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REVIEWS IN BASIC AND CLINICAL GASTROENTEROLOGY AND HEPATOLOGY

Evolving Concepts in *Helicobacter pylori* Management

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Helicobacter pylori **is the most common chronic bacterial infection worldwide and the most significant risk factor for gastric cancer, which remains a leading cause of cancer-related death globally. *H pylori* and gastric cancer continue to disproportionately impact racial and ethnic minority and immigrant groups in the United States. The approach to *H pylori* case-finding thus far has relied on opportunistic testing based on symptoms or high-risk indicators, such as racial or ethnic background and family history. However, this approach misses a substantial proportion of individuals infected with *H pylori* who remain at risk for gastric cancer because most infections remain clinically silent. Moreover, individuals with chronic *H pylori* infection are at risk for gastric preneoplastic lesions, which are also asymptomatic and only reliably diagnosed using endoscopy and biopsy. Thus, to make a significant impact in gastric cancer prevention, a systematic approach is needed to better identify individuals at highest risk of both *H pylori* infection and its complications, including gastric preneoplasia and cancer. The approach to *H pylori* eradication must also be optimized given sharply decreasing rates of successful eradication with commonly used therapies and increasing antimicrobial resistance. With growing acceptance that *H pylori* should be managed as an infectious disease and the increasing availability of susceptibility testing, we now have the momentum to abandon empirical therapies demonstrated to have inadequate eradication rates. Molecular-based susceptibility profiling facilitates selection of a personalized eradication regimen without necessitating an invasive procedure. An improved approach to *H pylori* eradication coupled with population-level programs for screening and treatment could be an effective and efficient strategy to prevent gastric cancer, especially in minority and potentially marginalized populations that bear the heaviest burden of *H pylori* infection and its complications.**

Keywords: Helicobacter pylori; Gastric Cancer; Gastric Cancer Screening; *H pylori* Treatment; Antibiotic Resistance; Susceptibility Testing; Gastric Intestinal Metaplasia; Under-represented Minorities.

Early enthusiasm and rapid progress in *Helicobacter pylori* management of the 1980s and 1990s were followed in the 21st century by relative disinterest in the United States (U.S.) and decreasing eradication rates and increasing antibiotic resistance globally.[1]

There is now overwhelming evidence that *H pylori* eradication is beneficial, evidenced by reduction in peptic ulcer recurrence, cure of most gastric mucosa-associated lymphoid tissue lymphomas, and approximately 50% reduction in gastric adenocarcinoma incidence.[2] Although it has been proposed that harboring *H pylori* might have some advantage (including an inverse association with some immune-mediated diseases and esophageal adenocarcinoma),[3] clinical studies do not show harm after *H pylori* eradication, especially in low-prevalence areas.[4–6] Because *H pylori* is usually clinically silent, the only way to identify individuals infected with *H pylori* and at risk for complications is through directed testing. In the U.S., opportunistic testing is symptom-based or risk-based among asymptomatic individuals (for example, based on family history of gastric cancer[7]). Although there is published guidance on who to test, implementation of risk-based testing in clinical practice is low; consequently, many individuals remain unknowingly at risk for downstream complications, including cancer.

Because it is not possible to predict who will develop complications, *H pylori* eradication is recommended for anyone diagnosed with active infection. Recognizing *H pylori*–induced gastritis as a distinct entity and categorizing *H pylori* as an infectious disease in 2015 reset the treatment paradigm according to principles of antimicrobial susceptibility profiling and stewardship.[8] This contrasts with the current strategy of empiric therapies without awareness of susceptibility profiles. Although this was universally acceptable when clarithromycin resistance was not as pervasive and *H pylori* eradication rates were high with empiric triple therapy, this is now inappropriate in the U.S..

Substantial room exists to improve *H pylori* management in the U.S.. Opportunistic testing is often not implemented in practice, less effective treatment regimens continue to be used and reused, and clinical guidelines cannot keep up with ever-changing antimicrobial resistance and are not consistently followed.[9,10] Moreover, national, regional, and

Abbreviations used in this paper: **ASIR, age-standardized incidence rate; CI, confidence interval; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; IL, interleukin; LYG, life-year gained; NGS, next-generation sequencing; OR, odds ratio; PCAB, potassium-competitive acid blocker; PPI, proton pump inhibitor; QALY, quality-adjusted life-year; RCT, randomized controlled trial; U.S, United States.**

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local antibiotic resistance data, which should factor into clinical decision making, are lacking, further compromising implementation of guideline recommendations. Test of cure after eradication therapy is not performed consistently,[10,11] yet is critical, given poor correlation between clinical symptoms and treatment success.

H pylori rates are highest in racial and ethnic minority and immigrant groups who consequently have the highest rates of gastric cancer[12]; thus, there are substantial unmet opportunities for improved resource allocation and targeted cancer prevention efforts to reduce these observed health-care disparities. Without systematic endoscopic gastric cancer screening in the U.S., most cases are diagnosed at an advanced, incurable stage. Consequently, 5-year survival after gastric cancer diagnosis is approximately 36% in the U.S. in contrast to Japan and Korea, where 5-year survival now exceeds 60%, directly attributed to gastric cancer screening.[13,14] Yet, although endoscopic screening has reduced gastric cancer mortality, it has not reduced gastric cancer incidence.[15] On the other hand, mass *H pylori* eradication campaigns in certain endemic countries have reduced both gastric cancer incidence and mortality.[5]

Here, we review how emerging trends in *H pylori* management can improve clinical outcomes by focusing on overcoming increasing antimicrobial resistance through susceptibility testing and applying risk stratification tools for gastric cancer prevention and early detection. We use the U.S. population as the principal example.

H pylori Screening for Gastric Cancer Prevention

H pylori and Gastric Cancer Global Epidemiology

Although rates of *H pylori* infection are decreasing, worldwide prevalence is still approximately 43.1%.[16] Based on pooled data from 2011-2022 stratified by World Health Organization region, *H pylori* prevalence is highest in the Eastern Mediterranean (56.1%; 95% confidence interval [CI], 37.3–74.9) and in Africa (53.3%; 95% CI, 42.4–64.2) and lowest in the Western Pacific (37.9%; 95% CI, 33.8–42.1) and the Americas (32.8%; 95% CI, 19.3%–46.4%), albeit with notable inter-country and within-country variation. In the U.S., *H pylori* prevalence varies substantially according to race and ethnicity, and is highest in non-Hispanic Black (40.2%), Hispanic (36.7%),[17] and Asian American (70.1%) individuals.[18] Because *H pylori* infection is acquired in childhood, individuals born in high-prevalence countries who immigrate to countries with lower prevalence remain at increased risk for harboring *H pylori* infection.

Worldwide, more than 1 million new cases of gastric cancer are diagnosed annually with over 768,000 deaths, making gastric cancer the fourth leading cause of cancer-related death.[19] Most noncardia gastric cancer globally is attributed to *H pylori* infection,[20,21] and adenocarcinoma is the most common histology. Over the past 2 decades, noncardia gastric adenocarcinoma and mucosa-associated lymphoid tissue lymphoma, both of which are driven by *H pylori* infection, have decreased especially among individuals ≥50 years old.[22] Despite these promising trends, striking racial and ethnic disparities still define noncardia gastric adenocarcinoma in the U.S..[12,22] Asian and Pacific Islanders (age-standardized incidence rate [ASIR], 10.36 per 100,000), Hispanic (ASIR, 9.14), and non-Hispanic Black (ASIR, 8.32) Americans have the highest prevalence compared with non-Hispanic White Americans (ASIR, 2.73).[22] The role of *H pylori* in cardia adenocarcinoma, which constitutes about a quarter of all gastric cancer in the U.S., is less clear. *H pylori* has been associated with cardia adenocarcinoma in Asian populations, but less consistently so in Western populations.[23,24] It is possible that *H pylori* is the responsible trigger in some patients with gastroesophageal junction cancer,[25] whereas in others gastroesophageal reflux is the dominant risk factor.

Efficacy of H pylori Treatment in Reducing Gastric Cancer Risk

Chronic infection with *H pylori* is the strongest and most consistent predictor of noncardia gastric adenocarcinoma (hereafter referred to as gastric cancer).[26] Eradication of *H pylori* is associated with a significant reduction in gastric cancer risk.[27] A meta-analysis of 7 randomized controlled trials (RCTs), 6 conducted in Asia, reported that *H pylori* eradication decreases the risk of gastric cancer by approximately half in healthy individuals.[4] Further, a meta-analysis of 9 RCTs found *H pylori* eradication decreases the risk of metachronous gastric cancer by 53% (odds ratio [OR], 0.47; 95% confidence interval [CI], 0.33–0.67),[27–29] likely related to improving the severity or preventing the progression of preneoplastic changes in the remnant mucosa.[29] However, in patients with pre-existing gastric intestinal metaplasia or more advanced changes, *H pylori* eradication is not consistently associated with reduced gastric cancer incidence or mortality, underscoring the relevance of ongoing endoscopic surveillance for early cancer detection.

In a high-risk Chinese population, gastric cancer risk was reduced by 43% over 25 years (hazard ratio [HR], 0.57; 95% CI, 0.33–0.98) among asymptomatic persons treated for *H pylori* compared with placebo. The greatest benefit was among those without baseline premalignant changes (HR, 0.37; 95% CI, 0.15–0.95) and with confirmed eradication (HR, 0.46; 95% CI, 0.26–0.83).[30] A recent U.S. retrospective study also confirmed that the benefit of *H pylori* eradication in gastric cancer risk reduction may be delayed and not apparent for 8-10 years post–*H pylori* treatment.[31]

There are no RCTs or prospective studies in the U.S. examining the effect of *H pylori* treatment on gastric cancer risk. One retrospective Veterans Health Administration study of 371,813 patients demonstrated that treatment of *H pylori* with confirmed eradication was associated with a 76% reduction (HR, 0.24; 95% CI, 0.15–0.41) in gastric cancer risk compared with persistent infection.[32] Another retrospective study of 716,567 patients in Northern California found patients with untreated *H pylori* infection had a 6-fold higher risk of gastric cancer compared with *H pylori*–negative patients. The risk was lower but still 2-fold higher among those who received *H pylori* treatment.[31] One

notable limitation of both studies is that not all patients underwent post-treatment *H pylori* testing to confirm eradication. Although these retrospective data suggest that successful *H pylori* eradication would translate to reduced gastric cancer incidence and ideally mortality in U.S. populations, higher quality studies, ideally prospective and randomized, are needed to define the magnitude of benefit among distinct at-risk groups. Several large RCTs in China, Korea, and the United Kingdom are underway to examine the impact of confirmed *H pylori* eradication on gastric cancer risk.[33,34]

H pylori Screening as a Strategy for the Primary Prevention of Gastric Cancer

There are currently 3 strategies for *H pylori* testing. "Test and treat" is the predominant method used in the U.S. and other Western countries.[14] Individuals with associated symptoms or diseases are tested, so this is not true screening. It also includes testing asymptomatic individuals with risk factors, such as immigrants from countries with high–*H pylori* prevalence. "Family-based testing," focused on household adult family members of individuals with *H pylori*,[35] also qualifies as opportunistic testing and not true screening. It is recommended in several high-risk Asian countries[36] and in the U.S..[37]A meta-analysis of 12 RCTs reported higher eradication and lower reinfection rates with family-based testing and treatment compared with single-patient treatment.[38] The third "screen and treat" strategy extends true screening to the population level and is currently implemented in countries/regions with universally high–*H pylori* prevalence and gastric cancer incidence. An example of this approach is the *H pylori* mass testing and treatment effort in Taiwan's Matsu Islands[5] that resulted in a marked decrease in *H pylori* prevalence from 64% to 15% over 14 years, associated with a 53% (95% CI, 30%–69%) reduction in gastric cancer incidence and 25% (95% CI, −14% to 51%) reduction in mortality compared with historical controls.

Cost-Effectiveness of Gastric Cancer Prevention Through H pylori Testing and Treatment

Whether to implement universal *H pylori* screening to prevent gastric cancer depends in large part on tradeoffs between the costs and harms of testing and treating millions of individuals indiscriminately, against the desired reduction of gastric cancer incidence and mortality. A review of modeling studies indicates that *H pylori* screening can be cost-effective in both Eastern and Western populations if certain assumptions are met (Table 1). In Asian populations at high risk of both *H pylori* and gastric cancer, a "screen and treat" strategy was universally cost-effective with the lowest incremental cost-effectiveness ratio (ICER) of $1100/life-year gained (LYG) and $24/quality-adjusted life-year (QALY) gained compared with no screening.[39–42] In Western countries, the cost-effectiveness of universal *H pylori* screening is less obvious. North American studies reported serologic screening to be cost-effective (ICERs ranged from $6242–$33,000/LYG)[43–45] and varied from $4500/LYG in Japanese Americans to $34,900/LYG in non-Hispanic White Americans[43]). As a reference but not for direct comparisons, screening for breast cancer (annual mammogram), colorectal cancer (10-year colonoscopy), and lung cancer screening (1-time low-dose computed tomography for smokers) have reported ICERs of $50,223/QALY, $14,878/LYG, and $81,000/QALY, respectively.[46–48]

Numerous factors influence the cost-effectiveness of *H pylori* screening at the population level. The wide variability in ICERs among the Western studies is due to variability in the estimates of the model inputs. Among 5 U.S. studies,[43,44,49–51] all included *H pylori* prevalence (36%–50% among 40–50 year olds), expected reduction in gastric cancer (0.2%) or relative risk of cancer due to *H pylori* (1.5–3.6), *H pylori* test sensitivity (85%–90%) and specificity (79%–90%), effectiveness of *H pylori* eradication therapy (80%–90%), and direct cost estimates for the *H pylori* serology tests ($20–$33), eradication therapies ($80–$425), and cancer treatment ($50,000–$187,222). Some models additionally included severity of baseline gastric preneoplasia, risk of death from competing causes, probability of survival after cancer, reinfection rate, risk of adverse events from *H pylori* treatment, and indirect costs. *H pylori* screening and eradication has the greatest impact on cost-effectiveness through reduced gastric cancer incidence. Estimates of cancer risk reduction with *H pylori* testing among U.S. populations are lacking and not generalizable to the population level. For example, 1 modeling study only evaluated men, and reported that the risk reduction must exceed 15% in non-Hispanic White men to be cost-effective, whereas *H pylori* testing in non-Hispanic Black and Hispanic men was cost-effective at lower thresholds of gastric cancer risk reduction ($\leq$10%).[44]

Who to Screen for H pylori

One major consideration for screening is whether to focus on groups at high-risk for gastric cancer or the general population. Apart from *H pylori*, demographic risk factors for gastric cancer include non-White race or ethnicity, early generation immigration from a country where gastric cancer is endemic, older age, male sex, smoking, low socioeconomic status, and family history of gastric cancer.[52–54] One meta-analysis of 24 studies found that populations at intermediate or high risk of gastric cancer (incidence >10/100,000) experienced the greatest benefit from *H pylori* eradication.[27] Extrapolating this to the U.S., it is reasonable to consider concentrating *H pylori* screening efforts on those at the greatest risk of gastric cancer. However, individual risk factors poorly predict *H pylori* infection in the U.S.. One retrospective study from a U.S. safety-net hospital with high–*H pylori* prevalence (52%) reported that a predictive model combining first-generation immigrant status, non-Hispanic Black or Hispanic race/ethnicity, and the presence of dyspepsia or reflux symptoms predicted positive *H pylori* status better than any individual risk factor alone; however, the area under the receiver operating characteristic was still only 0.64.[55] Models incorporating additional predictors, including broader racial and ethnic groups, and perhaps host genetic factors should be developed and their predictive performance evaluated.

Table 1. Summary of Western and Eastern Cost-effectiveness Studies on *H pylori* Testing for Prevention of Gastric Cancer

Author/y	Country	Study population	Model type	Intervention vs control	Incremental cost-effectiveness ratio
Western Studies					
Parsonnet 1996[43]	U.S.	Adults 50 y	Markov simulation	Single serology vs no screening	$25,000/LYG Blacks: $13,700/LYG Japanese Americans: $4500/LYG Whites: $34,900/LYG
Fendrick 1999[44]	U.S.	White men 40 y	Markov simulation	Single serology vs no screening Single serology followed by confirmation of cure vs no screening	$6264/LYG $11,313/LYG
Harris 1999[49]	U.S. Finland	Adults 50–54 y	Markov simulation	Single serology vs no screening Single serology for CagA-positive *H pylori* vs no screening	$24,300/LYG $4400/LYG
Mason 2002[61]	U.K.	Adults 40–49 y	RCT, Markov simulation	UBT vs no screening	£14,200/LYG
Davies 2002[128]	U.K.	Adults <50 y	Markov simulation	Single serology vs no screening	£5860/LYG
Roderick 2003[59]	U.K.	Adults >20 y	Markov simulation	Single serology vs no screening	Age 40: £5866/LYG Age 20, 30, and 50: <£10,000/LYG
Xie 2009[45]	Canada	Men 35 y	Markov simulation	Single serology vs no screening Single stool antigen vs no screening Single UBT vs no screening	$33,000/QALY $29,800/QALY $50,400/QALY
Yeh 2016[50]	U.S.	Men 50 y	Markov simulation	Single serology, endoscopic screening, serum pepsinogen vs no screening	Pepsinogen: $105,400/QALY Serology and endoscopic screening: dominated by pepsinogen
Teng 2017[129]	New Zealand	Adults 25–69 y	Markov simulation	Single serology vs no screening Single stool antigen vs no screening	$16,500/QALY $19,400/QALY
Oh 2022[51]	U.S.	Adults 40 y	Markov simulation	Single UBT vs no screening Single endoscopy with gastric biopsy vs no screening	$116/QALY $2373/QALY

Table 1. Continued

Author/y	Country	Study population	Model type	Intervention vs control	Incremental cost-effectiveness ratio
Eastern Studies					
Harris 1999[49]	Japan	Adults 50–54 y	Markov simulation	Single serology for CagA-positive *H pylori* vs no screening	$1100/LYG
Lee 2007[130]	Matsu Island, Taiwan	Adults 30 y Adults 50 y	Population intervention program, Markov simulation	Single UBT vs no screening Annual pepsinogen then endoscopy vs no screening	$17,044/LYG $29,741/LYG
Xie 2008[40]	Singapore	Adults 40 y	Markov simulation	Single serology vs no screening Single UBT vs no screening	$25,881/QALY $53,602/QALY
Xie 2008[131]	Singapore	Men 40 y	Markov simulation	Single serology vs no screening Single UBT vs no screening	$13,571/QALY $32,525/QALY
Yeh 2009[39]	China	Adults >20 y	Markov simulation	Single serology vs no screening	Men age 20: $1340/LYG Women age 20: $1230/LYG Men age 30: $2050/LYG Women age 30: $1710/LYG Men age 40: $3940/LYG Women age 40: $2790/LYG Men age 50: $9420/LYG Women age 50: $5430/LGY
				Serology then rescreen if negative vs no screening	Dominated by single serology screening
Wong 2014[41]	Hong Kong	Adults 20 y	Markov simulation	Single serology vs no screening	Men: $17,886/QALY Women: $23,905/QALY
Han 2020[132]	China	Adults 40 y	Markov simulation	Single UBT vs no screening	$168.45/QALY
Feng 2022[133]	China	Adults 20–80 y	Markov simulation	Triennial, 5-yearly UBT vs annual UBT	Triennial UBT: $1317/QALY Five-yearly UBT: $1278/QALY
Wang 2022[134]	China	Adults born 1951–1980	Markov simulation	Single, annual, biennial, triennial endoscopy vs single serology	Annual endoscopy: CNY 70,000/QALY All others dominated
Kowada 2023[42]	Japan	Adults >20 y	Markov simulation	Single serology vs no screening	Age 20: $24/QALY Age 50: $494/QALY Age 60: $41/QALY Age 30, 40, 70, 80: dominated
				Annual, biennial, triennial endoscopy vs no screening	Dominated at all age groups
Zheng 2023[135]	High incidence country	Adults 40 y	Markov simulation	Single UBT vs no screening	CNY 536/QALY

CNY, Chinese yuan; UBT, urea breath test.

The greatest benefit of *H pylori* eradication on gastric cancer risk is early on in the course of the infection, before the development of atrophy or metaplasia.[56,57] Modeling studies from universally high-risk populations in Asia demonstrate that the highest cost-effectiveness is observed when screening starts at age 20 and decreases with increasing screening age.[39] This observation informed the Taipei Global Consensus recommendation to perform *H pylori* screening in adults 20–40 years of age.[58]

In Western countries, the timing for *H pylori* screening to achieve the optimal balance between gastric cancer prevention and cost is unclear. Modeling studies have shown increasing cost-effectiveness for serologic screening with increasing screening age,[59] and the optimum age at 50–70 years,[43] likely reflecting the birth cohort effect on high *H pylori* prevalence. However, serologic screening may be cost-effective even at younger ages in high-risk U.S. populations; screening Japanese Americans at any age or African Americans starting at age 20 was shown to be cost-effective.[43]

How to Screen for H pylori

Data from high-risk populations suggest that a 1-time screening test is likely sufficient.[45] Noninvasive screening modalities include serum antibody, stool antigen, and urea breath testing. Stool antigen testing is slightly more cost-effective than serology due to the higher sensitivity and specificity and equivalent cost.[45,60] Both tests cost less than urea breath testing, which is a viable option for "test and treat" strategy but has a less favorable cost-effectiveness profile.[45,51,61]

Given the wide variability in the performance of serum pepsinogen testing (pepsinogen I and pepsinogen I/pepsinogen II ratio) for detecting gastric cancers (sensitivity, 56%–69%; specificity, 71%–73%)[62–65] in Asian studies, low performance for detecting atrophic gastritis and intestinal metaplasia in high-risk U.S. populations,[65] and limited clinical availability in the U.S., this has not been recommended either for clinical use in the U.S., nor any longer in the most recent iteration of the Japanese gastric cancer screening guidelines.

Endoscopy is the most costly and invasive modality for *H pylori* screening but may have a role in screening older individuals (>50 years) for gastric preneoplasia (eg, atrophic gastritis, intestinal metaplasia) or neoplasia irrespective of *H pylori* status. One-time upper endoscopy (including screening for all upper gastrointestinal cancers) coupled with colonoscopy for colorectal cancer screening at age 50 was not cost-effective in the general U.S. population ($115,664/QALY gained)[66] but was cost-effective in non-Hispanic Black, Hispanic, and Asian American individuals ($71,451–$80,278/QALY gained).[67] Other studies in Western populations have shown conflicting results on the cost-effectiveness of 1-time and repeated upper endoscopy for gastric cancer screening.[50,66,68]

Individuals with atrophic gastritis and intestinal metaplasia are recommended for endoscopic surveillance using a risk-stratified approach. This is consistent with the recent American Gastroenterological Association practice guidelines, which recommended against routinely performing endoscopic surveillance among all-comers with gastric intestinal metaplasia due to the lack of direct evidence for benefit and otherwise very low-quality evidence,[69] based on studies published through 2018. However, this recommendation was qualified with the comment that it is reasonable to perform endoscopic surveillance for the purpose of early detection of gastric neoplasia among groups at increased risk for gastric cancer, such as racial and ethnic minority populations, immigrant groups from high–gastric cancer incidence regions, and those with a family history of gastric cancer, as well as those with gastric intestinal metaplasia with increased risk for neoplastic progression, such as incomplete or extensive gastric intestinal metaplasia.[69] This risk-stratified approach to surveillance aligns with other international guidelines for gastric preneoplasia surveillance.[70,71] A 2023 microsimulation study reported that endoscopic surveillance for incidentally diagnosed gastric intestinal metaplasia, independent of risk stratification, every 5 years was cost-effective compared with no surveillance, whereas a more intensified schedule (eg, every 3 years) was cost-effective in the presence of additional risk factors.[72] The LYG from upper endoscopic surveillance for high-risk gastric intestinal metaplasia compared with no surveillance (157–335 LYG/1000) is on par with colonoscopy for colorectal cancer screening in the average-risk population (vs no screening; LYG 286–335/1000).

Potential Limitations and Downstream Considerations of H pylori Screening

Even with a robust screening program, the observed impact of an *H pylori* "screen and treat" strategy for gastric cancer risk reduction is attenuated in older individuals due to potentially pre-existing precancerous gastric mucosal changes and competing causes of mortality.[31] Increased antibiotic resistance from treating millions of new individuals is a real concern, although no significant change in antibiotic resistance was documented during the Matsu Islands intervention program.[5] Antimicrobials for *H pylori* treatment do modify the gut microbiota, but these effects appear transient.[58]

From a practical standpoint, enacting an *H pylori* screening program would demand major infrastructural changes to ensure appropriate testing, eradication therapy, and post-treatment follow-up for millions of individuals, with considerable associated costs. One United Kingdom study estimated that an *H pylori* screening program for those aged older than 40 years would screen 25 million and treat more than 5 million individuals to prevent 34,456 deaths from gastric cancer and ulcers, costing £138 million in the first year of implementation.[59] The U.S. Preventive Services Task Force is currently reviewing many of these considerations as they investigate *H pylori* screening feasibility for the U.S..[73] We believe that demonstration projects are required in the U.S. to directly address the benefits,

risks, and costs of *H pylori* screening programs in well-defined populations.

Improving *H Pylori* Eradication by Considering Antimicrobial Resistance

H pylori eradication therapy requires multiple antibiotics combined with acid-suppressive medication given at least twice daily, ideally for 14 days. The development of proton pump inhibitor (PPI)-triple therapy (comprising clarithromycin, amoxicillin or metronidazole, and a PPI) in the 1990s provided a relatively simple twice-daily dosed regimen that initially achieved high (>90%) *H pylori* eradication rates. This regimen, especially when packaged into a single prescription, remains popular. Currently, most (52%–80%) *H pylori* treatments in the U.S. are still PPI-based clarithromycin-triple therapy[9–11,74] although eradication success with this regimen has decreased steadily since 2001 to 70% or less,[75] due to the global increase in clarithromycin resistance among *H pylori* strains.[1] A recent RCT reported an abysmal 31.9% success of PPI-based clarithromycin-triple therapy in patients with clarithromycin resistance.[76]

A recent meta-analysis of antimicrobial resistance in 2669 U.S. *H pylori* strains revealed resistance rates of more than 30% for clarithromycin, levofloxacin, and metronidazole compared with much lower rates for amoxicillin (2.6%) and tetracycline and rifabutin (both <1%).[77] In a subset of 455 strains from known treatment-naïve patients, resistance to clarithromycin was 16.7%, levofloxacin was 43%, and metronidazole was 29%. With such high resistance rates, PPI-triple treatments containing clarithromycin, levofloxacin, and/or metronidazole should only be used in patients harboring *H pylori* strains with proven susceptibility.[78]

In response to more failures with triple therapies, especially those containing clarithromycin, most national and international guidelines recommend the more complex, frequently dosed bismuth-quadruple therapy (comprising bismuth, metronidazole or tinidazole, tetracycline, and a PPI) for initial empiric therapy[7,79–81] because *H pylori* resistance to this regimen is low. This advice is based on expert opinion and network meta-analyses of RCTs performed primarily in the Western Pacific and Europe. By contrast, only 2 large RCTs of any *H pylori* therapies have been performed in the U.S. over the last decade, and neither included bismuth-quadruple therapy as a comparator.[76,82]

As first-line alternatives to bismuth-quadruple therapy, rifabutin-triple therapy (with PPI and amoxicillin) and dual potassium-competitive acid blocker (PCAB)-amoxicillin regimens have demonstrated high-eradication rates in U.S. clinical trials and contain antibiotics for which *H pylori* has demonstrated low resistance nationally. In 2 separate U.S.-based RCTs, rifabutin-triple therapy achieved an eradication rate of 84%[82] and dual PCAB-amoxicillin therapy achieved an eradication rate of 77%[76] (intention-to-treat), but whether these eradication rates can be achieved in routine clinical practice has not been evaluated.

Retrospective studies of *H pylori* eradication, although sparse, suggest that bismuth-quadruple therapy for 10–14 days is likely the current best choice for empiric therapy in the U.S. because eradication rates in these studies are consistently around 85%[10,11,83] (Figure 1). Tetracycline resistance is rare in the U.S., and, although in vitro metronidazole resistance is reported, it can largely be overcome by increasing the dose of metronidazole to 1.5–2.0 g daily in divided doses, thus having little impact on the in vivo efficacy of bismuth-quadruple regimens containing metronidazole.[84]

Selection of any empiric regimen should be guided by regimen-specific eradication success rates locally. However, this is challenging in the U.S. because verification of cure after treatment is not performed routinely,[85] despite recommendations by U.S. guidelines,[7] and there are no surveillance registries.

The observed decrease in eradication rates from increasing antimicrobial resistance and the lack of local surveillance registries to guide regimen selection has led to the realization that an empiric approach to *H pylori* eradication therapy is not sustainable nor does it align with antimicrobial stewardship[86] *H pylori* is an infectious disease and, as such, regimens should ideally be selected based on antibiotic susceptibility determined at the individual patient level or, if not available, using local population-based data from surveillance registries. However, more data are needed to inform the effectiveness and real-world implementation of this strategy.

More than 40 clinical trials of empiric vs susceptibility-tailored therapy have been performed during the last 2 decades.[87,88] The data are challenging to compare because of variability across study designs, study populations, susceptibility-testing methods, and treatment types and duration. Most studies were conducted in the Western Pacific, some in Europe, and none in North America. Further, not all were RCTs, and some combined tailoring based on antibiotic susceptibility with tailoring PPI dose and type based on a patient's *CYP2C19* genotype,[89] which predicts metabolism of certain PPIs. Meta-analyses of these studies report a small but significant advantage for the tailored approach for first-line treatment (risk ratio, 1.15; 95% CI, 1.11–1.20).[87,88] However, in the subset of trials where empiric therapy was a bismuth-based or non-bismuth-quadruple regimen, no advantage was evident for therapy tailored according to antimicrobial susceptibility. Thus, when bismuth-quadruple therapy is used as first-line empiric therapy, there seems to be little need for routine upfront susceptibility testing for tailored treatment so long as the local eradication success rate is high (ie, >85%).

There are surprisingly few RCTs of susceptibility-tailored therapy for refractory cases. Only 5 reporting on second-line and 3 on third-line treatments, with only 2 of these studies including at least 100 patients in each arm.[90,91] Although both the larger studies reported an advantage for the tailored approach, the overall results showed no superiority (risk ratio, 1.15; 95% CI, 0.97–1.36).[87,88] Furthermore, it is difficult to extrapolate these results to current clinical practice in the U.S. because

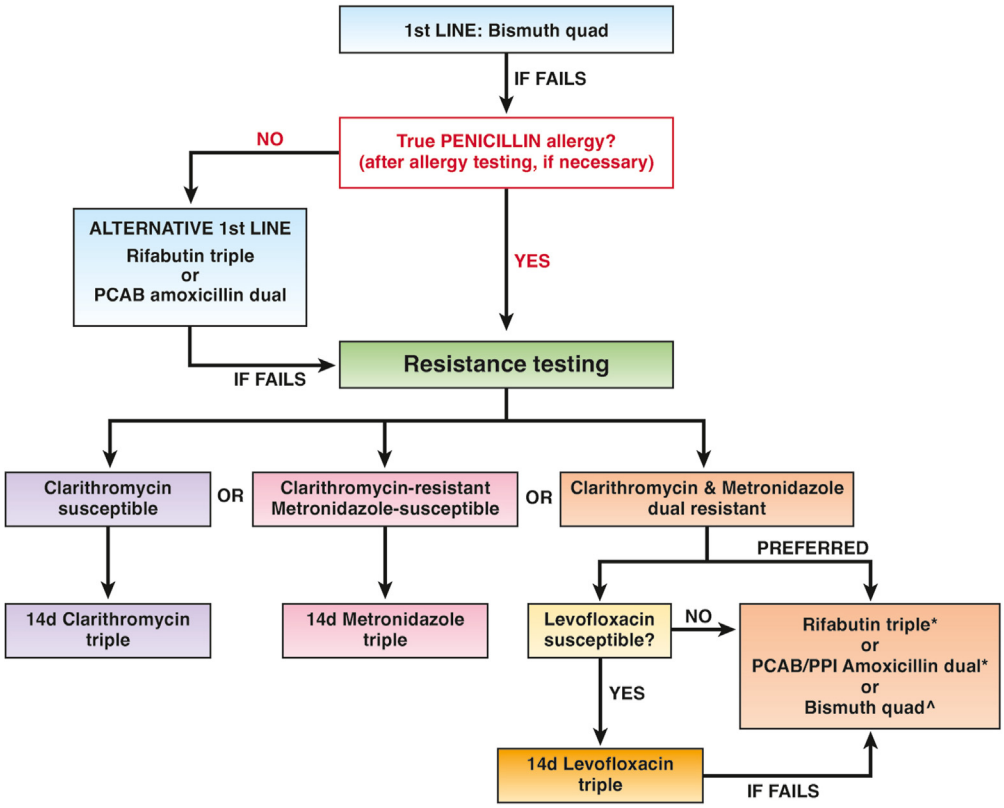

Figure 1. Incorporating antimicrobial resistance testing into practice. *If not allergic to penicillin and not previously tried. ^Using an optimized regimen if originally not used (rabeprazole 20 mg twice daily or esomeprazole 40 mg twice daily) and metronidazole 500 mg 4 times daily. Bismuth Quad, bismuth, tetracycline, metronidazole, and PPI; Rifabutin Triple, rifabutin, amoxicillin, and PPI; PCAB Amoxicillin dual, PCAB and amoxicillin; PCAB/PPI Amoxicillin dual, PCAB or PPI and amoxicillin; Clarithromycin Triple, clarithromycin, amoxicillin (or metronidazole), and PPI or PCAB; Metronidazole Triple, metronidazole, amoxicillin, and PPI; Levofloxacin Triple, levofloxacin, amoxicillin, and PPI. Notes: (1) Modified from algorithms developed by Shah et al[92] and Graham and Moss.[78] (2) Acceptable alternative empiric regimens to Bismuth Quadruple include Rifabutin Triple and PCAB Amoxicillin Dual, if shown to have adequately high local eradication success. (3) This suggested approach is primarily for U.S. patients and is based on some trial data from the U.S. but is mostly at the level of expert opinion. For detailed descriptions of medication doses and frequencies see Chey et al[7] and Shah et al.[92] For PCAB therapy dosing see Chey et al.[76]

empiric therapies in these refractory trials were 7- to 14-day triple therapies that are no longer recommended for refractory cases.[7,92] RCTs are needed to compare the tailored approach to relevant empiric regimens (ie, bismuth-quadruple, rifabutin-triple, PCAB-amoxicillin dual therapy) for refractory cases because these are the scenarios where treatment decisions are most challenging.

Until better and larger trials are performed, the statement from Maastricht VI that "the generalized use of such a susceptibility-guided strategy in routine clinical practice remains to be established" is reasonable.[81] However, susceptibility testing is recommended before embarking on subsequent treatment for patients whose infection does not respond to bismuth-quadruple, rifabutin-triple, and/or PCAB-amoxicillin dual therapy (Figure 1).

Evaluating Antimicrobial Resistance

Culture with susceptibility testing is the standard method for determining resistance in *H pylori* strains, but it is a cumbersome, slow process with suboptimal yield. Even if *H pylori* organisms are successfully cultured, the in vitro susceptibility results may not translate completely to in vivo susceptibility, especially for metronidazole-containing regimens.[93] To increase the chance of successful culture, patients should discontinue any antibiotics for 4 weeks and PPIs for 2 weeks at the time of biopsy. Because culture is rarely available in hospitals or ambulatory endoscopy centers, gastric biopsy samples are sent out to commercial laboratories under stringent shipping conditions. Although 80%–90% of strains are cultured in research studies, success rates are lower in U.S. clinical practice with reports as low as 30%.[94] Several methods can be used to test susceptibility when culture is successful. The Clinical and Laboratory Standards Institute–preferred method is agar dilution to measure minimum inhibitory concentration, but European regulations allow broth dilution. More uniformity in methodology and in defining susceptibility thresholds worldwide is needed.[95]

Microbiology services are increasingly using molecular genomic methods to increase the efficiency and reproducibility of susceptibility testing. Molecular methods to detect *H pylori* and determine antimicrobial susceptibility profiles are expected to dominate the field shortly and guide clinical

Table 2. Mechanisms of Antimicrobial Resistance in *H pylori*

Antimicrobial	Mutation		Other mechanisms
	Most frequent	Others	
Clarithromycin	*23S rRNA (A2142G/C* and *A2143G)*	Very rare	
Levofloxacin	*gyrA* (codons 87 and 91)	Other codons in *gyrA* and *gyrB* described	
Metronidazole	*rdxA* (numerous types of mutations)	*fdxA* (also *fdxB, fldA*, and others)	Altered drug uptake/efflux
Tetracycline	*16s rRNA* (1, 2, or 3 mutation in tetracycline binding site)		Altered drug uptake/efflux
Amoxicillin	*pbp1* (multiple sites)	*pbp2* and *3*	Porins/efflux pumps
Rifabutin	*rpoB* (multiple sites)		
Multidrug resistance			Biofilm, efflux, coccoid formation

rRNA, ribosomal RNA.
Table adapted from Tshibangu-Kabamba and Yamaoka.[93]

practice, spurred by technologies made available by the COVID-19 pandemic and the need for rapid, accurate molecular testing.[96] Phenotypic resistance to clarithromycin and levofloxacin is almost entirely due to a few mutations in *H pylori's* 23S ribosomal RNA (rRNA) and gyrase A, respectively (Table 2). These can be detected using polymerase chain reaction or fluorescence probe hybridization directly from biopsies without culture.[93] Molecular testing for clarithromycin and levofloxacin resistance appears to be at least as accurate as culture-based susceptibility methods for tailoring regimen selection in both treatment-naïve and refractory cases.[97] The dominant mutations underlying resistance to amoxicillin, tetracycline, and rifabutin, albeit rare, are similarly well established and amenable to this culture-free methodology. Metronidazole resistance is more complicated; the influence of in vitro metronidazole resistance by either method is only weakly predictive of *H pylori* eradication failure. Metronidazole is a prodrug requiring activation by bacterial reductases, chiefly RdxA. Many different mutations in *RdxA* that impact metronidazole activation have been documented, but metronidazole-resistant strains have also been identified with mutations in other reductases, including *FdxB*, *FrxA*, and *FldA*.[93] Thus, characterizing an *H pylori* strain as metronidazole-resistant based on evaluation of a select number of mutational sites is not feasible.

Next-generation sequencing (NGS) also overcomes the need for *H pylori* cultures[98] and can be applied directly to fresh or paraffin-embedded formalin-fixed gastric biopsy specimens[99] to evaluate all possible *H pylori* strain mutations underlying resistance to multiple antimicrobials. NGS yields meaningful results in 95% of cases[99] and detects minor subpopulations of *H pylori* strains that could contribute to hetero-resistance.[99] It may also enable detection of *H pylori* in suspected cases with negative results based on conventional testing.[100] Results from early NGS studies indicate that predictions of clarithromycin and levofloxacin resistance from gastric biopsies agree closely with culture-based methods[101] and may correlate with clinical eradication success.[99] There is strong agreement between NGS and culture-based methods for rifabutin and tetracycline resistance, but metronidazole resistance (as determined using *RdxA* sequencing) is less closely related.[101] Amoxicillin resistance is more frequently detected by culture than NGS.[101] Larger studies with clinical outcomes are in progress to evaluate antimicrobial susceptibility and eradication success predicted by NGS compared with other methods.

Profiling *H pylori* resistance by NGS from stool samples obviates the need for endoscopy and its associated inconvenience and cost. Resistance to the 6 antibiotics commonly used in *H pylori* treatment can be evaluated from a single stool specimen mailed directly from the patient's home, yielding results identical to those from endoscopic biopsies.[102] Ideally, a diagnosis of *H pylori* based on stool testing could be followed by reflexive antimicrobial resistance testing via NGS. The utility of such reflexive testing to improve eradication success was recently demonstrated in a pilot study where the NGS resistance profile and specific recommendations on regimen selection were included whenever *H pylori* was detected using gastric biopsy histopathology.[103]

We appear to have reached a tipping point where resistance testing using accurate molecular techniques, such as NGS, is available in some countries, including the U.S., and has demonstrated clinical utility. Stool-based resistance testing should eliminate the practice of endoscopy for the sole purpose of *H pylori* resistance profiling. Indeed, an accompanying *H pylori* susceptibility report could become routine whenever *H pylori* is detected in stool or gastric biopsy, analogous to urinary or respiratory tract infection management. The next hurdles to the widespread incorporation of *H pylori* resistance testing into clinical practice include comparing the implementation and cost-effectiveness of various competing strategies and disrupting provider behaviors.

In the absence of these newer tests and technologies, the underlying principles are to use the first-line most effective

treatment regimen, incorporate local and regional knowledge of bacterial resistance to select locally effective regimens, and use best available methods for initial diagnosis and to confirm treatment success.

Additional Strategies to Improve *H pylori* Eradication

H pylori eradication failure rates of 10%–20% are common even among patients treated with antibiotics to which they have demonstrated in vitro susceptibility.[76,87] The reasons for this are summarized in Figure 2. Optimizing the initial therapeutic regimen, even when leveraging susceptibility-guided treatment, is key because the likelihood of successful *H pylori* eradication decreases with each subsequent regimen.

Intragastric Acid Suppression

Achieving and maintaining sufficient intragastric acid suppression, ideally at near-neutral pH, plays a significant role in *H pylori* eradication. *H pylori* not only survives but thrives in the low pH environment of the stomach whereby the extracellular pH modulates its intracellular urease activity and enables acid acclimation. *H pylori* survives at pH 4–8 but replicates best at neutral pH.[104–107] At lower pH, *H pylori* is dormant and effectively resistant to bactericidal antibiotics such as amoxicillin and clarithromycin. Furthermore, the intragastric concentrations of clarithromycin and amoxicillin are significantly higher at or above pH 4; this contrasts with metronidazole, which is not particularly sensitive to gastric pH.[108]

In cases of clarithromycin resistance, clarithromycin-triple therapy is effectively dual PPI-amoxicillin; thus, the effectiveness solely relies on amoxicillin activity, which is dependent on gastric acid suppression and amoxicillin concentration. The degree of gastric acid suppression achieved by PPIs depends on dose, frequency,[109] potency,[110] CYP2C19 metabolizer phenotype,[111,112] and possibly dosing in relation to food.

The PCABs are a novel class of acid inhibitors that bind to the H,K-ATPase (proton pump) on parietal cells but, in contrast to PPIs, bind both active and inactive pumps and do not require an acidic environment for activation (ie, they are not prodrugs like PPIs). These mechanistic differences make PCABs more potent, rapid, and durable acid inhibitors compared with PPIs.[113–118] Vonoprazan has been used for many years in East Asia and is now approved in the U.S. in combination with amoxicillin with or without clarithromycin for *H pylori* treatment. However, the eradication success rates with the PCAB regimens in the landmark U.S./European trial were disappointingly lower (79%–85% in susceptible strains) than those observed in RCTs and observational studies from East Asia,[119] perhaps due to differences in body mass index, parietal cell mass, dosage, meal-timing, or compliance.[76] Further optimization studies, particularly in Western populations, are eagerly awaited as are clinical trials substituting PCABs for PPIs in other regimens (eg, bismuth-based quadruple therapy).

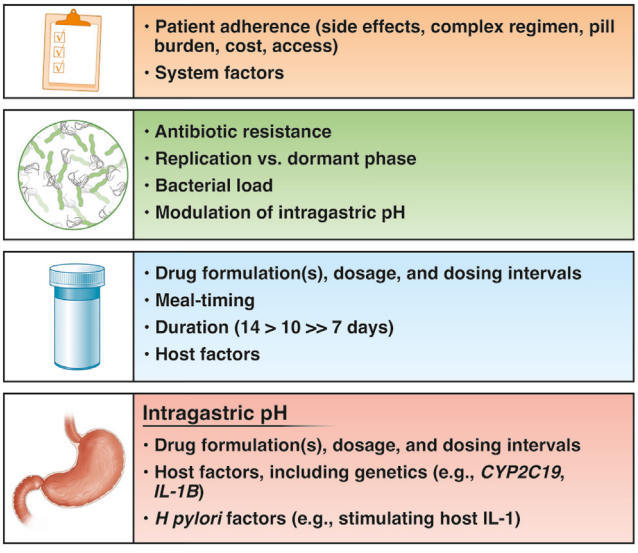

Figure 2. Multifactorial mechanisms contributing to *H pylori* eradication failure.

Host Genetics

Some *H pylori* eradication failure is not explicable by poor adherence or antimicrobial resistance, suggesting other factors, including host genetics, might be responsible. The largest body of data regarding host genetic effects is for *CYP2C19*. Most PPIs are primarily metabolized by cytochrome P450 2C19. People of Asian ancestry are more commonly poor metabolizers compared with those of European, African, or admixed American ancestry.[112] This might explain the higher eradication success rates with high-dose dual PPI-amoxicillin regimens in Asian vs European/U.S. populations. In a meta-analysis of patients receiving PPIs extensively metabolized by CYP2C19 (omeprazole, lansoprazole, pantoprazole) as part of a clarithromycin-based treatment regimen where local clarithromycin resistance was <15% or susceptibility was confirmed, CYP2C19-enhanced metabolizers had a 4.44-fold (95% CI, 1.94–10.2) higher likelihood of *H pylori* eradication failure compared with poor metabolizers.[111] Polymorphisms of the *interleukin-1B (IL1B)* gene encoding IL1B, a cytokine with potent gastric acid–suppressing activity, are also associated with *H pylori* treatment failure. There are little data for other host genetic determinants underlying *H pylori* treatment response,[111] but this remains a promising precision medicine approach for future investigation.

Duration

In the U.S., 14-day regimens are recommended to optimize eradication rates, although some 10-day regimens (such as Pylera) with proven high-eradication rates may be acceptable. Success with shorter regimens in other regions globally (such as Asia) may relate to more prevalent CYP2C19-poor metabolizer phenotypes or other mechanisms.[111]

Table 3. Strategies to Improve *H pylori* Eradication and Prevent Associated Gastric Cancer

I. Use the existing knowledge of epidemiology and risk factors to develop and test the effectiveness and cost-effectiveness of targeted population screening programs.
II. Identify populations at highest risk for *H pylori* sequelae (especially gastric cancer) by documenting and mapping known preneoplastic lesions (ie, atrophic gastritis, intestinal metaplasia) using standardized criteria and by specialized gastrointestinal pathologists.
III. Use knowledge of antimicrobial resistance to inform more effective treatment strategies at both individual and population levels. This effort includes starting with the most effective, first-line empirical therapy and will be aided or replaced in the future by more practical, rapid, molecular-based methodologies, including stool testing instead of culturing of *H pylori*, which requires more expensive, invasive endoscopy with gastric biopsies.
IV. Emphasize eradication testing post-treatment, which confirms cure in the individual, thus reducing cancer risk, provides feedback to practitioners about regimen effectiveness, and indirectly provides estimations of antimicrobial resistance in the population.
V. Develop systems-based approaches to overcome knowledge gaps and practice barriers especially for primary care providers who overwhelmingly diagnose and treat most *H pylori* cases.
VI. Monitor prescribing patterns and outcomes (local, regional, and national) corresponding to antimicrobial resistance rates and maintain accountability with quality metric developments for prescribers and institutions.

Dosing

Inappropriate medication dosage or frequency contributes not only to *H pylori* eradication failure but also to antibiotic resistance. Metronidazole should be dosed at 1.5 g–2 g/d, divided 3–4 times/d. Amoxicillin should be dosed 2 g–3 g/d in divided doses, ideally 3 or 4 times daily instead of twice daily. With twice-daily amoxicillin dosing (as in conventional triple therapy), the time above minimum inhibitory concentration 1 μg/mL is only 45.8% compared with 83.3% with the same total split 4 times daily.[120] Similarly, more frequent PPI dosing avoids low pH troughs, which occur even among high-potency PPIs such as rabeprazole. Optimizing amoxicillin-dual therapy, especially among Western populations, remains a worthwhile goal because this regimen is among the simplest, safest, and best-tolerated *H pylori* regimens and because *H pylori* resistance to amoxicillin is rare. Timing in relation to meals is also likely relevant due to temporal fluctuations in intragastric antibiotic concentrations. Dosing antibiotics with or shortly after meals when gastric emptying is delayed may increase antibiotic efficacy through higher intragastric antibiotic concentrations.[121]

Patient Adherence and Patient/Provider Education

One of the most common reasons for eradication failure is patient nonadherence to treatment, stemming from patient, provider, and/or systems factors. In the U.S., *H pylori* predominantly affects immigrants from endemic countries, people from lower socioeconomic statuses, non-White individuals, and other underserved populations; these groups are also challenged by communication barriers, exclusion from medical care, and economic obstacles. The patient experience surrounding *H pylori* diagnosis and treatment is predominantly negative, attributed to suboptimal patient-provider interactions.[122] Accordingly, efforts to form a trusting patient-provider relationship are important. Providers must ensure that patients understand the rationale for treatment (principally to reduce the risk of gastric cancer and peptic ulcer disease, but not necessarily dyspeptic symptoms), the treatment instructions, and the anticipated side effects. They must explore financial barriers before prescribing treatment.[123] Patients should be counseled a priori regarding the potential for treatment failure necessitating additional regimens, and those who smoke should be counseled to stop because active smoking is associated dose-dependently with *H pylori* eradication failure.[124] Written instructions that are language- and literacy-level appropriate should be provided. Intermittent check-ins from nurses and/or automated texts that trigger a live person as needed may also improve adherence.

To assist providers, implementation of decision support systems within the electronic medical record that include integrated clinical decision-making tools, up-to-date medication recommendations, and prompt for post-treatment eradication testing may improve outcomes. Clinical decision-making tools can also be used to prompt providers to refer a patient with an unconfirmed nonanaphylactic penicillin allergy to an allergist for formal testing and penicillin desensitization instead of prematurely avoiding all amoxicillin-based regimens.

Conclusions and Future Directions

Since *H pylori* was first cultured in the 1980s, considerable progress has been made in developing novel diagnostic tests and improving treatment regimens.[125] We are in an era where empiric treatments can be superseded by tailored susceptibility-guided regimens using conventional cultures of gastric biopsies with the expected wider use of molecular tests on biopsy as well as stool samples. This is consistent with the goals of antimicrobial stewardship, coupled with eradication testing to determine treatment success individually and locally. The availability

of PCAB-based therapies is also likely to improve treatment success.

High-quality evidence from Asian and Western studies supports the benefit of *H pylori* eradication in reducing the risk of primary and metachronous gastric cancer. Although cost-effectiveness analyses support systematic *H pylori* screening in Eastern and Western populations within parameters related to age, prevalence of *H pylori*, and risk of gastric cancer, few countries have adopted it. The U.S. Preventive Services Task Force is considering the merit of such programs in the U.S..[73]

Despite being a 2017 World Health Organization priority pathogen,[126] *H pylori* remains a relatively neglected infectious disease. There is a need to boost interest by pharmaceutical and federal research funding agencies. Our knowledge on the epidemiology and risk factors can be leveraged to construct and test risk stratification algorithms for cost-effective population- or community-based screening programs in the U.S.. The success of such programs to prevent and reduce mortality from gastric cancer depends on both the efficient detection and optimal treatment of *H pylori* as well as standardizing screening and management of gastric preneoplasia and early neoplasia. We believe that further progress needs to be made toward the practice of guideline implementation to optimize the diagnosis, treatment, and outcomes of individuals with *H pylori* (Table 3).

Treatment regimens comprising multiple antimicrobials remain cumbersome, expensive, and fraught with side effects and are, in some instances, ineffective. Truly novel therapies are needed, including vaccines, with a focus on specific anti–*H pylori* targets. Conducting head-to-head comparative drug trials among approved first-line empiric therapies and evaluating the benefit of susceptibility-tailored therapies is essential. Starting U.S. registries of regional antibiotic resistance patterns would facilitate linking up-to-date antibiotic resistance and eradication success in the population to clinical guideline recommendations.[127]

Implementation research is needed to improve the integration of clinical practice guidelines into the workflow of practitioners, especially in primary care and community settings, with potential to integrate health information technology applied to electronic health records and smart applications. *H pylori* management should be a top priority for learning health system initiatives of iterative quality improvement and practice audit. Now is the time to apply the abundance of theoretical knowledge and change the landscape of *H pylori* management and its associated diseases.

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Conflicts of interest
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