Update on Helicobacter pylori Treatment

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One half of the world’s population has Helicobacter pylori infection, with an estimated prevalence of 30 percent in North America. Although it is unclear whether eradication of H. pylori improves symptoms in patients with nonulcer dyspepsia, there is strong evidence that eradication of this bacteria improves healing and reduces the risk of recurrence or rebleeding in patients with duodenal or gastric ulcer. A “test-and-treat” strategy is recommended for most patients with undifferentiated dyspepsia. With this approach, patients undergo a noninvasive test for H. pylori infection and, if positive, are treated with eradication therapy. This strategy reduces the need for antisecretory medications as well as the number of endoscopies. The urea breath test or stool antigen test is recommended. Until recently, the recommended duration of therapy for H. pylori eradication was 10 to 14 days. Shorter courses of treatment (i.e., one to five days) have demonstrated eradication rates of 89 to 95 percent with the potential for greater patient compliance. A one-day treatment course consists of bismuth subsalicylate, amoxicillin, and metronidazole, all given four times with a one-time dose of lansoprazole. In children with documented H. pylori infection, however, all regimens should continue to be prescribed for seven to 14 days until short-course treatment is studied and its effectiveness has been established in this population. (Am Fam Physician 2007;75:351-8. Copyright © 2007 American Academy of Family Physicians.)
for malignancy or complicated ulcer (e.g., dysphagia, early satiety, protracted vomiting, anorexia, loss of more than 10 percent of body weight, melena, rectal bleeding, abdominal mass, previous peptic ulcer disease, jaundice, family history of gastric cancer). If infected, patients are treated with *H. pylori* eradication therapy.

Several recent economic analyses show that the test-and-treat strategy improves symptoms and is cost-effective compared with other strategies. A long-term follow-up study comparing a test-and-treat strategy versus prompt endoscopy in patients with dyspepsia showed that the former reduced the number of endoscopies performed as well as the number of antisecretory medications administered.

Patients can be tested for the presence of *H. pylori* via invasive or noninvasive methods (Table 1). Although serology for immunoglobulin G often is chosen in the outpatient setting because of its convenience, it is less accurate than either the stool antigen or urea breath test. Indeed, the American Gastroenterological Association recommends one of the latter for optimal testing. In addition, the urea breath test and stool antigen test can be used to confirm eradication, whereas serology remains positive for months after eradication.

**Potential Benefits of Treatment**

**PEPTIC ULCER DISEASE**

In a meta-analysis of 34 studies of patients with duodenal ulcers, *H. pylori* eradication plus antisecretory therapy was superior to an antisecretory drug alone for healing of the ulcer (number needed to treat [NNT] = 14). One-time *H. pylori* eradication was just as effective as long-term antisecretory therapy in preventing duodenal ulcer recurrence and was much more effective than no treatment.

In a meta-analysis of 13 studies of patients with gastric ulcers, there was no statistically significant difference between *H. pylori* eradication therapy plus antisecretory drugs and antisecretory drugs alone for healing. However, gastric ulcer recurrence was significantly less likely following *H. pylori* eradication when compared with no treatment in nine of the studies (NNT = 4). Four trials reported on symptom resolution at four to six weeks, but the diversity of the study designs made it difficult to draw any conclusions about the superiority of eradication therapy versus antisecretory therapy alone.

Eradication therapy has been reviewed and compared with antisecretory therapy specifically for the prevention of recurrent bleeding from peptic ulcer. In patients taking long-term antisecretory drugs after the initial treatment of an ulcer, rebleeding was less common in those who also received *H. pylori* eradication therapy (1.6 percent versus 5.6 percent, NNT = 25). Thus, *H. pylori* eradication therapy is recommended to prevent rebleeding in patients with peptic ulcer.

In summary, *H. pylori* eradication significantly reduces the risk of ulcer recurrence and rebleeding and is less expensive than chronic antisecretory therapy. Continuing antisecretory maintenance therapy for more than two weeks following antibiotic treatment is unnecessary after *H. pylori* eradication unless patients have concomitant GERD. A 2005 evidence-based guideline from the University of Michigan provides a useful algorithm and
is consistent with these recommendations (http://cme.med.umich.edu/pdf/guideline/PUD05.pdf).25

NONULCER DYSPEPSIA
At best, *H. pylori* eradication provides a small and highly variable symptomatic benefit in patients with nonulcer dyspepsia. Although a meta-analysis of 10 studies failed to demonstrate an improvement in symptoms with eradication therapy,26 an updated systematic review of 17 trials revealed a small but statistically significant benefit (NNT = 18).27 The American College of Gastroenterology suggests an empiric trial of acid suppression with a proton pump inhibitor for four to eight weeks as an option for initial treatment of dyspepsia in areas with a low prevalence of *H. pylori* infection.28

GERD
Testing and treating for *H. pylori* in patients with GERD has not been shown to improve symptoms.29 In guidelines published in November 2005, the American College of Gastroenterology does not mention testing or treating for *H. pylori* in the diagnosis and treatment of GERD.30

GASTRIC CANCER PREVENTION
*H. pylori* has been identified as a group 1 carcinogen by the World Health Organization and is associated with the development of gastric cancer. The risk of developing gastric cancer is increased by three to six times in infected persons.31,32 A meta-analysis of 51 studies revealed a decrease in mucosal inflammation and possible improvement in gastric mucosal atrophy when *H. pylori* is eradicated.32 In a Japanese study with a mean follow-up of 3.4 years, investigators found that patients with documented gastric ulcer had a decreased likelihood of developing gastric cancer after eradication therapy.33 The results of a small randomized controlled trial involving healthy patients suggest that those treated for *H. pylori* infection had a lower incidence of preneoplastic findings on endoscopy after one year.34 However, preliminary results from large trials with follow-up extending to seven years demonstrate no difference in the rates of gastric cancer among patients who underwent *H. pylori* eradication therapy.35,36

In the absence of guidelines or good-quality clinical trials, eradication of *H. pylori* purely to prevent gastric cancer in otherwise asymptomatic patients is not recommended.

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**TABLE 1**

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Usefulness</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Invasive</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endoscopy with biopsy</td>
<td></td>
<td></td>
<td>Diagnostic strategy of choice in children with persistent or severe upper abdominal symptoms</td>
</tr>
<tr>
<td>Histology</td>
<td>&gt;95</td>
<td>100</td>
<td>Sensitivity reduced by PPIs, antibiotics, and bismuth-containing compounds</td>
</tr>
<tr>
<td>Urease activity</td>
<td>93 to 97</td>
<td>&gt;95</td>
<td>Sensitivity reduced by PPIs, antibiotics, bismuth-containing compounds, and active bleeding</td>
</tr>
<tr>
<td>Culture</td>
<td>70 to 80</td>
<td>100</td>
<td>Technically demanding</td>
</tr>
<tr>
<td><strong>Noninvasive</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serology for immunoglobulin G</td>
<td>85</td>
<td>79</td>
<td>Sensitivity and specificity vary widely; positive result may persist for months after eradication</td>
</tr>
<tr>
<td>Urea breath test</td>
<td>95 to 100</td>
<td>91 to 98</td>
<td>Reliability in children not adequately validated; not recommended</td>
</tr>
<tr>
<td><em>H. pylori</em> stool antigen</td>
<td>91 to 98</td>
<td>94 to 99</td>
<td>Requires separate appointments; sensitivity reduced by PPIs, antibiotics, and bismuth-containing compounds; reliable test for cure</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Best available noninvasive test in children but higher false-positive rates in infants and children younger than six years compared with school-age children and adolescents</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Test for cure seven days after therapy is accurate; sensitivity reduced by PPIs, antibiotics, and bismuth-containing compounds</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Easy to perform independent of age; possible alternative to urea breath test; monoclonal antibody-based test most reliable</td>
</tr>
</tbody>
</table>

PPI = proton pump inhibitor.
Information from references 16 through 22.
Treatment of *H. pylori*

**Selection of Therapy to Eradicate *H. pylori***

When selecting a therapy to eradicate *H. pylori*, duration of treatment and adverse effects should be considered.

**DURATION OF THERAPY**

Until recently, the recommended duration of therapy for *H. pylori* eradication was 10 to 14 days. The most widely recommended regimens are summarized in Table 2. Studies evaluating one-, five-, and seven-day regimens to eradicate *H. pylori* are summarized in Table 3. Although not proven, potential benefits of shorter regimens include better compliance, fewer adverse drug effects, and reduced cost to the patient.

**ADVERSE EFFECTS**

In a meta-analysis of 52 studies, adverse effects were noted in 39 trials comparing *H. pylori* eradication therapy plus an antisecretory agent versus antisecretory therapy alone (in 22 percent and 8 percent of patients, respectively [number needed to harm = 7 for *H. pylori* eradication]). The most commonly reported adverse events were nausea, vomiting, and diarrhea. A bitter or metallic taste in the mouth is associated with eradication regimens containing clarithromycin. Bismuth subsalicylate (Pepto-Bismol) may cause a temporary grayish-black discoloration of the stool.

**Special Considerations**

**H. pylori** **ERADICATION IN CHILDREN**

Endoscopy with biopsy remains the diagnostic strategy of choice in children with persistent or severe upper abdominal pain (Table 1). The goal is to detect the underlying pathophysiology and cause of symptoms, not simply the presence of *H. pylori*. The urea breath test is the noninvasive diagnostic test of choice for *H. pylori* detection. The stool antigen test is an alternative, with the monoclonal antibody-based test being most reliable. Both the urea breath and stool antigen tests are reliable tests for cure.

With respect to pharmacologic treatment, the North American Society for Pediatric Gastroenterology and Nutrition recommends eradication therapy in children with an endoscopically proven duodenal or gastric ulcer with *H. pylori* documented via histopathology. Another indication is documentation of *H. pylori* in patients with previous ulcer disease or iron deficiency anemia. The guideline does not support eradication therapy or withholding treatment in children with gastritis, even if positive for *H. pylori*, because of a lack of data demonstrating that eradication prevents peptic ulcer disease. Nevertheless, the clinical trend, in the absence of updated practice guidelines, is to treat children who are *H. pylori* positive.

As in adults, various dosages of antibiotics and bismuth salts along with proton pump inhibitors in regimens ranging from seven days to six weeks have been used to treat *H. pylori* infection in children. Eradication rates of more than 90 percent have been demonstrated in children and adolescents using triple-drug therapies. Based on studies of adults and children, the recommended regimens for *H. pylori* eradication are listed in Table 4.

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**TABLE 2**

**Selected Long-Duration Regimens for Helicobacter pylori Eradication**

<table>
<thead>
<tr>
<th>Treatment regimen</th>
<th>Duration</th>
<th>Eradication rate (%)</th>
<th>Cost (generic) per day*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omeprazole (Prilosec), 20 mg twice daily, plus amoxicillin, 1 g twice daily, plus clarithromycin (Biaxin), 500 mg twice daily</td>
<td>14 days</td>
<td>80 to 86</td>
<td>Omeprazole: $9 (8) Amoxicillin: $2 (2 to 3) Clarithromycin: $10 (9)</td>
</tr>
<tr>
<td>Lansoprazole (Prevacid), 30 mg twice daily, plus amoxicillin, 1 g twice daily, plus clarithromycin, 500 mg twice daily</td>
<td>10 to 14 days</td>
<td>86</td>
<td>Lansoprazole: $10 Amoxicillin: $2 (2 to 3) Clarithromycin: $10 (9)</td>
</tr>
<tr>
<td>Bismuth subsalicylate (Pepto-Bismol), 525 mg four times daily, plus metronidazole (Flagyl), 250 mg four times daily, plus tetracycline, 500 mg four times daily, plus histamine H2 blocker</td>
<td>14 days (H2 blocker alone for an additional 14 days taken once or twice daily)</td>
<td>80</td>
<td>Bismuth subsalicylate: $1 Metronidazole: $10 (2) Tetracycline: $2 (1)</td>
</tr>
</tbody>
</table>

*—Estimated cost to the pharmacist based on average wholesale prices (rounded to the nearest dollar) in Red Book. Montvale, N.J.: Medical Economics Data, 2006. Cost to the patient will be higher, depending on prescription filling fee.

Adapted with permission from Meurer LN, Bower DJ. Management of Helicobacter pylori infection. Am Fam Physician 2002;65:1333.
Although first-line therapy will successfully eradicate the bacteria in most infected patients, antibiotic resistance of *H. pylori* is a growing concern.42,43 Resistant *H. pylori* has been documented in cases of failed eradication therapy based on biopsy and culture results and is of great concern in patients at high risk for complications of *H. pylori* infection.

In one small trial, 70 percent of patients failing one or more regimens responded well to triple-drug therapy that included pantoprazole (Protonix), amoxicillin, and levofloxacin (Levaquin) for 10 days.44 A meta-analysis of current literature on treatment of resistant *H. pylori* showed some benefit in using quadruple-drug therapy, including the addition of clarithromycin to ranitidine (Zantac), bismuth, and amoxicillin (1 g twice daily) therapy, as well as a combination of proton-pump inhibitors (standard dosage for 10 days), bismuth, metronidazole (Flagyl), and tetracycline.43 Regimens that include rifabutin (Mycobutin), 300 mg per day, also have been successful in 38 percent of resistant cases.42

### TABLE 3
Short-Course Therapy for Eradication of *Helicobacter pylori*

<table>
<thead>
<tr>
<th>Treatment regimen</th>
<th>Duration (days)</th>
<th>Number of patients studied</th>
<th>Population studied</th>
<th>Eradication rate (%)</th>
<th>Cost (generic) per day*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bismuth subsalicylate (Pepto-Bismol), 524 mg four times a day, <em>plus</em> amoxicillin, 2 g four times a day, <em>plus</em> metronidazole (Flagyl), 500 mg four times a day, <em>plus</em> lansoprazole (Prevacid), 60 mg once</td>
<td>1</td>
<td>80</td>
<td><em>H. pylori</em>-positive patients with dyspepsia</td>
<td>95</td>
<td>Bismuth subsalicylate: $1 Amoxicillin: $9 (8 to 12) Metronidazole: $18 (2 to 7) Lansoprazole: $20</td>
</tr>
<tr>
<td>Clarithromycin (Biaxin), 500 mg twice daily, <em>plus</em> amoxicillin, 1 g twice daily, <em>plus</em> lansoprazole, 30 mg twice daily</td>
<td>7</td>
<td>80</td>
<td><em>H. pylori</em>-positive patients with dyspepsia</td>
<td>90</td>
<td>Clarithromycin: $10 (9) Amoxicillin: $2 (2 to 3) Lansoprazole: $10</td>
</tr>
<tr>
<td>Amoxicillin, 1 g twice daily, <em>plus</em> metronidazole, 400 mg twice daily, <em>plus</em> clarithromycin, 250 mg twice daily, <em>plus</em> lansoprazole, 30 mg twice daily</td>
<td>5</td>
<td>83</td>
<td><em>H. pylori</em>-positive patients with dyspepsia for three months or endoscopically confirmed ulcers</td>
<td>89</td>
<td>Amoxicillin: $2 (2 to 3) Metronidazole: $9 (1 to 4) for 500-mg strength Clarithromycin: $10 (9) Lansoprazole: $10</td>
</tr>
<tr>
<td>Amoxicillin, 1 g twice daily, <em>plus</em> metronidazole, 400 mg twice daily, <em>plus</em> clarithromycin, 250 mg twice daily, <em>plus</em> ranitidine (Zantac), 300 mg twice daily</td>
<td>5</td>
<td>80</td>
<td><em>H. pylori</em>-positive patients with dyspepsia for three months or endoscopically confirmed ulcers</td>
<td>89</td>
<td>Amoxicillin: $2 (2 to 3) Metronidazole: $9 (1 to 4) for 500-mg strength Clarithromycin: $10 (9) Ranitidine: $10 (6)</td>
</tr>
<tr>
<td>Lansoprazole, 30 mg twice daily for two days (pretreatment), <em>plus</em> amoxicillin, 1 g twice daily, <em>plus</em> metronidazole, 400 mg twice daily, <em>plus</em> clarithromycin, 250 mg twice daily, <em>plus</em> lansoprazole, 30 mg twice daily</td>
<td>5</td>
<td>80</td>
<td><em>H. pylori</em>-positive patients with dyspepsia for three months or endoscopically confirmed ulcers</td>
<td>81</td>
<td>Lansoprazole (pretreatment): $10 Amoxicillin: $2 (2 to 3) Metronidazole: $9 (1 to 4) for 500-mg strength Clarithromycin: $10 (9) Lansoprazole: $10</td>
</tr>
</tbody>
</table>

**NOTE:** Based on two separate studies.

*—Estimated cost to the pharmacist based on average wholesale prices (rounded to the nearest dollar) in Red Book. Montvale, N.J.: Medical Economics Data, 2006. Cost to the patient will be higher, depending on prescription filling fee.

Information from references 38 and 39.
Treatment of *Helicobacter pylori*

**RECURRANCE**

Recurrence of *H. pylori* infection usually is defined by a positive result on urea breath or stool antigen testing six or more months after documented successful eradication therapy. Risk factors for recurrence include nonulcer dyspepsia, persistence of chronic gastritis after eradication therapy, female sex, intellectual disability, younger age, high rates of primary infection, and higher urea breath test values. 45,46 Recurrence rates worldwide vary but are lower in developed countries. 47 Patients with infected spouses do not appear to have a higher risk of reinfection. 48

In the primary care setting, physicians may choose to treat recurrences with an alternative eradication regimen (see Resistance), depending on individual symptoms and risk factors for complications of infection. It is too early to know whether shorter courses of eradication therapy will be associated with a higher resistance rate.

**NONSTEROIDAL ANTI-INFLAMMATORY DRUGS**

Although the use of nonsteroidal anti-inflammatory drugs (NSAIDs) and *H. pylori* infection are independent risk factors for peptic ulcer disease, the use of NSAIDs increases the risk of peptic ulcer disease and ulcer bleeding in patients with *H. pylori* infection. 49 Patients requiring chronic NSAID therapy who have a history of dyspepsia may benefit from testing and eradication of *H. pylori* before initiation of treatment to prevent these complications.

In one study, 92 patients who tested positive for *H. pylori* without preexisting ulcer were randomized to either eradication therapy with bismuth, tetracycline, and metronidazole or placebo for one week. 50 All patients then received naproxen (Naprosyn), 750 mg daily for eight weeks. On repeat endoscopy, 26 percent of placebo-treated patients developed ulcers compared with 7 percent of patients who were pretreated with eradication therapy (NNT = 5). Symptomatic ulcers occurred in 13 percent of patients in the placebo group and in 2 percent of patients in the eradication therapy group (NNT = 9).

In a study of 660 *H. pylori*-positive patients without current or previous ulcer requiring long-term treatment with diclofenac (Voltaren), eradication therapy was as effective as, but no better than, antisecretory therapy and was more effective than placebo in reducing endoscopically proven ulcers (NNT = 17 to 22). 51 Interestingly, there is some evidence that NSAID use may be protective, in a dose-dependent manner, against gastric cancer. 52 Further studies are needed to clarify risk versus benefit for NSAID users at high risk of peptic ulcer disease and gastric cancer.

Members of various family medicine departments develop articles for "Clinical Pharmacology." This is one in a series coordinated by Allen F. Shaughnessy, Pharm. D., and Andrea E. Gordon, M.D., Tufts University Family Medicine Residency, Malden, Mass.

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**TABLE 4**

<table>
<thead>
<tr>
<th>Drug regimen*</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amoxicillin</td>
<td>50 mg per kg per day divided twice daily, to maximum of 1 g twice daily</td>
</tr>
<tr>
<td>Clarithromycin (Biaxin)</td>
<td>15 mg per kg per day divided twice daily, to maximum of 500 mg twice daily</td>
</tr>
<tr>
<td>Omeprazole (Prilosec; or comparable dose of another proton pump inhibitor)</td>
<td>1 mg per kg per day divided twice daily, to maximum of 20 mg twice daily</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>50 mg per kg per day divided twice daily, to maximum of 1 g twice daily</td>
</tr>
<tr>
<td>Metronidazole (Flagyl)</td>
<td>20 mg per kg per day to maximum of 500 mg twice daily</td>
</tr>
<tr>
<td>Omeprazole (or comparable dose of another proton pump inhibitor)</td>
<td>1 mg per kg per day divided twice daily, to maximum of 20 mg twice daily</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>15 mg per kg per day divided twice daily, to maximum of 500 mg twice daily</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>20 mg per kg per day to maximum of 500 mg twice daily</td>
</tr>
<tr>
<td>Omeprazole (or comparable dose of another proton pump inhibitor)</td>
<td>1 mg per kg per day divided twice daily, to maximum of 20 mg twice daily</td>
</tr>
</tbody>
</table>

*—All regimens consist of three drugs given simultaneously and should be prescribed initially for seven to 14 days.

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Author disclosure: Nothing to disclose.

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33. Thomson AB, Barkun AN, Armstrong D, Chiba N, White RJ, Daniels S, et al. The prevalence of clinically significant endoscopic findings in primary care patients with uninvestigated dyspepsia: the Canadian Adult Dyspepsia Empire Treatment–Prompt Endoscopy (CADET-PE) study [Published correction appears in Aliment Pharmacol Ther 2004;20:702].
41. Thomson AB, Barkun AN, Armstrong D, Chiba N, White RJ, Daniels S, et al. The prevalence of clinically significant endoscopic findings in primary care patients with uninvestigated dyspepsia: the Canadian Adult Dyspepsia Empire Treatment–Prompt Endoscopy (CADET-PE) study [Published correction appears in Aliment Pharmacol Ther 2004;20:702].
Treatment of *H. pylori*


