CLINICAL UPDATE

Advances in *Helicobacter pylori* From ACG 2014

Rallying Community Health Care Providers to Close the Gap Between *H pylori* Guidelines and the Challenges of Eradication

Neil H. Stollman, MD
Chairman, Department of Medicine
Alta Bates Summit Medical Center
Oakland, California
Associate Clinical Professor of Medicine
University of California San Francisco
San Francisco, California

David Y. Graham, MD
Professor of Medicine and
Molecular Virology and Microbiology
Baylor College of Medicine
Houston, Texas

Based on a Symposium at ACG 2014

Helicobacter pylori is among the most common infections worldwide, affecting approximately half of the global population.[1,2] A satellite symposium presented at the 2014 American College of Gastroenterology meeting examined the diagnosis and management of patients with *H pylori.* Dr Stollman began the symposium with a discussion of *H pylori* prevalence, which varies considerably with geographic location, ethnicity, and socioeconomic status. The prevalence is generally higher in developing countries; infections are reported in 88% of adults in India and 80% in parts of South America, including Brazil and Chile.[2] In the United States, approximately 30% of adults are infected with *H pylori*.[3,4] In developed countries, prevalence is often increased in first- and second-generation immigrants from countries with higher rates of infection. Adults raised in lower socioeconomic conditions are also at higher risk.

H pylori infection is predominantly acquired in childhood. Routes of transmission include gastro-oral, fecal-oral, and oral-oral.[5,6] Most children contract *H pylori* from their mother, siblings, and fathers (to a lesser extent). Adults in developed countries rarely contract *H pylori* infection (<1%).[5] Rates of *H pylori* infection increase with age; however, this trend has been linked to a birth cohort effect reflecting decreasing rates of infection in children throughout the past several decades.

Clinical Sequelae

Approximately 80% of people with *H pylori* infection do not develop symptoms.[7] However, in all people, the infection causes progressive damage to the lining of the stomach that may be irreversible. The infection can have a long asymptomatic phase. It always causes gastritis, which affects the gastric mucosa and may be associated with dyspepsia or nausea.[8] According to Dr Graham, the sensation has been likened to having "gastric termites." Children can develop various symptoms, such as a sensation of burning in the stomach, nausea, vomiting, and loss of appetite. Chronic, active gastritis is the primary condition related to *H pylori* colonization, and other disorders result from the chronic inflammation.[6] *H pylori* infection plays a key role in the pathogenesis of gastric cancer, gastric mucosa–associated lymphoid tissue (MALT) lymphoma, and peptic ulcer disease.

Gastric Cancer

H pylori leads to gastric cancer in approximately 1% to more than 12% of individuals depending on the region, underscoring the interest in eradicating the infection.[9] *H pylori* infection and the associated atrophic gastritis are recognized as the main risk factors for gastric cancer.[10] Nearly all gastric cancer cases, 95%, result from *H pylori* infection.[11] The World Health Organization recently pub-

lished a monograph underscoring the need to eradicate *H pylori* in order to prevent gastric cancer,[2] and recent studies have demonstrated a reduction in the risk of gastric cancer after eradication. For example, a meta-analysis of 6 randomized controlled trials showed a decline in the incidence of gastric cancer from 2.4% without eradication to 1.6% with eradication in asymptomatic adults (95% CI, 0.46-0.95; relative risk, 0.66).[12] Although results from such studies support eradication in asymptomatic patients, populations vary in risk, and therefore potential benefits must be balanced with the use of limited resources.[9] As a measure of the relative benefit of treating various populations, a study by Ford and colleagues showed that the number needed to treat to prevent 1 case ranged from a low of 15 for Chinese men to a high of 245 for women in the United States.[12]

H pylori also causes more than 90% of gastric MALT lymphoma cases, which in turn account for approximately 5% of all primary gastric cancers.[13] Eradication of *H pylori* has been shown to induce lasting remission in approximately 80% of patients with early-stage gastric MALT lymphoma.[14]

Peptic Ulcer Disease

H pylori infection is associated with both gastric and duodenal ulcers, and approximately 1 in 7 patients with the infection will develop peptic ulcer disease.[15] A study from the United States suggested that currently approximately half of peptic ulcers are caused by *H pylori* infection and half by nonsteroidal anti-inflammatory drugs (NSAIDs); however, the proportion caused by the bacterial infection has been decreasing with the rise in NSAID use.[16] A meta-analysis of 52 trials demonstrated that patients whose *H pylori* infection was successfully treated had a significantly lower rate of recurrence at 1 year for duodenal ulcers (64% vs 14%; $P<.001$) or gastric ulcers (40% vs 21%; $P<.05$) compared with no treatment.[17] The number needed to treat was 2.5 (95% CI, 2-4) for duodenal ulcers and 3 (95% CI, 2.3-5) for gastric ulcers.

Who to Test

The challenge remains regarding which patients should undergo testing. A high-priority goal is to identify patients with the infection before they develop atrophic gastritis, because eradication of the bacterial infection prior to the emergence of this pivotal condition reduces the risk of peptic ulcer disease, gastric cancer, and other related diseases. In 1983, Japan implemented a successful screening program for all residents ages 40 years and older, and now nearly 60% of gastric cancers are detected in the early stage.[18] Early detection has led to 5-year survival rates of approximately 65% in Japan[19] vs 10% to 25% in the United States and Europe.[20,21] The incidence of gastric cancer could likely be further reduced by the eradication of *H pylori* infection.[22] In 2013, the Japanese government expanded this strategy with a new program of test and treat for the entire population, along with an endoscopic surveillance program for those with atrophic gastritis after eradication.

Diagnostic Strategies

Testing for *H pylori* should be based on symptoms as well as risk factors, as discussed above. Dr Graham discussed several diagnostic tools based on different methods for identifying *H pylori* infection. Histology is the standard method for diagnosing *H pylori* infection because it reveals critical information on mucosal inflammation and preneoplastic changes to the tissue structure.[23] However, observer subjectivity can result in false negatives, and an endoscopy is required to obtain a tissue sample.

Guidelines recommend a noninvasive test, such as the fecal antigen test or the urea breath test, both of which have high specificity and sensitivity.[24,25] The ^{13}C urea breath test (BreathTek, Otsuka America Pharmaceutical) was recently approved for children (≥3 years); accurate results require a calculation based on the patient's age, height, and weight.[26] The fecal antigen test and the ^{13}C urea breath test may give false-negative results in patients taking proton pump inhibitors (PPIs), bismuth, or antibiotics; therefore, these treatments should be discontinued 2 weeks prior to administering the tests.[24] Although pediatricians still often use endoscopy in these patients, it is expected that noninvasive testing will become more common.

In Dr Stollman's experience, compliance is higher with the ^{13}C urea breath test than the fecal antigen test, which requires that patients obtain a stool sample and bring it to the office. He mentioned that patients who use public transportation may find this requirement particularly problematic.

Although serology has been used for many years to test for *H pylori*, the lack of specificity limits the value of this approach to situations with a high pretest probability of infection, such as the presence of a duodenal ulcer.[24,27] In addition, serology cannot be used for eradication testing because antibodies may persist after successful treatment.[24] Current data suggest that serology lacks any utility in these patients.

Treatment

The Maastricht Consensus Conference Guidelines state that every patient with *H pylori* should be treated.[25] A single one-size-fits-all optimal treatment cannot be defined for all patients, partly due to the increase in antibiotic-resistant strains; however, an acceptable treatment should be effective in at least 90% of patients.

Various drug combinations have been used. The efficacy of triple therapy was established in the early 1990s, and this strategy remained the cornerstone of *H pylori* treatment for many years.[28] However, increasing antibiotic resistance has decreased the success of triple therapy; according to Dr Graham, this approach is currently considered obsolete. The 2 regimens that are recommended today are concomitant therapy (PPI, amoxicillin, metronidazole, and clarithromycin) twice daily for 14 days or bismuth quadruple therapy consisting of a PPI, bismuth, tetracycline, and metronidazole.[29] In treatment-naive patients, concomitant therapy is recommended because it is well tolerated and is only undermined by dual clarithromycin and metronidazole resistance. Bismuth therapy is the alternative and is ideal for patients with penicillin resistance or after failure of concomitant therapy. When metronidazole resistance is suspected, this regimen should be given for 14 days. In a randomized, open-label, noninferiority, phase 3 clinical trial of 438 patients in Europe, eradication rates were superior with first-line quadruple therapy compared with triple therapy (80% vs 55%; $P<.0001$), with a comparable safety profile.[30] Although the intention-to-treat cure rate was only 80%, the per protocol rate was greater than 90%, confirming that efforts should be made to maintain adherence.

Antibiotic Resistance

Dr Stollman discussed antibiotic resistance and reasons for treatment failure. Decades of overuse of antibiotics has led to increasing resistance in *H pylori* strains worldwide.[31] Because resistance to specific antibiotics varies regionally, it is imperative to choose treatment regimens based on the local population.[23] In addition, the most effective regimens will be adapted to the patient's history of antibiotic use, particularly for previous treatment of *H pylori*.

Metronidazole and clarithromycin are key components of standard triple therapy, and resistance to these agents has highlighted the need for treatment alternatives. In many developing countries, the prevalence of metronidazole resistance is greater than 40%; in some places, it can reach 80% or higher.[29] A Japanese study illustrated the impact of rising antibiotic resistance to *H pylori* during the past 2 decades.[32] Primary resistance to clarithromycin was observed in 8.7% of patients treated from 1995 to 2000 and rose to 34.4% in patients treated from 2007 to 2008. Concomitantly, treatment success with triple therapy decreased from 91.2% to 69.0%.

The Importance of Posttreatment Testing

Treatment failure rates are often unacceptably high and can be attributed to several factors. Many insurance companies do not cover the combined pill treatment, thus resulting in several prescriptions for pills that must be taken on different schedules, a complicated regimen that may decrease patient adherence. Many of the antibiotics themselves induce dyspepsia, further discouraging some patients from continuing treatment. Dr Stollman estimated that at least one-third of his patients take less than 90% of their medication. Moreover, the treatments themselves may be inadequate if local antibiotic resistance is not considered or the duration is too short.[33,34]

Treatment success is difficult to predict and depends partly on the characteristics of the local population, the specific infectious strains, antibiotic resistance of individual patients, and the patient's ability to complete the treatment regimen. The only way to accurately assess treatment outcomes is by retesting for *H pylori* infection after the completion of treatment. The Maastricht guidelines recommend the ^{13}C urea breath test or the fecal antigen test as noninvasive methods for posttreatment testing, while discouraging use of serology due to its inability to distinguish between past infection and current infection.[25] Dr Stollman mentioned that, in his clinics, all patients are scheduled for a follow-up ^{13}C urea breath test when they receive a prescription for treatment of *H pylori* due to markedly declining eradication rates in this population.

This column is based on a satellite symposium of the 2014 American College of Gastroenterology meeting sponsored by Otsuka America Pharmaceutical. Dr Stollman is a member of the speakers bureaus of Otsuka America (OAPI) and Quest Laboratories. Dr Graham is an unpaid consultant for Novartis in relation to vaccine development for the treatment or prevention of Helicobacter pylori *infection, and a paid consultant for RedHill Biopharma regarding novel* H pylori *therapies and for Otsuka Pharmaceuticals regarding diagnostic testing. He has received royalties from Baylor College of Medicine patents covering materials related to the ^{13}C urea breath test.*

References

1. Tonkic A, Tonkic M, Lehours P, Mégraud F. Epidemiology and diagnosis of *Helicobacter pylori* infection. *Helicobacter.* 2012;17(suppl 1):1-8.
2. Hunt RH, Xiao SD, Megraud F, et al; WGO-OMGE Global Guidelines Task Force. WHO Practice Guidelines—*Helicobacter pylori* in developing countries. World Gastroenterology Organisation. http://www.worldgastroenterology.org/assets/downloads/en/pdf/guidelines/11_helicobacter_pylori_developing_countries_en.pdf. Posted August 2010. Accessed November 6, 2014.
3. Graham DY, Malaty HM, Evans DG, Evans DJ Jr, Klein PD, Adam E. Epidemiology of *Helicobacter pylori* in an asymptomatic population in the United States. Effect of age, race, and socioeconomic status. *Gastroenterology.* 1991;100(6):1495-1501.
4. Grad YH, Lipsitch M, Aiello AE. Secular trends in *Helicobacter pylori* seroprevalence in adults in the United States: evidence for sustained race/ethnic disparities. *Am J Epidemiol.* 2012;175(1):54-59.
5. Logan RP, Walker MM. ABC of the upper gastrointestinal tract: epidemiology and diagnosis of *Helicobacter pylori* infection. *BMJ.* 2001;323(7318):920-922.
6. Kusters JG, van Vliet AH, Kuipers EJ. Pathogenesis of *Helicobacter pylori* infection. *Clin Microbiol Rev.* 2006;19(3):449-490.

7. Boyanova L. Helicobacter pylori. Poole, United Kingdom: Caister Academic Press; 2011.
8. Marshall BJ, Warren JR. Unidentified curved bacilli in the stomach of patients with gastritis and peptic ulceration. *Lancet*. 1984;1(8390):1311-1315.
9. Herrero R, Parsonnet J, Greenberg ER. Prevention of gastric cancer. *JAMA*. 2014;312(12):1197-1198.
10. Ohata H, Kitauchi S, Yoshimura N, et al. Progression of chronic atrophic gastritis associated with *Helicobacter pylori* infection increases risk of gastric cancer. *Int J Cancer*. 2004;109(1):138-143.
11. Graham DY. General session on gastric cancer—etiology, development, and implications for therapy. Paper presented at: 2014 Gastrointestinal Cancers Symposium; January 16, 2014; San Francisco, California.
12. Ford AC, Forman D, Hunt RH, Yuan Y, Moayyedi P. *Helicobacter pylori* eradication therapy to prevent gastric cancer in healthy asymptomatic infected individuals: systematic review and meta-analysis of randomised controlled trials. *BMJ*. 2014;348:g3174.
13. Wotherspoon AC, Ortiz-Hidalgo C, Falzon MR, Isaacson PG. *Helicobacter pylori*–associated gastritis and primary B-cell gastric lymphoma. *Lancet*. 1991;338(8776):1175-1176.
14. Zullo A, Hassan C, Cristofari F, et al. Effects of *Helicobacter pylori* eradication on early stage gastric mucosa–associated lymphoid tissue lymphoma. *Clin Gastroenterol Hepatol*. 2010;8(2):105-110.
15. Sipponen P, Varis K, Fräki O, Korri UM, Seppälä K, Siurala M. Cumulative 10-year risk of symptomatic duodenal and gastric ulcer in patients with or without chronic gastritis. A clinical follow-up study of 454 outpatients. *Scand J Gastroenterol*. 1990;25(10):966-973.
16. Jensen DM, Savides T, Sitzer M, et al. Demographics, risk factors, and outcomes of peptic ulcer hemorrhage in the United States: results of a large multicenter study. *Gastroenterology*. 2003;124(4):A17.
17. Ford AC, Delaney BC, Forman D, Moayyedi P. Eradication therapy in *Helicobacter pylori* positive peptic ulcer disease: systematic review and economic analysis. *Am J Gastroenterol*. 2004;99(9):1833-1855.
18. Asaka M, Kato M, Sakamoto N. Roadmap to eliminate gastric cancer with *Helicobacter pylori* eradication and consecutive surveillance in Japan. *J Gastroenterol*. 2014;49(1):1-8.
19. 5-Year Survival Rate in Population-Based Cancer Registry (diagnosed in 2000-2002). Cancer Information Service. http://ganjoho.jp/data/professional/statistics/backnumber/2012/data06.pdf. Updated January 13, 2013. Accessed November 14, 2014.
20. Noguchi Y, Yoshikawa T, Tsuburaya A, Motohashi H, Karpeh MS, Brennan MF. Is gastric carcinoma different between Japan and the United States? *Cancer*. 2000;89(11):2237-2246.
21. Hundahl SA, Phillips JL, Menck HR. The National Cancer Data Base Report on poor survival of U.S. gastric carcinoma patients treated with gastrectomy: Fifth Edition American Joint Committee on Cancer staging, proximal disease, and the "different disease" hypothesis. *Cancer*. 2000;88(4):921-932.
22. IARC *Helicobacter pylori* Working Group (2014). *Helicobacter pylori* Eradication as a Strategy for Preventing Gastric Cancer. Lyon, France: International Agency for Research on Cancer (IARC Working Group Reports, No. 8). http://www.iarc.fr/en/publications/pdfs-online/wrk/wrk8/index.php. Accessed November 11, 2014.
23. Garza-González E, Perez-Perez GI, Maldonado-Garza HJ, Bosques-Padilla FJ. A review of *Helicobacter pylori* diagnosis, treatment, and methods to detect eradication. *World J Gastroenterol*. 2014;20(6):1438-1449.
24. Chey WD, Wong BC; Practice Parameters Committee of the American College of Gastroenterology. American College of Gastroenterology guideline on the management of *Helicobacter pylori* infection. *Am J Gastroenterol*. 2007;102(8):1808-1825.
25. Malfertheiner P, Megraud F, O'Morain CA, et al. Management of *Helicobacter pylori* infection—the Maastricht IV/Florence Consensus Report. *Gut*. 2012;61(5):646-664.
26. BreathTek (urea breath test *H. pylori* kit) [package insert]. Rockville, MD: Otsuka America Pharmaceutical, Inc.; revised May 2013.
27. Fock KM, Katelaris P, Sugano K, et al; Second Asia-Pacific Conference. Second Asia-Pacific Consensus Guidelines for *Helicobacter pylori* infection. *J Gastroenterol Hepatol*. 2009;24(10):1587-1600.
28. Bazzoli F, Zagari RM, Fossi S, Pozzato P, Roda A, Roda E. Efficacy and tolerability of a short-term low-dose triple therapy for eradication of *Helicobacter pylori*. *Gastroenterology*. 1993;104:40A.
29. Graham DY, Lee YC, Wu MS. Rational *Helicobacter pylori* therapy: evidence-based medicine rather than medicine-based evidence. *Clin Gastroenterol Hepatol*. 2014;12(2):177-186.
30. Malfertheiner P, Bazzoli F, Delchier JC, et al. *Helicobacter pylori* eradication with a capsule containing bismuth subcitrate potassium, metronidazole, and tetracycline given with omeprazole versus clarithromycin-based triple therapy: a randomised, open-label, non-inferiority, phase 3 trial. *Lancet*. 2011;377(9769):905-913.
31. Testerman TL, Morris J. Beyond the stomach: an updated view of *Helicobacter pylori* pathogenesis, diagnosis, and treatment. *World J Gastroenterol*. 2014;20(36):12781-12808.
32. Sasaki M, Ogasawara N, Utsumi K, et al. Changes in 12-year first-line eradication rate of *Helicobacter pylori* based on triple therapy with proton pump inhibitor, amoxicillin and clarithromycin. *J Clin Biochem Nutr*. 2010;47(1):53-58.
33. Hsu PI, Wu DC, Wu JY, Graham DY. Modified sequential *Helicobacter pylori* therapy: proton pump inhibitor and amoxicillin for 14 days with clarithromycin and metronidazole added as a quadruple (hybrid) therapy for the final 7 days. *Helicobacter*. 2011;16(2):139-145.
34. Graham DY, Fischbach L. *Helicobacter pylori* treatment in the era of increasing antibiotic resistance. *Gut*. 2010;59(8):1143-1153.