ulcer disease changed peptic ulcer from a chronic disease into a one-off, as cure of *H. pylori* infection prevented ulcer recurrences as well as development of new cases of peptic ulcer disease.

It had long been recognized that atrophic gastritis was tightly linked to gastric cancer (6). Despite the recognition that *H. pylori* was the primary cause of atrophic gastritis, acceptance of the hypothesis that eradication of *H. pylori* could both prevent and reduce the incidence of gastric cancer was slow and seemingly reluctant. It took more than a decade after *H. pylori* was defined as a human carcinogen before it was widely accepted that *H. pylori* infection caused gastric cancer and that cure of the infection would also reduce the incidence of, or prevent the development of, gastric cancer.

In more affluent countries, the prevalence of *H. pylori* infection has steadily declined due to a fall in the rate of transmission of *H. pylori* to children. This change was related to improvements in sanitation, standards of living, and housing, especially provisions for indoor plumbing and clean water. These advances resulted in a marked fall in the prevalence of many infectious diseases including *H. pylori* gastritis. Overall, the reduction in disease acquisition resulted in successive birth cohorts each having a progressively lower prevalence of *H. pylori* infection and ultimately of gastric cancer. This process is now being repeated in many of the rapidly developing regions of the world. Even in affluent populations, prevalence relates to socioeconomic status such that previously disadvantaged subpopulations still have a relatively high proportion of infected individuals (7–9). In addition, immigrants from populations with high *H. pylori* prevalence, such as Central and South America, the Caribbean, Eastern Europe, Asia, and India, serve as a reservoir for

H. pylori. Not only do they import the infection to countries with low *H. pylori* prevalence, but their risk of gastric cancer remains similar to that of their home country, thus increasing the healthcare burden of the host country (10).

The purpose of this review is to provide an update on the diagnosis and treatment of *H. pylori* infection. In the last decade, the importance of the infection and the advantages associated with its eradication have become increasingly recognized (11–13). Countries with a high prevalence of gastric cancer such as Japan, Korea, Taiwan, and China have either introduced or are planning to introduce population-wide *H. pylori* eradication programs especially designed to eliminate gastric cancer (14). The United States is a low-prevalence country but includes subpopulations that retain an increased risk of gastric cancer (e.g., Native Americans, blacks, Hispanics, and immigrants from high cancer risk countries) (15). Whether it is cost effective to institute formal eradication programs, general or targeted, in the United States remains unclear. Nonetheless, the criteria guiding when to test and whom, and how to treat *H. pylori* infections, have recently undergone major revisions, which are discussed here. The current consensus is that *H. pylori* gastritis is associated with significant risk to the host and provides no proven benefits.

DIAGNOSIS OF *H. PYLORI* INFECTION

In 2015, the gastroenterology community formally recognized *H. pylori* gastritis as an infectious disease and recommended that whenever *H. pylori* infection was diagnosed, it should be eradicated (11). This recommendation has repeatedly been confirmed by more recent consensus statements (12, 13). The most recent consensus conferences on testing for *H. pylori* infection recommended proactive testing and *H. pylori* eradication (**Table 1**) (12, 13). For example, it was recommended that *H. pylori* testing should be offered to patients with uninvestigated dyspepsia, a history of current or past gastric or duodenal ulcer, a diagnosis of gastric mucosa-associated lymphoid tissue

Table 1 Recommendations for *H. pylori* testing for individuals and populations (adapted from References 12 and 13 with permission)

Houston Consensus Conference recommendations: Which individuals to test?	**Agreement (%)**	**Evidence level**
Individuals with suspected *H. pylori* infection (e.g., active duodenal ulcer)	100	High
Individuals with current or past gastric or duodenal ulcers	100	High
Individuals with uninvestigated dyspepsia	100	High
Individuals with gastric mucosa-associated lymphoid tissue lymphoma	100	Moderate
Family members residing in same household of patients with proven active *H. pylori* infections	91	Moderate
Individuals with family history of peptic ulcer disease	91	Moderate
Individuals with family history of gastric cancer	100	Moderate
First-generation immigrants from high-prevalence areas	82	High
High-risk groups (e.g., in the United States, Latino and African American, and other racial or ethnic groups)	91	Low
Taipei Global Consensus recommendations: Which specific populations to screen?	**Agreement (%)**	**Evidence level**
Populations with high prevalence of gastric cancer	84	Low
Young adults in high-prevalent populations before the development of atrophic gastritis and intestinal metaplasia	84	Low
Young adults in high-prevalent populations to reduce the transmission to their children	92	Low
Populations with high prevalence being integrated or included into the national healthcare priorities	92	Low

lymphoma, a family history of peptic ulcer or gastric cancer, and regular use of nonsteroidal anti-inflammatory drugs (12). Potential high-risk populations such as first-generation immigrants from high-prevalence countries were also targeted for testing. For example, in the United States, the prevalence of *H. pylori* is 2.6-fold higher among Hispanics and 3.2-fold higher among East Asians compared with the general population (16). Once the presence of the infection has been documented, outreach to family members of the index patient is suggested because person-to-person transmission occurs within families (17). Testing all family members and treating the *H. pylori* infected individuals can protect other members from infection, reinfection, and *H. pylori* related diseases. Also, this approach may engage those who test positive to comply with the eradication treatment (18, 19).

METHODS OF DIAGNOSIS

A wide variety of methods is available to detect *H. pylori* infection (20). Because the organism is trophic for gastric epithelium, it is found primarily in the stomach, where it causes a characteristic and easily recognized histologic pattern of acute-on-chronic inflammation (21). Typically, organisms are plentiful and can be detected using special stains, the most accurate of which is immunohistochemistry with *H. pylori* specific antibodies (22, 23). A wide variety of other tests is available, ranging from serologic tests for anti–*H. pylori* IgG antibodies to molecular testing using next-generation sequencing (24). Some tests are noninvasive, while others require endoscopy to sample gastric contents (**Table 2**). Generally, noninvasive testing is preferred (25, 26).

The diagnostic strategy utilized should reflect not only the clinical indication but also the local availability and costs of the different tests, as well as patient preferences. The presence of the infection elicits a serum immune response, and a number of tests for anti–*H. pylori* IgG are commercially available. Until recently, serology was the most commonly used diagnostic test (12). Currently, serology is generally neither recommended nor reimbursed by Medicare. IgA and IgM anti–*H. pylori* tests are also available from some laboratories but are generally not approved by the US Food and Drug Administration (FDA) and are not recommended, or to be trusted, because of their low specificity and sensitivity. When using large commercial laboratories in the United States, it is important to request only FDA-approved tests because commercial laboratories also offer, and often preferentially use, in-house derived tests of unknown specificity and sensitivity. Panels of IgG, IgA, and IgM tests provide no added benefit over IgG tests and generally consist of non-FDA-approved tests of unclear diagnostic value. Serologic tests remain positive long after the infection has been eradicated (a serologic "scar"), and therapeutic decisions should not entirely rely on the results of serologic testing. Current criteria for use of IgG serology include the presence of a very high pretest probability of an *H. pylori* related disease such as an active duodenal ulcer. If serology is done in the absence of a very high pretest probability, it is recommended that before starting treatment, the presence of an active infection be confirmed by a urea breath test (UBT), stool antigen test, or endoscopy depending on the presentation.

Noninvasive tests for active infection include the UBT and the stool antigen test (27, 28). These tests are susceptible to any action that decreases the bacterial load in the stomach, such as use of antibiotics, bismuth, or proton pump inhibitors (PPIs), which temporally reduce the bacterial load and thus can produce false negative rapid urease tests, culture, histology, UBT, and stool antigen tests. Histamine-2 receptor antagonists do not affect bacterial load and can be substituted for a PPI. It is unclear how long the patients should be off such medications; the standard recommendation is 2 weeks. However, since these factors do not produce false positive tests, a positive result can be trusted. When in doubt about a possible false negative test, it is best to repeat the test after a suitable interval (at least 2 weeks). False positive tests

Table 2 Tests for *H. pylori* infection

Tests	Strengths	Weaknesses
Noninvasive		
Serology	Widely available Least expensive Does not require medication modifications prior to testing	Does not reliably delineate between active and previous infection Cannot be used to confirm eradication
Stool antigen test	High sensitivity and specificity Can be used to test for active infection and evaluate for eradication	Stool sample needed, patient aversion Requires prior cessation of antibiotics, bismuth products, or proton pump inhibitors to reduce risk of false negative results
Urea breath test	High sensitivity and specificity Can be used to test for active infection and evaluate for eradication	Resources and trained personnel needed to reliably reproduce test Requires prior cessation of antibiotics, bismuth products, or proton pump inhibitors to reduce risk of false negative results
Endoscopic		
Culture	Allows testing antibiotic susceptibilities	Poor availability in some countries. In the United States, now available from some major laboratories (see text)
Molecular-based testing	Detects infection and can assess susceptibility/resistance for all six commonly used antibiotics Stool can be used Rapid results (days)	May not be covered by insurance Available only as a "send out," e.g., American Molecular Laboratories, Inc. (**http://amlaboratories.com**)
Histology	Can be used to test for infection and evaluate for eradication Provides additional information such as degree of inflammation and associated pathology (e.g., intestinal metaplasia, atrophic gastritis)	Accurate results require interested pathologist and use of special stain, preferably immunohistochemical
Rapid urease tests[a]	Rapid Inexpensive Good sensitivity and specificity	Requires prior cessation of antibiotics, bismuth products, or proton pump inhibitors to reduce risk of false negative results

[a]Also called CLO (*Campylobacter*-like organism) test.

are particularly associated with serology but also can occur with the UBT. For example, the presence of achlorhydria promotes overgrowth of non–*H. pylori* organisms that produce urease (e.g., in a patient with pernicious anemia or atrophic gastritis) and can cause false positive UBTs. False positive tests are a cause of apparent failure of repeated treatment. When false positive tests are suspected, one should confirm the UBT result with a stool antigen test or endoscopy before giving another course of therapy. In histologic specimens, one would expect to find *H. pylori* associated inflammation even if the organism is difficult to find. When there is any doubt, the pathologist should utilize immunohistochemical staining for *H. pylori* (22).

The choice of diagnostic technique depends upon the clinical situation. For example, the best test for a patient presenting with signs and symptoms suggestive of a significant upper gastrointestinal disease such as a peptic ulcer or gastric cancer would be endoscopy with *H. pylori* testing. In contrast, an asymptomatic relative of a patient with peptic ulcer disease would likely

be better served by a noninvasive test such as the UBT or stool antigen test, with the proviso that only stool antigen tests utilizing monoclonal antibodies should be used (29).

H. PYLORI'S MOST DREADED OUTCOME: GASTRIC CANCER

Gastric cancer is the end product of the progression of chronic active gastritis to atrophic gastritis to metaplastic epithelia, intraepithelial neoplasia, and finally invasive carcinoma. Gastric cancer is an inflammation-induced cancer in which *H. pylori* infection both initiates and maintains mucosal inflammation. As noted above, *H. pylori* is typically acquired in childhood, which results in a lifetime of exposure to this carcinogen. All infected develop gastritis and are at risk for developing an *H. pylori* associated disease ranging from dyspepsia to potentially life-threatening diseases. The risk of gastric cancer depends on developing atrophic gastritis, the prevalence of which varies geographically (30). For example, a man's lifetime risk (to age 75) of developing gastric cancer is approximately 0.6% in the United States but can reach 20% in Japan and China (31, 32). The natural history of gastric cancer risk is an exponential increase with age. With eradication of the infection, the mucosa heals, which does not eliminate the risk but halts the increase of risk, alters the natural history of the disease, and reduces the overall risk of gastric cancer (33, 34). Elimination of gastric cancer will require elimination of *H. pylori* infection. This possibility has been the topic of consensus meetings that have recently updated the clinical recommendations (**Table 1**) from either the viewpoint of an individual patient's care (12) or the viewpoint of public health policy (13).

The actual approach depends on the prevalence of gastric cancer in general, as well as within specific subpopulations with proven high risk of gastric cancer. As noted above, in the United States, where overall gastric cancer is rare, the existence of high-risk subpopulations leads to a specific recommendation to increase awareness and focus testing among these high-risk groups (e.g., family members of patients with *H. pylori* infection and high-risk minority populations). In countries with intermediate or high risk of gastric cancer (i.e., a gastric cancer incidence rate of 20 per 100,000 person-years or more), the prevalence rate of *H. pylori* infection also tends to be high; commonly, more than one-third of the population has been infected (35). In such a population, testing for *H. pylori* infection can be designed as an outreach service, similar to other ongoing cancer prevention programs such as those for colorectal cancer, cervical cancer, or breast cancer. Studies in the Matsu Islands have shown that such an approach is both practical and effective to rapidly reduce the incidence rate of *H. pylori* infection. In the Matsu Islands, this approach resulted in reductions of 67% in peptic ulcer, 77% in premalignant gastric lesions, 53% in gastric cancer incidence, and 25% in deaths related to gastric cancer, which clearly accelerated the already declining trends in stomach diseases (36, 37).

For a population with high gastric cancer risk, in addition to the steps of standardizing screening tests and eradication treatment, the action plan must include a sustainable program to invite the target population to utilize screening, along with routine referral of those who test positive to receive the eradication treatment (**Figure 1**). The Taipei Consensus recommended such an organized screening program in areas with a high incidence rate of gastric cancer (13). It would seem logical to consider also utilizing such programs for high-risk populations in developed countries, such as Native Americans and Native Alaskans in the United States (1, 38). Although all will benefit from screening and *H. pylori* eradication, young adults receive the greatest benefit as progression can be interrupted before irreversible molecular damage to their gastric mucosa has occurred. Screening and treating young adults would further augment the relative cost-effectiveness of the program (39). Active screening of newcomers to the high-risk community and monitoring of post-eradication subjects are also recommended to eliminate any potential risk of transmission to the infected person's next generation of relatives.

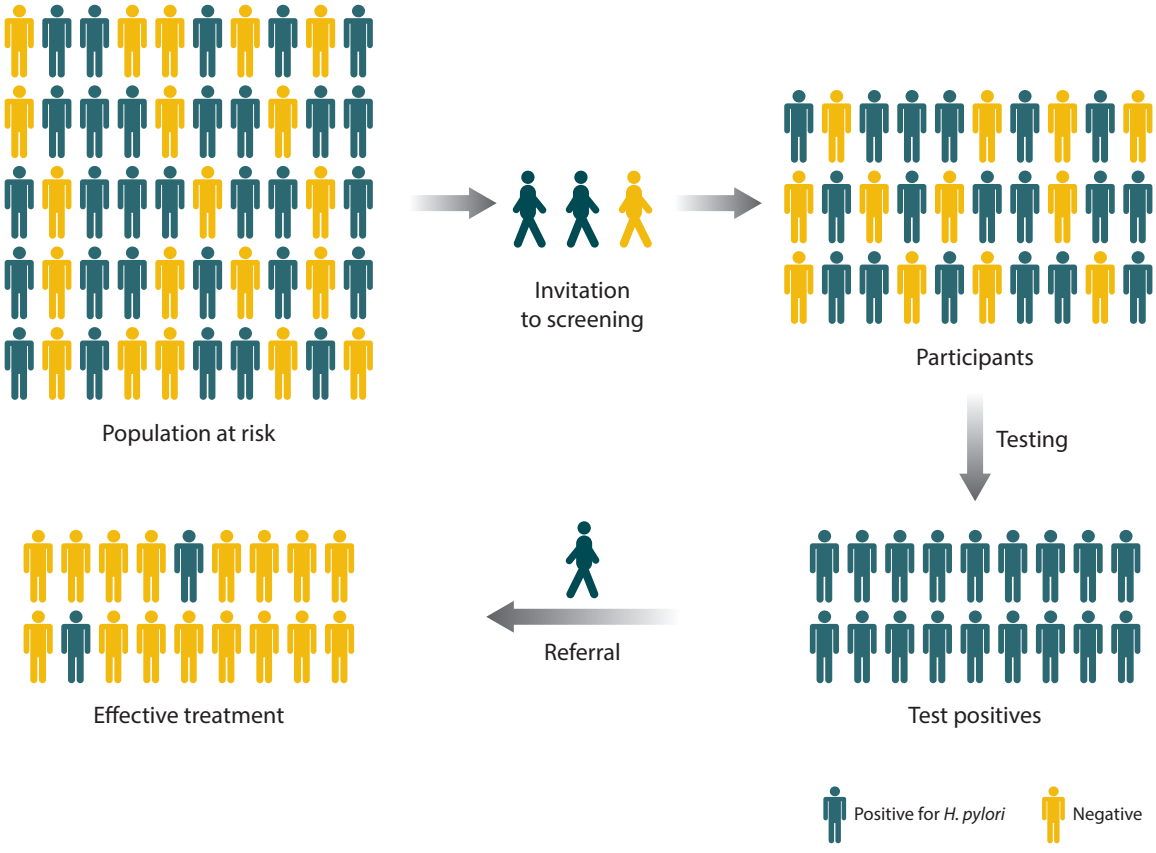

Figure 1

The step-by-step process of population *Helicobacter pylori* screening. The overall effectiveness of a program is maximized by standardizing the invitation, participation, testing, and referral for eradication treatment. Figure adapted with permission from Reference 37.

Discrepancies commonly exist between patients' perception of risk and the proposed benefit perceived by physicians. To increase participation in screening and treatment, it is imperative to motivate the asymptomatic as well as those with documented *H. pylori* infection through programs of disease awareness, social mobilization, and education activities (17). For country-wide screening in high-risk countries, the gastric cancer prevention program should be integrated or included in the national healthcare priorities to optimize resource utilization. For example, *H. pylori* stool antigen testing can be performed together with fecal immunochemical testing (40). Combining screening programs, such as colorectal and *H. pylori* screening, especially in patients with common risks for upper and lower digestive tract cancers, can also increase the participation rate.

TREATMENT OF *H. PYLORI* INFECTION

Currently, the cure rates of most *H. pylori* therapies are relatively low (e.g., 80% or lower). Most therapies are given empirically even though the increase in antimicrobial resistance has resulted in triple therapies (consisting of a PPI; amoxicillin; and clarithromycin, metronidazole, or levofloxacin) becoming ineffective when used empirically (41). Most treatment guidelines are based on comparisons (e.g., meta-analyses) of randomized trials that focus on relative rather

than absolute effectiveness, and the actual trials included in these meta-analyses generally vary significantly in the specifics of dosing, the relative potency of the PPI used, and the prevalence of resistance in the populations (42). Because of these limitations, the recommendations include therapies that generally fail to achieve acceptable cure rates. In other infectious diseases, treatment recommendations are typically susceptibility based and are designed to reliably achieve prespecified cure rates, such as reliably greater than 90% or 95%.

Other *H. pylori* treatment recommendations result in the prescription of at least one antibiotic that is unnecessary and plays no role in treatment outcome. This practice contributes to global antibiotic resistance. Examples include the popular four-drug regimens called concomitant, sequential, or hybrid therapies. For instance, concomitant therapy consists of combining clarithromycin and metronidazole triple therapies into a regimen containing amoxicillin, clarithromycin, and metronidazole along with a PPI with the hope that the infection may be susceptible to either clarithromycin or metronidazole. At minimum, this would produce 14,000 kg of unneeded antibiotic per 1 million successful treatments and 28,000 kg per 1 million treatment failures (41). It has become clear that the approach to develop therapies and treatment recommendations has failed and should be abandoned (43, 44). Efforts are under way to shift guidance for development and use of *H. pylori* therapies from trial and error to application of the general principles of antibiotic usage (45) and of antimicrobial stewardship (41, 46).

The principles of antimicrobial stewardship judge antimicrobial therapies based on the absolute cure rate (the ability to reliably achieve a prespecified cure rate such as ≥95% with susceptible infections). Recommended therapies are also optimized to reliably achieve the highest cure rates possible. Optimization includes all aspects of therapy, such as drug selection, dosage, dosing intervals, duration, and administration in relation to meals. By definition, empiric therapy is restricted to those regimens proven to reliably achieve high cure rates in the population intended to receive therapy. Clinical programs that include assessment of targeted cure rates should be undertaken to provide surveillance of treatment outcomes and to notify clinicians and public health officials of the outcomes while informing them when cure rates begin to fall (e.g., resistance has increased).

Keys to Effective *H. pylori* Therapy

The optimal duration of *H. pylori* therapy is 14 days. Therapies should be susceptibility based, relying either on susceptibility testing or on proven high local success rates. Success should always be confirmed by a test of cure after treatment of every patient (e.g., UBT performed 4 or more weeks after therapy). Test of cure also provides an indirect measure of resistance/susceptibility in the population. This information should be compiled and shared, as it distinguishes locally reliably highly successful regimens from those that should be avoided.

The prevalence of antibiotic resistance has increased such that clarithromycin, metronidazole, or fluoroquinolone triple therapies can no longer be used empirically. However, they remain effective when susceptibility has been confirmed. The first step in identifying and prescribing an effective therapy is to exclude antibiotics where preexisting resistance is likely. This can be accomplished by history and/or susceptibility testing. History entails taking a thorough history of prior antibiotic use including review of the medical and, if possible, pharmacy records (47–52). Susceptibility testing has recently become available, at least in the United States. Culture of gastric biopsies is available from Mayo Clinic Laboratories® (HELIS), ARUP Laboratories® (MC HPYL), Labcorp® (180885), Quest Diagnostics (36994), Microbiology Specialists (Msi@microbiologyspecialists.com), and possibly other laboratories. Molecular antimicrobial resistance testing using next-generation sequencing (NGS) is available from American Molecular Laboratories® for susceptibility to amoxicillin, clarithromycin, levofloxacin,

tetracycline, metronidazole, and rifabutin using stools or fresh or formalin-fixed gastric biopsies. Combined *H. pylori* diagnosis and molecular testing is also available. A stool from a patient with suspected *H. pylori* infection is submitted and, if the stool test is positive, molecular testing is automatically done (reflex testing). Reflex stool testing is especially attractive because, if the test is negative, the patient is only charged for the initial test, whereas positive *H. pylori* stool tests are automatically tested for antimicrobial susceptibility (clarithromycin at Mayo Clinic Laboratories, and the six commonly used antibiotics at American Molecular Laboratories). Outside of the United States, there are various commercial kits that hospital laboratories can use for molecular testing for clarithromycin resistance alone or clarithromycin and levofloxacin resistance (24, 53). It behooves clinicians to request the laboratories they utilize for stool antigen testing to also offer reflex testing, where approved, using one of these kits.

All successful antimicrobial therapy is susceptibility based and optimized to reliably achieve high cure rates (e.g., ≥95%). The therapy can be chosen on the basis of susceptibility results from the actual patient or on the basis of population data and local treatment results to identify and confirm which specific empiric therapies have been, and continue to be, highly effective locally. Obtaining reliable local data requires clinician involvement, first to obtain and utilize antibiotic use history to assist in treatment selection and second to routinely obtain posttreatment tests of cure to provide feedback regarding treatment effectiveness (46, 49). Ideally, these data would be shared within the community to provide regular updates and early identification of increasing antimicrobial resistance. This approach is also consistent with the new regulations from the US Centers for Medicare and Medicaid Services' new regulation requiring all hospitals participating in its programs to establish antimicrobial stewardship programs that include prescription and outcome monitoring for common infectious diseases (**https://federalregister.gov/d/2019-20736**) (54). Long-term success depends on developing active feedback loops between the recommended therapy and actual cure rates and requires active physician involvement.

Currently Effective Empiric Therapies

In most areas, the only therapies that can be given empirically are bismuth quadruple therapy for 14 days and rifabutin triple therapy (**Table 3**). However, a 14-day therapy duration may represent a problem with the combination product Pylera®, as it is packaged for 10-day therapy. In addition, in the United States, this drug costs more than $1,000 (or more than $900 with a coupon for the 10-day package). In Europe, Pylera® costs ~€70. Bismuth, tetracycline, and metronidazole can be prescribed separately. Even generic quadruple therapy is expensive in the United States, as generic tetracycline costs ~$660 retail. However, tetracycline can be obtained with a coupon, such as from GoodRx, for less than $100 for a 14-day supply. Doxycycline is even cheaper but cannot be substituted for tetracycline, as typically the results are significantly inferior.

Talicia® is a new formulation of rifabutin triple therapy (55). One theoretical advantage of rifabutin is that resistance is rare. Talicia®, like all combination therapies, is more expensive than the individual components. The triple therapy includes amoxicillin, rifabutin, and a high-dose PPI. Generic rifabutin alone costs ~$400 in the United States but can be obtained for ~$150 with a coupon such as from GoodRx. Talicia® costs $700 with or without a GoodRx coupon. Clinical experience with Talicia® is limited but encouraging (**Table 3**).

There is hope that amoxicillin dual therapy can simplify treatment of *H. pylori* infection. Amoxicillin has generally failed to achieve high cure rates with PPIs but has shown success with vonoprazan, a new potassium-competitive acid blocker. Clinical trials of vonoprazan–amoxicillin dual therapy are in progress (56).

Table 3 *H. pylori* **therapies in current use**

Empiric therapies	
Therapy and duration	**Dosage**
Bismuth quadruple therapy Bismuth subsalicylate q.i.d. 14 days	Bismuth (e.g., PeptoBismol®) 2 tablets or 2 capsules q.i.d. 30 min before meals Tetracycline HCl 500 mg and metronidazole 500 mg q.i.d. 30 min after meals plus a PPI[a] b.i.d. 30 min before meals and bedtime
Bismuth quadruple therapy Bismuth subsalicylate b.i.d. 14 days	Bismuth (e.g., PeptoBismol®) 2 tablets or 2 capsules q.i.d. 30 min before meals, tetracycline HCl 500 mg b.i.d. and metronidazole 500 mg, 30 min after meals q.i.d. plus a PPI[a] b.i.d. 30 min before morning and evening meals
Bismuth quadruple therapy Pylera® formulation (bismuth citrate) 14 days	Combination tablets with meals plus a PPI[a] q.i.d. 30 min before meals and bedtime (see text for details)
Rifabutin triple therapy 14 days	Rifabutin 150 mg b.i.d., amoxicillin 1 g t.i.d. plus 40 mg esomeprazole or rabeprazole b.i.d. 30 min before meals (see text for details)
Talicia® formulation of rifabutin triple therapy 14 days	As directed by package insert
Therapies effective only when susceptibility based[b]	
Therapy and duration	**Dosage**
Clarithromycin triple therapy 14 days	Clarithromycin 500 mg b.i.d., amoxicillin 1 g b.i.d. 30 min after meals
Metronidazole triple therapy 14 days	Metronidazole 500 mg b.i.d., amoxicillin 1 g b.i.d., 30 min after meals
Levofloxacin triple therapy 14 days[c]	Levofloxacin 500 mg in morning, amoxicillin 1 g b.i.d., 30 min after meals
Obsolete therapies	
Therapy	**Comment**
Concomitant therapies Hybrid therapies Reverse hybrid therapies Sequential therapies	All include at least one antibiotic that offers no therapeutic benefit and only serves to increase global antimicrobial resistance

[a]PPI (proton pump inhibitor) dose should at a minimum be 40 mg of omeprazole or equivalent b.i.d. (e.g., 45 mg lansoprazole, 20 mg rabeprazole or esomeprazole). If cost is equivalent, we recommend 40 mg of rabeprazole or esomeprazole b.i.d.

[b]Do not use empirically unless proven to cure >90% locally.

[c]The FDA recommends fluoroquinolones be used as a last choice because of the risk of serious side effects (60).

Choice of Proton Pump Inhibitor

PPIs vary remarkably in terms of relative potency. As a rule, especially with amoxicillin-containing regimens, the outcome is best if higher-potency PPIs are utilized b.i.d. and pantoprazole is avoided (40 mg pantoprazole = 9 mg omeprazole; 30 mg lansoprazole = 27 mg omeprazole; 20 mg esomeprazole = 32 mg omeprazole; 20 mg rabeprazole = 36 mg omeprazole). We recommend 20–40 mg esomeprazole or rabeprazole b.i.d. (57, 58).

FUTURE DIRECTIONS

The management of *H. pylori* infection is in the midst of a major transformation as gastroenterologists increasingly embrace the concept that delivery of effective therapy requires substituting the tried and true methods used to treat infectious diseases for the trial and error approach that has characterized *H. pylori* therapy since its inception (46, 59). With infectious diseases, it is generally possible to reliably cure almost 100% of cases. The major outcome variable is the cure rate, and

the primary comparator is the theoretical cure rate of 100%. The typical gastroenterology disease has an unclear etiology; treatment success is modest, actual cures are rare, and there is a large placebo response to therapy. Together, these characteristics require treatment studies to include a comparator and often a placebo and to focus outcome on the comparison of treatment success with another antibiotic and/or a placebo. In contrast, viewing *H. pylori* gastritis as an infectious disease, the ability to reliably achieve high cure rates along with the lack of a placebo response makes actual cure rates the primary outcome variable. In the future, *H. pylori* treatment trials will focus on actual cure rates, and comparisons will be restricted to deciding which of two highly successful therapies (e.g., average cure rate of at least 90%, preferably ≥95%) is best. This will require abandoning the prior approach and the majority of current treatment guidelines based on comparisons of often poorly effective therapies. Those skilled in the prior art of treating *H. pylori* gastritis as another gastroenterological disease rather than an infectious disease may find the transition difficult, especially because the focus is now on identifying locally highly effective therapies and building feedback loops to help clinicians identify, optimize, utilize, monitor, and, when necessary, change the recommended regimens to ensure continuing locally highly effective therapy.

DISCLOSURE STATEMENT

Dr. Graham is a consultant for RedHill Biopharma and Phathom Pharmaceuticals regarding novel *H. pylori* therapies and has received research support for culture of *H. pylori*. He is also a consultant for DiaSorin regarding *H. pylori* diagnostics and for Otsuka Japan regarding novel breath tests. He has ongoing collaborative research projects with American Molecular regarding molecular diagnostics for *H. pylori*. He was the principal investigator of an international study of the use of antimycobacterial therapy for Crohn's disease.

ACKNOWLEDGMENTS

Dr. Graham is supported in part by the Office of Research and Development Medical Research Service Department of Veterans Affairs, Public Health Service grant DK56338, which funds the Digestive Diseases Center of the Texas Medical Center.

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Annual Review of Medicine

Volume 73, 2022

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