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.)

The discovery of *Helicobacter pylori* as a causative agent of peptic ulcer disease has revolutionized the medical field's understanding of the treatment of this condition.[1] Many patients still attribute symptoms of dyspepsia to an ulcer, and believe that ulcers are caused by diet, stress, and lifestyle factors; however, it is now clear that eradication of *H. pylori* is central to the management of this illness. Primary care physicians are typically faced with patients who present with undifferentiated dyspepsia rather than documented peptic ulcer disease. This article briefly describes the evaluation of the patient with dyspepsia in light of our knowledge of the epidemiology of *H. pylori* infection, and reports new information about special populations and eradication using short-duration treatment regimens.

Definition and Epidemiology

Dyspepsia is classified as ulcer-like, with symptoms of pain centered in the upper abdomen; dysmotility-like, with symptoms of upper abdominal fullness, early satiety, bloating, or nausea; or unspecified, with symptoms not fitting either of these classifications.[2] Even though symptoms of gastroesophageal reflux disease (GERD) and dyspepsia overlap considerably, they usually are viewed as distinct entities.[2] Approximately 30 percent of patients with dyspepsia in North America are infected with *H. pylori*[3,4] compared with a prevalence of 80 to 90 percent in the developing world.[5] The annual incidence of new *H. pylori* infections in industrialized countries is approximately 0.5 per 100 persons of the susceptible population compared with three or more per 100 persons in developing countries.[6,7]

Risk factors for acquiring *H. pylori* infection include residence in a developing country, poor socioeconomic conditions, family overcrowding, and possibly an ethnic or genetic predisposition.[6] In North America, the prevalence of *H. pylori* among Asian Americans, African Americans, and Hispanics is similar to that among persons in developing countries.[8]

Initial Evaluation of the Patient with Dyspepsia

In the primary care office, the underlying pathology in patients with dyspepsia often is unknown. Rather than recommending endoscopy for all patients, most national guidelines suggest a "test-and-treat" strategy.[9-11] With this approach, patients who have symptoms of dyspepsia should be tested for *H. pylori* using a noninvasive method if they are younger than 45 to 55 years (depending on the guideline) and do not have "red flags"

SORT: KEY RECOMMENDATIONS FOR PRACTICE

Clinical recommendation	*Evidence rating*	*References*	*Comment*
A "test-and-treat" strategy is recommended in patients with symptoms of dyspepsia.	A	9-15, 27	Test-and-treat strategy reduces endoscopies and use of antisecretory medications.
Helicobacter pylori eradication therapy is recommended to prevent recurrence and rebleeding in patients with peptic ulcer.	A	24	It is unnecessary to continue antisecretory maintenance therapy in patients after *H. pylori* eradication.
Short-course drug therapy is an option for *H. pylori* eradication in adult patients.	C	38, 39	Eradication rates using short-course therapy are similar to those of traditional treatment with the potential for greater compliance.
The urea breath test is the most reliable noninvasive diagnostic test in children with suspected *H. pylori* infection.	C	20, 21	Urea breath test is more reliable in children older than six years; monoclonal antibody-based stool antigen is an alternative.

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, see page 295 or http://www.aafp.org/afpsort.xml.

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.[12-14] 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.[15]

Patients can be tested for the presence of *H. pylori* via invasive or noninvasive methods *(Table 1*[16-22]*)*. 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.[11] In addition, the urea breath test and stool antigen test can be used to confirm eradication, whereas serology remains positive for months after eradication.[18]

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.[23]

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.[23] 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.[24] 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.[24] A 2005 evidence-based guideline from the University of Michigan provides a useful algorithm and

TABLE 1
Diagnostic Tests for *Helicobacter pylori*

Test	*Sensitivity (%)*	*Specificity (%)*	*Usefulness*
Invasive			
Endoscopy with biopsy			Diagnostic strategy of choice in children with persistent or severe upper abdominal symptoms
Histology	>95	100	Sensitivity reduced by PPIs, antibiotics, and bismuth-containing compounds
Urease activity	93 to 97	>95	Sensitivity reduced by PPIs, antibiotics, bismuth-containing compounds, and active bleeding
Culture	70 to 80	100	Technically demanding
Noninvasive			
Serology for immunoglobulin G	85	79	Sensitivity and specificity vary widely; positive result may persist for months after eradication Reliability in children not adequately validated; not recommended
Urea breath test	95 to 100	91 to 98	Requires separate appointments; sensitivity reduced by PPIs, antibiotics, and bismuth-containing compounds; reliable test for cure 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
H. pylori stool antigen	91 to 98	94 to 99	Test for cure seven days after therapy is accurate; sensitivity reduced by PPIs, antibiotics, and bismuth-containing compounds Easy to perform independent of age; possible alternative to urea breath test; monoclonal antibody-based test most reliable

PPI = proton pump inhibitor.

Information from references 16 through 22.

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.

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*.[37] Studies evaluating one-, five-, and seven-day regimens to eradicate *H. pylori* are summarized in *Table 3*.[38,39] 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]).[23] 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 (Biaxin).[28] Bismuth subsalicylate (Pepto-Bismol) may cause a temporary grayish-black discoloration of the stool.[40]

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[6,20,21] *(Table 1*[16-22]*)*. 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.[6] Another indication is documentation of *H. pylori* in patients with previous ulcer disease or iron deficiency anemia.[21] 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.[41] 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*.[6]

TABLE 2
Selected Long-Duration Regimens for *Helicobacter pylori* Eradication

Treatment regimen	*Duration*	*Eradication rate (%)*	*Cost (generic) per day**
Omeprazole (Prilosec), 20 mg twice daily, *plus* amoxicillin, 1 g twice daily, *plus* clarithromycin (Biaxin), 500 mg twice daily	14 days	80 to 86	Omeprazole: $9 (8) Amoxicillin: $2 (2 to 3) Clarithromycin: $10 (9)
Lansoprazole (Prevacid), 30 mg twice daily, *plus* amoxicillin, 1 g twice daily, *plus* clarithromycin, 500 mg twice daily	10 to 14 days	86	Lansoprazole: $10 Amoxicillin: $2 (2 to 3) Clarithromycin: $10 (9)
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 H_2 blocker	14 days (H_2 blocker alone for an additional 14 days taken once or twice daily)	80	Bismuth subsalicylate: $1 Metronidazole: $10 (2) Tetracycline: $2 (1)

**—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.*

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

Treatment regimen	*Duration (days)*	*Number of patients studied*	*Population studied*	*Eradication rate (%)*	*Cost (generic) per day**
Bismuth subsalicylate (Pepto-Bismol), 524 mg four times a day, *plus* amoxicillin, 2 g four times a day, *plus* metronidazole (Flagyl), 500 mg four times a day, *plus* lansoprazole (Prevacid), 60 mg once[38]	1	80	*H. pylori*–positive patients with dyspepsia	95	Bismuth subsalicylate: $1 Amoxicillin: $9 (8 to 12) Metronidazole: $18 (2 to 7) Lansoprazole: $20
Clarithromycin (Biaxin), 500 mg twice daily, *plus* amoxicillin, 1 g twice daily, *plus* lansoprazole, 30 mg twice daily[38]	7	80	*H. pylori*–positive patients with dyspepsia	90	Clarithromycin: $10 (9) Amoxicillin: $2 (2 to 3) Lansoprazole: $10
Amoxicillin, 1 g twice daily, *plus* metronidazole, 400 mg twice daily, *plus* clarithromycin, 250 mg twice daily, *plus* lansoprazole, 30 mg twice daily[39]	5	83	*H. pylori*–positive patients with dyspepsia for three months or endoscopically confirmed ulcers	89	Amoxicillin: $2 (2 to 3) Metronidazole: $9 (1 to 4) for 500-mg strength Clarithromycin: $10 (9) Lansoprazole: $10
Amoxicillin, 1 g twice daily, *plus* metronidazole, 400 mg twice daily, *plus* clarithromycin, 250 mg twice daily, *plus* ranitidine (Zantac), 300 mg twice daily[39]	5	80	*H. pylori*–positive patients with dyspepsia for three months or endoscopically confirmed ulcers	89	Amoxicillin: $2 (2 to 3) Metronidazole: $9 (1 to 4) for 500-mg strength Clarithromycin: $10 (9) Ranitidine: $10 (6)
Lansoprazole, 30 mg twice daily for two days (pretreatment), *plus* amoxicillin, 1 g twice daily, *plus* metronidazole, 400 mg twice daily, *plus* clarithromycin, 250 mg twice daily, *plus* lansoprazole, 30 mg twice daily[39]	5	80	*H. pylori*–positive patients with dyspepsia for three months or endoscopically confirmed ulcers	81	Lansoprazole (pretreatment): $10 Amoxicillin: $2 (2 to 3) Metronidazole: $9 (1 to 4) for 500-mg strength Clarithromycin: $10 (9) Lansoprazole: $10

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.

RESISTANCE

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]

RECURRENCE

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.

TABLE 4
Three Drug Regimens for Eradication of *Helicobacter pylori* in Children

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

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

Adapted with permission from Gold BD, Colletti RB, Abbott M, Czinn SJ, Elitsur Y, Hassall E, et al. North American Society for Pediatric Gastroenterology and Nutrition. Helicobacter pylori *infection in children: recommendations for diagnosis and treatment. J Pediatr Gastroenterol Nutr 2000;31:496.*

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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