Recent Developments Pertaining to *H. pylori* Infection

Colin W. Howden, MD, FACP and David Y. Graham, MD, MACG

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A 2017 guideline from the American College of Gastroenterology (ACG) expanded potential indications for testing for *Helicobacter pylori* infection, altered recommendations for first- and second-line treatment, and called for routine post-treatment testing (1). Some more recent publications suggest that current practice can be improved.

**H. pylori and Gastric Cancer**

*H. pylori* is the major etiologic factor for gastric adenocarcinoma and may cause more cancers worldwide than hepatitis B and C viruses combined (2). The American Cancer Society has predicted more new cases and attributable deaths annually from gastric cancer than from both types of esophageal cancer (3). Pangastritis with metaplastic epithelia (psuedopyloric and intestinal metaplasia) signifies an increased risk of gastric cancer; all patients with metaplastic epithelium should be tested for *H. pylori* infection and treated for it if positive (4,5).

The Kyoto and Houston consensus conferences also recommended treating all individuals with proven *H. pylori* infection (6,7). An updated Cochrane Collaboration systematic review and meta-analysis of randomized controlled trials (RCTs) reported that *H. pylori* eradication in otherwise healthy adults was associated with a 46% reduced incidence of, and a 39% reduced mortality from, gastric cancer (8). However, because all included RCTs were from Asia or South America, the results may not be automatically generalizable to the United States. From South Korea, another RCT showed that treating the infection in first-degree relatives of gastric cancer patients significantly reduced their risk of gastric cancer (9). This was despite the known higher rate of reinfection in Asia than elsewhere.

Recent evidence from the United States using the Veterans Health Administration database showed that eradication of *H. pylori* infection was associated with a 76% reduced incidence of gastric cancer among those participants who were diagnosed accurately, treated, and had a post-treatment test that confirmed eradication (10). Finally, a large cohort study from Taiwan has demonstrated the effectiveness of a mass screening and treatment program among a population with a high prevalence of *H. pylori* infection and gastric cancer (11). With intensive screening and treatment, the incidence of—and mortality from—gastric cancer fell by 53% and 25%, respectively.

**Opportunities for Improving Diagnosis and Treatment in US Practice**

An important precept in the 2017 ACG guideline was that all patients be retested post-treatment (1). However, in the recent Veterans Health Administration study (10), only approximately 20% of treated patients had documented post-treatment testing (10,12) and other studies confirm that post-treatment testing is performed infrequently and inconsistently (13,14).

Traditionally, antimicrobial therapy is predicated on results of susceptibility testing. With *H. pylori*, susceptibility testing is available from a few large commercial laboratories. Molecular testing using gastric biopsies or fecal samples is in development but is available commercially (e.g., www.amlabatories.com). There are scarce data available concerning contemporary antimicrobial resistance rates in North America; Table 1 lists estimates from the ACG 2017 guideline (1) and more recent results from subsequent studies (15–17). A systematic review and meta-analysis of international studies (18) included only 2 from North America that were referenced in the 2017 ACG guideline (1).

**Developments in Treatment of *H. pylori* Infection**

Given the high rates of resistance to clarithromycin, metronidazole, and levofloxacin, these should no longer be used in triple regimens unless based on susceptibility testing. Treatment decisions regarding the use of empiric therapy should be based on knowledge of the patient’s antibiotic history and the presence or absence of true penicillin allergy (1). Empiric therapy should reliably achieve high local cure rates despite the absence of susceptibility testing. Two regimens approved by the US Food and Drug Administration (FDA) that can be used empirically are bismuth quadruple therapy (BQT) and rifabutin triple therapy.

BQT should contain tetracycline rather than doxycycline and be given for 14 days (19). BQT empiric therapy proved as successful as susceptibility-guided therapy in a RCT from China (20). However, problems persist with BQT including its complexity, large pill burden, adverse effects, and availability and cost of tetracycline, which may be obtained less expensively using GoodRx or similar services. A combination product (Pylera, Allergan, Madison, NJ) is available but is expensive and packaged as a 10-day course (21), which may cause issues when prescribed for the desired 14 days.

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1University of Tennessee College of Medicine, Memphis, Tennessee; 2Baylor College of Medicine, Houston, Texas. Correspondence: Colin W. Howden, MD, FACP. 
E-mail: chowden@uthsc.edu.

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The 2017 ACG guideline also recommended concomitant/ non-bismuth quadruple therapy as first-line (1). However, it has fallen into disfavor because it requires giving clarithromycin and metronidazole together such that failure requires dual clarithromycin-metronidazole resistance. However, when successful, all patients will receive one unnecessary antibiotic, which can only contribute to global antimicrobial resistance.

In 2019, the FDA approved a 3-in-1 combination product of omeprazole, amoxicillin, and rifabutin for the treatment of *H. pylori* infection in adults (Talicea, RedHill Biopharma, Raleigh, NC). Eradication rates were not influenced by clarithromycin or metronidazole resistance, and no resistance was documented to rifabutin either pretreatment or post-treatment (Table 1). In a RCT, non-Asian, treatment-naive patients given the triple combination had an intent-to-treat (ITT) eradication rate of 83.8% compared with 57.7% in those given equivalent doses of omeprazole and amoxicillin without rifabutin (16). It was well tolerated with high adherence. This product only became available after the 2017 ACG guideline (1). It is appropriate for either first-line or salvage treatment based on its FDA approval.

Potassium-competitive acid blockers are acid-suppressing agents that interact with the gastric proton pump differently to conventional proton pump inhibitors. They produce earlier onset of acid suppression and more consistent 24-hour control of intragastric acidity than proton pump inhibitors (22,23). The potassium-competitive acid blocker vonoprazan is licensed in some Asian and South American countries but not currently available in the United States. A RCT from Japan compared 7 days of treatment with relatively low doses of vonoprazan and amoxicillin with vonoprazan, amoxicillin, and clarithromycin. ITT eradication rates were 84.5% and 89.2%, respectively. Among patients with clarithromycin-resistant strains, eradication rates were 92.3% and 76.2% for the dual and triple regimens, respectively (24). Optimization of dosing and treatment duration will likely produce even higher eradication rates. Vonoprazan dual and triple regimens are currently being evaluated in a phase 3 trial in the United States and Europe (Phathom Pharmaceuticals, Buffalo Grove, IL) in which patients are being treated for 14 days and with higher doses.

**Table 1. Reported antimicrobial resistance rates by *H. pylori***

<table>
<thead>
<tr>
<th>Ref</th>
<th>Years of study</th>
<th>CLA</th>
<th>MET</th>
<th>AMOX</th>
<th>TET</th>
<th>LEVO</th>
<th>RIF</th>
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<td>Chey et al. (1)</td>
<td>2009–2011</td>
<td>16</td>
<td>20</td>
<td>&lt;2</td>
<td>&lt;2</td>
<td>31</td>
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<tr>
<td>Kumar et al. (15)</td>
<td>2009–2019</td>
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<td>N/A</td>
<td>69</td>
<td>N/A</td>
</tr>
<tr>
<td>Graham et al. (16)</td>
<td>2017–2018</td>
<td>17</td>
<td>44</td>
<td>6</td>
<td>N/A</td>
<td>N/A</td>
<td>0</td>
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<tr>
<td>Nyssen et al. (17)</td>
<td>2013–2017</td>
<td>23</td>
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</tr>
</tbody>
</table>

AMOX, amoxicillin; CLA, clarithromycin; MET, metronidazole; LEVO, levofloxacin; N/A, not available; RiF, rifabutin; TET, tetracycline.

*Patients from one geographic region of the United States with persistent infection after treatment.

*Treatment-naive patients across the United States who participated in a clinical trial.

*European multinational registry data; treatment-naive patients (Dual resistance rate to CLA and MET was 13%).

**SUMMARY**

Recent guidelines recommend treating all individuals infected with *H. pylori*. Despite practice recommendations (1), post-treatment testing is still not being performed routinely (10,12–14). This prevents patients from knowing whether they have been cured—and physicians from learning whether their treatment was effective. Triple regimens containing clarithromycin, metronidazole, or levofloxacin should no longer be used without pretreatment susceptibility testing. Concomitant therapy exposes patients to unnecessary antibiotics. Approved therapies that can be used empirically are BQT and rifabutin triple therapy.

**CONFLICTS OF INTEREST**

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**REFERENCES**


