Management of *Helicobacter pylori* Infection

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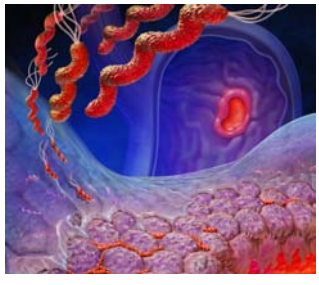
Helicobacter pylori **is the cause of most peptic ulcer disease and a primary risk factor for gastric cancer. Eradication of the organism results in ulcer healing and reduces the risk of ulcer recurrence and complications. Testing and treatment have no clear value in patients with documented nonulcer dyspepsia; however, a test-and-treat strategy is recommended but for patients with undifferentiated dyspepsia who have not undergone endoscopy. In the office setting, initial serology testing is practical and affordable, with endoscopy reserved for use in patients with alarm symptoms for ulcer complications or cancer, or those who do not respond to treatment. Treatment involves 10- to 14-day multidrug regimens including antibiotics and acid suppressants, combined with education about avoidance of other ulcer-causing factors and the need for close follow-up. Follow-up testing (i.e., urea breath or stool antigen test) is recommended for patients who do not respond to therapy or those with a history of ulcer complications or cancer. (Am Fam Physician 2002;65:1327-36,1339. Copyright© 2002 American Academy of Family Physicians.)**

A patient information handout on H. pylori *infection, written by the authors of this article, is provided on page 1339.*

See page 1246 for definitions of strength-of-evidence levels contained in this article.



Members of various family practice departments develop articles for "Practical Therapeutics." This article is one in a series developed by the Department of Family and Community Medicine at the Medical College of Wisconsin, Milwaukee. Guest editors of the series are Linda N. Meurer, M.D., M.P.H., and Douglas J. Bower, M.D.

The spiral-shaped, gram-negative bacterium *Heliocobacater pylori* is found in colonized gastric mucosa or adherent to the epithelial lining of the stomach. Acute infection, acquired most likely by ingestion of the organism, is most commonly asymptomatic but may be associated with epigastric burning, abdominal distention or bloating, belching, nausea, flatulence, and halitosis.[1] Virtually all patients infected with *H. pylori* who have had endoscopic biopsies are found to have histologic gastritis.[2] *H. pylori* infection can lead to ulceration of the gastric mucosa and duodenum and has been found to be strongly associated with the development of epithelial and lymphoid malignancies of the stomach. It has been classified by the International Agency for Research on Cancer[3] as a group I carcinogen and a definite cause of gastric cancer in humans.

H. pylori gastritis produces no symptoms in 90 percent of infected persons. The prevalence of *H. pylori* infection varies geographically and has been demonstrated to be as high as 52 percent in the United States.[4] Factors associated with higher infection rates are increasing age, African-American or Hispanic race, lower levels of education, and birth in a developing country.

The pathogenic role of *H. pylori* in peptic ulcer disease, both duodenal and gastric, is well recognized—up to 95 percent of patients with duodenal ulcers and 80 percent of patients with gastric ulcers are infected.[5] Eradication of the organism leads to ulcer healing and a markedly lower incidence of recurrence. The role of *H. pylori* in nonulcer dyspepsia has not been proved and, in most patients, eradication is not associated with improvement of symptoms.[6] Most patients, however, present to the family physician with undifferentiated dyspepsia, not knowing whether an ulcer exists.

Treatment of patients with H. pylori *infection typically requires a multidrug regimen given for 10 to 14 days.*

When to Test and Treat

The decision to test for the presence of *H. pylori* is closely tied to the intention to treat, as there is no benefit in identifying the presence of the organism without having a plan to eradicate it.[7] In the

TABLE 1
Alarm Signs for Risk of Gastric Cancer or Complicated Ulcer Disease

Older than 45 years	Jaundice
Rectal bleeding or melena	Family history of gastric cancer
Weight loss of >10 percent of body weight	Previous history of peptic ulcer
Anemia	Anorexia/early satiety
Dysphagia	
Abdominal mass	

Information from American Gastroenterological Association medical position statement: evaluation of dyspepsia. Gastroenterology 1998;114:579-81.

absence of alarm symptoms for cancer or complicated ulcer disease *(Table 1)*,[8] the approach to testing in patients with dyspepsia *(Table 2)*[7,9-16] can be divided into four clinical scenarios: (1) known peptic ulcer disease, currently or previously documented; (2) known nonulcer dyspepsia; (3) undifferentiated dyspepsia, and (4) gastroesophageal reflux disease (GERD).

PEPTIC ULCER DISEASE

The best evidence for the effectiveness of *H. pylori* eradication exists for the treatment of *H. pylori*-associated ulcers. In this case, treatment of *H. pylori* infection in patients with ulcers almost always cures the disease and reduces the risk for serious complications (e.g., perforation or bleeding).[9,10] [Evidence level A, meta-analyses/RCTs]. Compared with acid suppression therapy alone, eradication of *H. pylori* results in a dramatic reduction in recurrence of duodenal ulcers and gastric ulcers that are not related to the use of nonsteroidal anti-inflammatory drugs (NSAIDs)—12 percent versus 95 percent at one year.[11] A previously documented peptic ulcer in a patient who has never been treated for *H. pylori* infection is an indication for testing and treatment.[7]

NONULCER DYSPEPSIA

To date, there is no convincing evidence that empiric eradication of *H. pylori* in patients with nonulcer dyspepsia improves symptoms. One recent meta-analysis[12] showed no improvement of symptoms with *H. pylori* eradication, and another[13] revealed a statistically significant benefit, but the effect was small, with one patient cured for every 19 treated (NNT = 19).

UNDIFFERENTIATED DYSPEPSIA

In primary care, the typical patient who presents with dyspepsia will not have had endoscopy performed and, therefore, the presence of an underlying lesion will be unknown. Symptom complexes have not been shown to predict endoscopic findings, and the high prevalence of dyspeptic symptoms makes definitive testing of all patients impractical.

Several consensus panels have advocated a test-and-treat strategy in which patients with dyspepsia are tested for the presence of *H. pylori* with serology and treated with eradication therapy if the results are positive.[14,15] This strategy reserves endoscopy for use in patients with alarm signs or those with persistent symptoms despite appropriate empiric therapy, and is supported by cost-benefit analysis. One such approach is shown in *Figure 1*. This approach is supported by cost-benefit analysis.[16]

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TABLE 2
Evaluation for *Helicobacter pylori*–Related Disease

Clinical scenario	*Recommended test*	*Levels of evidence† and comments*
Dyspepsia* in patient with alarm symptoms for cancer or complicated ulcer (e.g., bleeding, perforation)	Promptly refer to a gastroenterologist for endoscopy.	A
Known PUD, uncomplicated	Serology antibody test; treat if result is positive.	A—Best evidence for eradication in presence of documented gastric or duodenal ulcer
Dyspepsia in patient with previous history of PUD not previously treated with eradication therapy	Serology antibody test; treat if result is positive.	A
Dyspepsia in patient with PUD previously treated for *H. pylori*	Stool antigen or urea breath test; if positive, treat with regimen different from the one previously used; retest to confirm eradication. Consider endoscopy.	B—Urea breath test should be delayed for four weeks following treatment, as acid suppression can lead to false-positive results.
Undifferentiated dyspepsia (without endoscopy)	Serology antibody test; treat if result is positive.	B—Supported by cost-benefit analyses and recent small RCTs
Documented nonulcer dyspepsia (after endoscopy)	Unnecessary	B—RCTs and meta-analyses on this topic are mixed but indicate that few patients benefit from treatment.
GERD	Unnecessary	B—GERD is not associated with *H. pylori* infection.
Asymptomatic with history of documented PUD not previously treated with eradication therapy	Serology antibody test; treat if result is positive.	C
Asymptomatic	Screening unnecessary	C

PUD = peptic ulcer disease; GERD = gastroesophageal reflux disease; RCT = randomized controlled clinical trial.

**—Defined as pain or discomfort centered in the upper abdomen and persisting or recurring for more than four weeks.*
†—Levels of evidence: A = strong evidence, based on good-quality RCTs or meta-analysis of RCTs; B = moderate evidence, based on high-quality cohort studies, case control studies or systematic reviews of observational studies or lower-quality RCT; C = based on consensus or expert opinion.

Information from references 7 through 15.

GASTROESOPHAGEAL REFLUX DISEASE

H. pylori infection does not increase the risk of GERD and is actually associated with a lower severity of symptoms and a lower incidence of Barrett's esophagus. In fact, GERD-like symptoms (e.g., a rising sensation of burning and regurgitation) are associated with a decreased likelihood of *H. pylori* infection.[17] Eradication therapy does not eliminate GERD symptoms.

Helicobacter pylori Tests

Once testing and eradication are chosen, several diagnostic tests are available *(Table 3)*.[18,19] Unless endoscopy is planned, a practical approach is to use serology to identify initial infection and the stool antigen test or urea breath test to determine cure, if indicated.

ENDOSCOPY AND BIOPSY

Alarm symptoms for cancer or ulcer complication warrant prompt endoscopic evalua-

FIGURE 1. Suggested approach to managing undifferentiated dyspepsia. (NSAID = nonsteroidal anti-inflammatory drug; H_2 = histamine H_2 receptor; PPI = protein pump inhibitor; *H. pylori* = *Helicobacter pylori*; GI = gastrointestinal; GERD = gastroesophageal reflux disease)

TABLE 3
Testing Options for Detecting *Helicobacter pylori*

Test	*What does it measure?*	*Sensitivity (%)*	*Specificity (%)*	*Test of cure?*	*Comments*
Invasive (requiring endoscopic biopsy)					
Steiner's stain of gastric biopsy specimen	Histologic identification of organisms	82 to 95	99 to 100	Yes	Considered the "gold standard"
Rapid urease test (CLO test, Delta Wenst, Bently, Western Australia)	Urease activity of biopsy specimen	85 to 90	98 to 100	Yes	Sensitivity reduced by acid suppression and active bleeding
Culture	Presence of organisms; antimicrobial sensitivities	70 to 80	100	Yes	Especially useful in research and to guide management in treatment failures; requires experienced laboratory
Noninvasive					
Serology: laboratory-based ELISA	IgG	90 to 93	95 to 96	No	Accurate; convenient for initial infection; titers diminish slowly after eradication and may remain positive after one year
Whole blood: office-based ELISA	IgG	50 to 85	75 to 100	No	Less accurate but fast, convenient, inexpensive
Stool: HpSA	*H. pylori* antigens	95 to 98	92 to 95	Yes	Relatively convenient and available
Urea breath test	Urease activity	95 to 100	95	Yes	Sensitivity reduced by acid suppression
String test (swallowed and recovered polymeric string)	Culture or polymerase chain reaction on gastric mucus	75 to 80	75 to 100	No	Minimally invasive method to obtain viable organisms, but retrieval rate less than with endoscopy
Urine ELISA	IgG	70 to 96	77 to 85	No	Greater patient acceptance and convenience than stool test; not yet readily available
Saliva ELISA	IgG	82 to 91	71 to 85	No	Greater patient acceptance and convenience than stool test; not yet readily available

CLO = Campylobacter-like organism; ELISA = enzyme-linked immunosorbent assay; HpSA = H. pylori *stool antigen.*

Information from Snyder JD, Veldhuyzen Van Zanten S. Novel diagnostic tests to detect Helicobacter pylori *infection: a pediatric perspective. Can J Gastroenterol 1999;13:585-9, and Veldhuyzen Van Zanten S, Tytgat KM, deGara CJ, Goldie J, Rashid FA, Bowen BM, et al. A prospective comparison of symptoms and five diagnostic tests in patients with* Helicobacter pylori *positive and negative dyspepsia. Eur J Gastroenterol Hepatol 1991;3:463-8.*

tion. A Steiner's stain for microscopic examination of gastric antral biopsy specimens is considered the gold standard for detecting the presence of *H. pylori*. A rapid urease test is highly specific and simple, and can also be performed on biopsy samples; however, it may have false-negative results, particularly if the patient has recently taken a proton pump inhibitor (PPI).[20] Cultures of biopsy specimens obtained during endoscopy can be tested for antimicrobial resistance in cases of treatment failure. If necessary, a specimen for culture can also be obtained using a string test, a less invasive but also less reliable technique

Serology is a useful technique to identify initial H. pylori *infection in patients who have not undergone endoscopy.*

in which a highly absorbent polymer string is partially swallowed and then removed manually to recover gastric material.[21]

SEROLOGY/ELISA

When endoscopy is not performed, the most commonly used diagnostic approach is the laboratory-based serologic antibody test. This enzyme-linked immunosorbent assay (ELISA) detects IgG antibodies to *H. pylori*, indicating current or past infection. Because *H. pylori* infection is not known to spontaneously resolve, a positive serologic test suggests active infection in patients who have not undergone eradication therapy. The serologic test results may or may not revert to negative once the organism is eradicated; therefore, the test is not used to identify persistent infection, although a negative test result does reliably identify cure.[22]

Although they are convenient and inexpensive, rapid, office-based, whole-blood tests are less accurate than laboratory-based serologic tests.[20]

UREA BREATH TEST

The urea breath test is a reliable test for cure and can detect the presence or absence of active *H. pylori* infection with greater accuracy than the serologic test. It is usually administered in the hospital outpatient setting because it requires time and special equipment. Breath tests involve patient consumption of carbon 13- or carbon 14-labeled urea. The bacterium metabolizes urea rapidly, and the labeled carbon is absorbed into the patient's circulation. In 15 to 20 minutes, the labeled carbon dioxide in an exhaled breath sample can be measured. As with other tests of urease activity, false-negative results can result from acid suppression with PPIs[23]; therefore, acid suppression therapy should be withheld for two weeks before the test is administered and for at least four weeks following completion of eradication therapy if the test is to be used to check for cure.

NEWER TESTS

Several new, noninvasive tests of stool, saliva, and urine samples are being investigated. The most promising of these is an enzyme-linked immunoassay detecting *H. pylori* antigen in stool specimens. Highly sensitive and specific, the stool antigen test reverts to negative from five days to a few months after eradication of the organism, with 90 percent specificity.[24,25] This test, which is currently available, is useful in confirming eradication, and, because it is office-based, is less costly and more convenient than the urea breath test. False-positive results may occur even four weeks following eradication therapy.

Principles of Treatment

Antimicrobial resistance and incomplete treatment are major reasons for treatment failure.[26,27] The treatment of *H. pylori* infection can be likened to the treatment of tuberculosis because multidrug regimens and an adequate length of treatment are needed to eradicate the organism. Because of the lengthy period of therapy, convenience and tolerability become important considerations in choosing a treatment plan.[28] While success with shorter durations of treatment has been reported, continued therapy for 14 days is the most reliable and effective regimen and is recommended in the United States.[7]

PHARMACOLOGIC THERAPY

Table 4 provides a practical list of selected effective drug combinations used for treating patients with *H. pylori* infection. Only triple and quadruple therapies with reported eradication rates approaching 90 percent or more are included. Single and dual drug therapies have unacceptably low cure rates and are not

TABLE 4
Four Treatment Regimens for *Helicobacter pylori* Infection

Treatment (10 to 14 days of therapy recommended)	*Cost*	*Convenience factor*	*Tolerability*
Triple therapy			
1. Omeprazole (Prilosec), 20 mg two times daily	$260 (LAC†)	Twice-daily dosing	Fewer significant side effects, but more abnormal taste versus other regimens
or			
Lansoprazole (Prevacid), 30 mg two times daily	195 (LAC†‡)		
plus			
Metronidazole (Flagyl), 500 mg two times daily	200 (OAC)		
or			
Amoxicillin, 1 g two times daily	194 (LMC)		
plus			
Clarithromycin (Biaxin), 500 mg two times daily	199 (OMC)		
2. Ranitidine bismuth citrate (Tritec), 400 mg twice daily	118 (RCT)	Twice-daily dosing	Increased diarrhea versus other regimens
plus			
Clarithromycin, 500 mg twice daily			
or			
Metronidazole, 500 mg twice daily	136 (RCA)		
plus			
Tetracycline, 500 mg twice daily	73 (RMT)		
or			
Amoxicillin, 1 g twice daily	92 (RMA)		
Quadruple therapy			
3. Bismuth subsalicylate (Pepto Bismol), 525 mg four times daily/2 tablets four times daily	142 (BMT§ plus H_2R†)	18 pills daily	More side effects; increased nausea versus other regimens
plus			
Metronidazole, 250 mg four times daily	87 (BMT [separately] plus H_2R†)		
plus			
Tetracycline, 500 mg four times daily			
plus			
H_2RA for 28 days			
4. Bismuth subsalicylate, 525 mg four times daily/2 tablets four times daily	206 (BMT plus PPI)	18 pills daily	Increased nausea
plus			
Metronidazole, 250 mg four times daily			
plus			
Tetracycline, 500 mg four times daily	153 (BMT separately] plus PPI)		
plus			
PPI for 14 days			

LAC = lansoprazole, amoxicillin, clarithromycin; OAC = omeprazole, amoxicillin, clarithromycin; LMC = lansoprazole, metronidazole, clarithromycin; RCT = ranitidine bismuth citrate, clarithromycin, tetracycline; RCA = ranitidine bismuth citrate, clarithromycin, amoxicillin; RMT = ranitidine bismuth citrate, metronidazole, tetracycline; RMA = ranitidine bismuth citrate, metronidazole, amoxicillin; BMT = bismuth subsalicylate, metronidazole, tetracycline; H_2RA = histamine H_2-receptor antagonist; PPI = proton pump inhibitor.

NOTE: *Several dual therapy regimens that have been approved by the U.S. Food and Drug Administration should not be used because of their lower eradication rates and potential for antimicrobial resistance.*

**—Costs are average wholesale prices for 14 days of therapy from Red Book. Montvale, N.J.: Medical Economics Data, 2001, rounded to the nearest dollar. Cost to patient will be higher depending on filling fees.*
†—*Regimens approved by the FDA as of July 1998.*
‡—*Lansoprazole, amoxicillin and clarithromycin are available in a daily administration combination pack (Prevpac).*
§—*Bismuth subsalicylate, metronidazole and tetracycline are available in a combination pack (Helidac).*

Virtually all patients infected with H. pylori *who have undergone endoscopy are found to have histologic gastritis.*

recommended. Because microbial resistances are rapidly developing, regional surveillance may become important in determining the best treatment courses in the future.

Antibiotics. Amoxicillin, a semi-synthetic penicillin, is an effective antibiotic for *H. pylori* infection. The frequency of amoxicillin-resistant *H. pylori* organisms is low. The drug rapidly accumulates in antral mucosa via systemic circulation. Its antimicrobial activity against *H. pylori* depends on the pH level; the minimal inhibitory concentration (MIC) decreases as the pH increases.[29] Clarithromycin is also quite effective, although more resistant organisms are emerging.[30] Co-administration with a PPI significantly increases the concentration of clarithromycin in the antral mucosa and the mucus layer. Erythromycin and azithromycin are much less effective macrolides in vivo and should not be used in *H. pylori* treatment.[31] Metronidazole is active against *H. pylori*, and its bioavailability is not influenced by acid suppression; however, resistance to metronidazole is high.[31] Furazolidone has been described as an alternative to metronidazole in resistant cases but, as a monoamine oxidase inhibitor, it may be associated with food and drug interactions.[31]

Acid Reducers. The *H. pylori* organism prefers an acidic environment. Increasing the gastric pH with the use of a histamine H_2-receptor antagonist (H_2RA) or a PPI has been shown to improve the effectiveness of antibiotic therapy.[32] In the presence of ulcer disease, PPIs have largely replaced H_2RAs because of their ability to provide more rapid pain relief and better control of pH. In addition, PPIs have demonstrated antimicrobial activity against *H. pylori*.[33] It appears that all the PPIs are comparable; however, larger head-to-head comparisons are not available.

Bismuth Compounds. Bismuth salts have no substantial acid-neutralizing capacity but inhibit pepsin, increase secretion of mucus, and form a barrier to the diffusion of acid in the ulcer crater. They also cause detachment of *H. pylori* from the gastric epithelium and disrupt bacterial cell walls, resulting in lysis of the bacterium. Side effects include darkening of the oral cavity and stool. Ranitidine bismuth citrate is a combination salt with intrinsic antisecretory and antimicrobial activity that is effective in combination with antibiotics in the eradication of *H. pylori*. It is not effective as monotherapy.[34]

Because patient adherence to therapy is critical, simpler regimens with twice-daily dosing may be more successful in eradicating the *H. pylori* organism. Based on efficacy, PPI triple therapy or bismuth quadruple therapy for 14 days are recommended in the United States as first-line treatments for patients with *H. pylori* infection. PPI quadruple therapy or a regimen including furazolidone may serve as second-line treatment for eradication of initial failures and in cases of metronidazole resistance.[31,35]

Patient Education

In addition to *H. pylori* eradication therapy, patients should be counseled to avoid other factors that increase their risk of dyspepsia and peptic ulcer disease. The use of NSAIDs and tobacco increase the risk of peptic ulcer disease, particularly of the stomach.[36] While it is hypothesized that both *H. pylori* and NSAIDs disrupt the integrity of the stomach lining, results of studies have not demonstrated an interaction between *H. pylori* and NSAID use in the development of ulcerations. NSAIDs are known to delay ulcer healing, however, and NSAID therapy should be stopped regardless of the underlying cause of the ulcer.[37] Smoking appears to have a synergistic relationship with *H. pylori* and should also be stopped.

Patient education about the need for effective eradication therapy and the necessity of

completing the initial drug regimen is critical. A follow-up plan must be emphasized because further diagnostic testing may be needed to ensure eradication of the *H. pylori* organism, particularly if symptoms persist.

Post-treatment Follow-Up

Patients with a history of ulcer complications, gastric mucosa-associated lymphoid tissue (MALT), or early gastric cancer should undergo a routine post-treatment urea breath test or endoscopy to ensure successful eradication. These patients will usually be followed in collaboration with a gastroenterologist. Routine, noninvasive follow-up testing also can be considered in patients who have persistent symptoms following eradication therapy. In these patients, the stool antigen test, performed four weeks following therapy, is a convenient alternative. Because of the risk of ulcer recurrence and the potential for malignant transformation caused by *H. pylori* infection, follow-up is important—whether through testing or watchful waiting under the presumption that a long symptom-free period indicates cure.

Serology is not practical as a test for cure because it can take more than one year to revert to negative; however, a negative result is predictive of successful eradication. To date, good evidence does not exist to support routine laboratory testing for cure in patients whose symptoms respond to eradication therapy for uncomplicated ulcer disease or undifferentiated dyspepsia.

TREATMENT FAILURE

Patients with persistent *H. pylori* infection despite initial therapy should be retreated using an alternate combination regimen. Data from one study[38] in which patients were treated with quadruple therapy that included lansoprazole (30 mg twice daily), tetracycline (500 mg four times daily), metronidazole (500 mg three times daily) and bismuth subcitrate (120 mg four times daily) for one week resulted in eradication in 20 of 21 patients who had not responded to triple therapy. When treatment fails a second time, patients should be referred to a gastroenterologist.

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REFERENCES

1. Schubert TT, Schubert AB, Ma CK. Symptoms, gastritis, and *Helicobacter pylori* in patients referred for endoscopy. Gastrointest Endosc 1992;38:357-60.
2. Dooley CP, Cohen H, Fitzgibbons PL, Bauer M, Appleman MD, Perez-Perez GI, et al. Prevalence of *Helicobacter pylori* infection and histologic gastritis in asymptomatic persons. N Engl J Med 1989;321:1562-6.
3. Infection with *Helicobacter pylori*. IARC Monogr Eval Carcinog Risks Hum 1994;61:177-240.
4. 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;100:1495-501.
5. Breuer T, Goodman KJ, Malaty HM, Sudhop T, Graham DY. How do clinicians practicing in the U.S. manage *Helicobacter pylori*-related gastrointestinal diseases? A comparison of primary care and specialist physicians. Am J Gastroenterol 1998;93:553-61.
6. Blum AL, Talley NJ, O'Morain C, van Zanten SV, Labenz J, Stolte M, et al. Lack of effect of treating *Helicobacter pylori* infection in patients with nonulcer dyspepsia. N Engl J Med 1998;339:1875-81.
7. Howden CW, Hunt RH. Guidelines for the management of *Helicobacter pylori* infection. Ad Hoc Committee on Practice Parameters of the American College of Gastroenterology. Am J Gastroenterol 1998;93:2330-8.
8. American Gastroenterological Association medical position statement: evaluation of dyspepsia. Gastroenterology 1998;114:579-81.
9. Forbes GM, Glaser ME, Cullen DJ, Warren JR, Christiansen KJ, Marshall BJ, et al. Duodenal ulcer treated with *Helicobacter pylori* eradication: seven-year follow-up. Lancet 1994;343:258-60.
10. Laine L, Hopkins RJ, Girardi LS. Has the impact of *Helicobacter pylori* therapy on ulcer recurrence in the Unites States been overstated? A meta-analysis of rigorously designed trials. Am J Gastroenterol 1998;93:1409-15.
11. Graham DY, Lew GM, Klein PD, Evans DG, Evans DJ Jr., Saeed ZA, et al. Effect of treatment of *Helicobacter pylori* infection on the long-term recurrence of gastric or duodenal ulcer. Ann Intern Med 1992;116:705-8.
12. Laine L, Schoenfeld P, Fennerty MB. Therapy for *Helicobacter pylori* in patients with nonulcer dyspepsia. A meta-analysis of randomized, controlled trials. Ann Intern Med 2001;134:361-9.
13. Moayyedi P, Soo S, Deeks J, Delaney B, Harris A,

Innes M, et al. Eradication of *Helicobacter pylori* for non-ulcer dyspepsia. Cochrane Database Syst Rev 2001;1:CD002096.

14. *Helicobacter pylori* in peptic ulcer disease. NIH Consensus Development Panel on *Helicobacter pylori* in Peptic Ulcer Disease. JAMA 1994;272:65-9.
15. Sherman P, Hassall E, Hunt RH, Fallone CA, Veldhuyzen Van Zanten S, Thomson AB. Canadian Helicobacter Study Group Consensus Conference on the Approach to *Helicobacter pylori* Infection in Children and Adolescents. Can J Gastroenterol 1999;13:553-9.
16. Ebell MH, Warbasse L, Brenner C. Evaluation of the dyspeptic patient: a cost-utility study. J Fam Pract 1997;44:545-55.
17. Wu JC, Sung JJ, Ng EK, Go MY, Chan WB, Chan FK, et al. Prevalence and distribution of *Helicobacter pylori* in gastroesophageal reflux disease: a study from the East. Am J Gastroenterol 1999;94:1790-4.
18. Snyder JD, Veldhuyzen Van Zanten S. Novel diagnostic tests to detect *Helicobacter pylori* infection: a pediatric perspective. Can J Gastroenterol 1999; 13:585-9.
19. Veldhuyzen Van Zanten S, Tytgat KM, deGara CJ, Goldie J, Rashid FA, Bowen BM, et al. A prospective comparison of symptoms and five diagnostic tests in patients with *Helicobacter pylori* positive and negative dyspepsia. Eur J Gastroenterol Hepatol 1991;3:463-8.
20. Megraud F. How should *Helicobacter pylori* infection be diagnosed? Gastroenterology 1997;113 (6 suppl):S93-8.
21. Perez-Trallero E, Montes M, Alcorta M, Zubillaga P, Telleria E. Non-endoscopic method to obtain *Helicobacter pylori* for culture. Lancet 1995;345:622-3.
22. Feldman M, Cryer B, Lee E, Peterson WL. Role of seroconversion in confirming cure of *Helicobacter pylori* infection. JAMA 1998;280:363-5.
23. Connor SJ, Ngu MC, Katelaris PH. The impact of short-term ranitidine use on the precision of the 13C-urea breath test in subjects infected with *Helicobacter pylori*. Eur J Gastroenterol Hepatol 1999; 11:1135-8.
24. Trevisani L, Sartori S, Ruina M, Caselli M, Rossi MR, Costa F, et al. *Helicobacter pylori* stool antigen test: clinical evaluation and cost analysis of a new enzyme immunoassay. Dig Dis Sci 1999;44:2303-6.
25. Determination of eradication of *Helicobacter pylori* (Hp) by the HP stool antigen test (HPSAT) [Abstract]. European *Helicobacter pylori* Study Group. XIth International Workshop on Gastroduodenal Pathology and *Helicobacter pylori*. Budapest, Hungary, 2-5 September 1998. Gut 1998; 43(suppl 2):A50.
26. Megraud F. Resistance of *Helicobacter pylori* to antibiotics: the main limitation of current proton-pump inhibitor triple therapy. Eur J Gastroenterol Hepatol 1999;11(suppl 2):S35-7.
27. Graham DY, Lew GM, Malaty HM, Evans DG, Evans DJ Jr., Klein PD, et al. Factors influencing the eradication of *Helicobacter pylori* with triple therapy. Gastroenterology 1992;102:493-6.
28. Hopkins RJ. Current FDA-approved treatments for *Helicobacter pylori* and the FDA approval process. Gastroenterology 1997;113(6 suppl):S126-30.
29. Adamek RJ, Wegener M, Labenz J, Freitag M, Opferkuch W, Ruhl GH. Medium-term results of oral and intravenous omeprazole/amoxicillin *Helicobacter pylori* eradication therapy. Am J Gastroenterol 1994;89:39-42.
30. Pilotto A, Leandro G, Franceschi M, Rassu M, Bozzola L, Furlan F, et al. The effect of antibiotic resistance on the outcome of three 1-week triple therapies against *Helicobacter pylori*. Aliment Pharmacol Ther 1999;13:667-73.
31. Graham DY. Highlights from the 100th annual meeting of the American Gastroenterological Association and Digestive Disease Week. Orlando, FL, May 16-19, 1999; Helicobacter Today [Monograph]: Vol. 6, Series A.
32. de Boer W, Driessen W, Jansz A, Tytgat G. Effect of acid suppression on efficacy of treatment for *Helicobacter pylori* infection. Lancet 1995;345:817-20.
33. Miehlke S. Antimicrobial therapy of peptic ulcer. Int J Antimicrob Agents 1997;8:171-8.
34. Peterson WL, Ciociola AA, Sykes DL, McSorley DJ, Webb DD. Ranitidine bismuth citrate plus clarithromycin is effective for healing duodenal ulcers, eradicating *H. pylori* and reducing ulcer recurrence. Aliment Pharmacol Ther 1996;10:251-61.
35. van der Hulst RW, Keller JJ, Rauws EA, Tytgat GN. Treatment of *Helicobacter pylori* infection: a review of the world literature. Helicobacter 1996;1:6-19.
36. Kurata JH, Nogawa AN. Meta-analysis of risk factors for peptic ulcer. Nonsteroidal antiinflammatory drugs, *Helicobacter pylori*, and smoking. J Clin Gastroenterol 1997;24:2-17.
37. Graham DY. Nonsteroidal anti-inflammatory drugs, *Helicobacter pylori*, and ulcers: where we stand. Am J Gastroenterol 1996;91:2080-6.
38. Gomollon F, Ducons JA, Ferrero M, Garcia Cabezudo J, Guirao R, Simon MA, et al. Quadruple therapy is effective for eradicating *Helicobacter pylori* after failure of triple proton-pump inhibitor-based therapy: a detailed, prospective analysis of 21 consecutive cases. Helicobacter 1999;4:222-5.