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Eradication of *Helicobacter pylori*: Which Patients, Which Drugs?

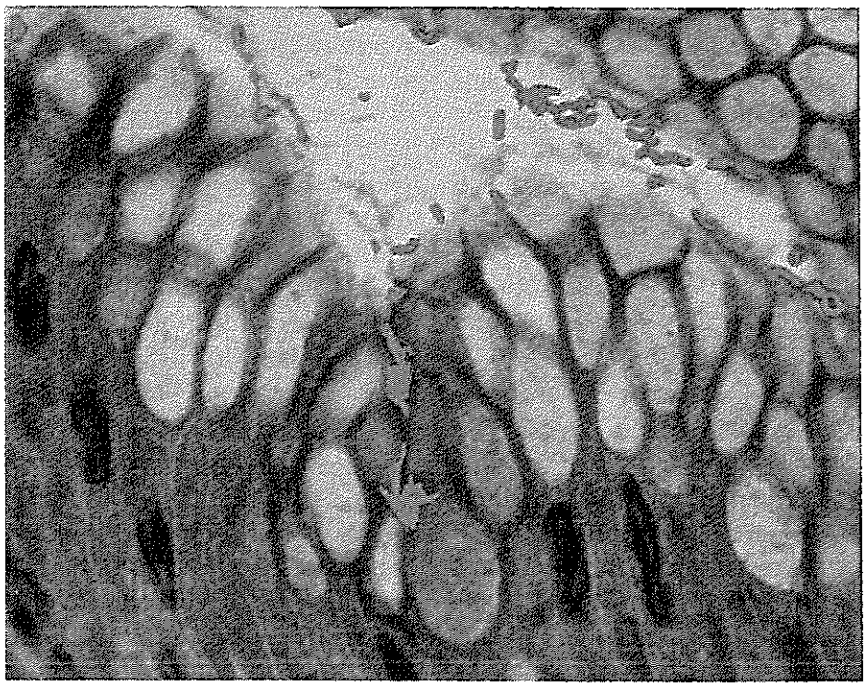
Arthur J. DeCross, MD, and Barry J. Marshall, MD

Helicobacter pylori, *first detected in gastritis patients a decade ago, has now been shown to be the major cause of active chronic gastritis, and the evidence that it plays a major role in the pathophysiology of duodenal ulcers and possibly gastric ulcers is compelling. The infection is generally diagnosed at the initial endoscopy by means of a rapid urease test, but it may be detected by serologic testing in patients not undergoing endoscopy.*

Treatment of the infection should be reserved for patients with duodenal ulcer disease that presents a significant management problem. The recommended therapy, commonly referred to as triple therapy, consists of bismuth subsalicylate, tetracycline, and metronidazole and has an 80% to 90% eradication success rate.

Drugs Discussed in This Article:

Amoxicillin
Ampicillin
Bismuth subcitrate, colloidal (DeNol)
Bismuth subsalicylate (Pepto-Bismol and others)
Ciprofloxacin (Cipro)
Clarithromycin (Biaxin Filmtabs)
Clindamycin
Erythromycin
Metronidazole
Norfloxacin (Noroxin)
Ofloxacin (Floxin)
Omeprazole (Prilosec)
Ranitidine (Zantac)
Rifampin (Rifadin, Rimactane)
Tetracycline
Tinidazole (Fasigyn, Simplotan)



Color-enhanced slide of stained histologic section showing *Helicobacter pylori* on the surface of gastric epithelium.

Acute dyspeptic symptoms respond well to a variety of treatments; nonetheless, the ubiquitous and recurrent nature of peptic disease makes its long-term management a costly affair. According to one estimate, 4 million Americans had gastric or duodenal ulcer disease in 1975, for a total cost of more than $3.2 billion.[1] The National Center for Health Statistics reports that approximately 1.2 million patients required hospitalization for peptic diseases in 1990.[2]

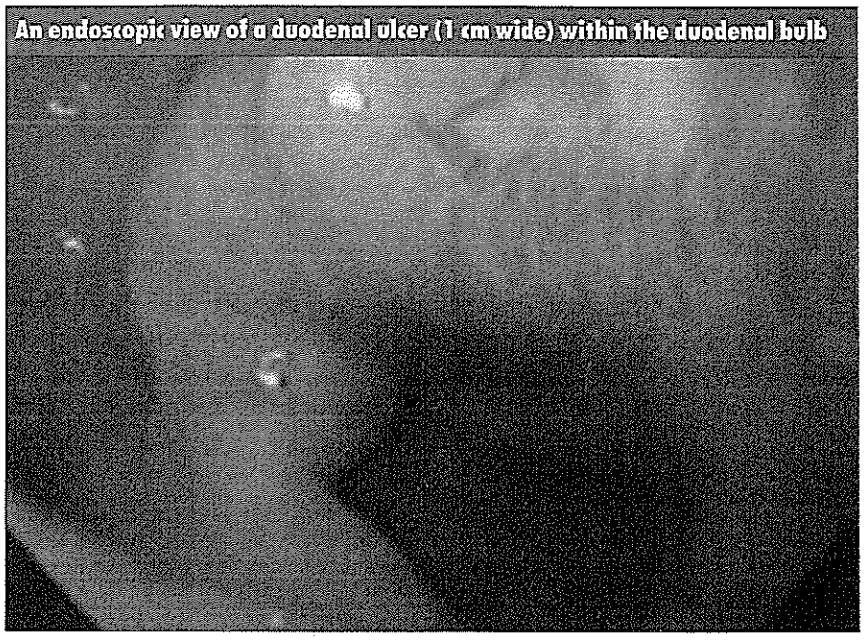
PATHOPHYSIOLOGY OF PEPTIC DISEASE

The pathophysiology of peptic disease can be viewed as an imbalance between mucosal-aggressive and mucosal-defensive factors. The major aggressive factor underlying ulcer disease is thought to be gastric acid. Gastric acid hypersecretion, which in the extreme accompanies such conditions as Zollinger-Ellison syndrome, can overwhelm the body's defensive mechanisms and produce unremitting ulcer disease.

Most peptic ulcers are not associated with acid hypersecretion, however. These ulcers are thought to result from a weakening of mucosal defense involving various alterations in bicarbonate secretion, mucosal blood flow, prostaglandin synthesis, mucus properties, or

Figure 1

An endoscopic view of a duodenal ulcer (1 cm wide) within the duodenal bulb



epithelial-cell turnover. Cigarette smoking, alcohol use, and nonsteroidal anti-inflammatory agents (NSAIDs) are also thought to impair defenses and increase susceptibility to gastric acid.[3]

Until recently, the treatment of peptic ulcer disease had focused on reestablishing mucosal balance by inhibiting acid with antacids, histamine-receptor antagonists (H_2-blockers), or proton-pump inhibitors and by coating the ulcerated tissue or using prostaglandin analogues for cytoprotection.[4] However, the substantial investigations that followed the discovery of *Helicobacter pylori* in 1982 have defined a role for this microorganism in the pathophysiology and treatment of peptic ulcer disease.

CLINICAL SIGNIFICANCE OF *H PYLORI*

Chronic Gastritis

H pylori has been shown to be the major cause of active chronic gastritis. It can be recovered 75% to 100% of the time in the setting of gastric inflammation with mononuclear-cell and neutrophilic infiltration.[5,6] Furthermore, epidemics of *H pylori*–associated gastritis have been reported; human volunteer studies indicate a cause-effect relationship; and antimicrobial eradication leads to healing of histologic abnormalities.[7] *H pylori* plays no role in the gastritis associated with autoimmunity, Crohn's disease, or Ménétrier's disease. Its role in NSAID-related gastritis remains controversial.

Duodenal Ulcers

Currently, there is no direct proof that *H pylori* infection causes duodenal ulcers (Figure 1). The indirect evidence, however, is extremely strong. The prevalence of infection in patients with duodenal ulcers approaches 100%[8]; antibacterial agents heal duodenal ulcers at the same rate as H_2-blockers[9,10]; and long-term ulcer recurrence rates are much lower when *H pylori* is eradicated (0% to 25% at 1 year) than when the organism persists (75% at 1 year).[11] Gastric acidity, however, remains a critical cofactor, since ulcers heal rapidly with acid suppression alone, and ulceration can occur in the absence of infection.

Gastric Ulcers

The role of *H pylori* in the formation of gastric ulcers has been less clear. This is due, in no small measure, to the prominence of NSAIDs in the etiology of many gastric ulcers. Another confounding factor is the poorly understood nature of the pathophysiology of gastric ulcers that are not related to NSAIDs. However, recent studies have helped clarify the role of *H pylori* in gastric ulcer by demonstrating that the eradication of this microorganism alters the natural history of the disease.

Specifically, the eradication of *H pylori* increases the rate of initial healing of *H pylori*–positive gastric ulcers (92% healed at 12 weeks when *H pylori* is eradicated versus 72% healed at 12 weeks when *H pylori* remains, $P<.05$),[12] and the healing of *H pylori*–positive gastric ulcers with eradicative therapy and ranitidine (Zantac) decreases the probability of recurrence within 1 year (13%) when compared with healing with ranitidine alone (95%, $P<.01$).[13]

Nonulcer Dyspepsia and Gastric Cancer

At this time, the role of *H pylori* in nonulcer dyspepsia remains unclear, largely because of difficulties in defining this patient population and following objective disease cri-

teria. Infection with *H pylori* has been shown to be associated with an increased risk of gastric carcinoma, although the mechanism for this is not understood.[14,15]

DIAGNOSIS

The decision to treat an *H pylori* infection requires a familiarity with the methods of diagnosing and following the infection.

Culture

Culture of the organism from the gastric mucosa is certainly the gold standard against which other tests should be validated, but the process is tedious, and accuracy depends on the sophistication and techniques available at the lab. A gastric biopsy for culture is not usually required during the initial endoscopy. It is more appropriate to reserve this test for the evaluation of a treatment failure so that antimicrobial sensitivity testing can be performed at the same time.

Rapid Urease Test

The test of choice at the initial endoscopy is a rapid urease test such as the commercially available *Campylobacter*-like organism test (CLOtest). A pinch biopsy from the antrum is placed into a well that contains urea, a pH indicator, and a bacteriostatic agent. If *H pylori* is present, its powerful urease enzyme will hydrolyze the urea to ammonia, producing a color change in the pH indicator from yellow to red.

CLOtest results are frequently available before the patient leaves the endoscopy unit, facilitating immediate management decisions. A biopsy for histologic examination can be a useful confirmatory test. However, it adds to the expense of the procedure and is not strictly required in the clinical setting.

Breath Testing

Breath testing is an exciting development because these tests are completely noninvasive and much less expensive than endoscopy. During the breath test for *H pylori*, the patient ingests a capsule of labeled urea (either ^{14}C-urea or ^{13}C-urea). If hydrolyzed by the urease of *H pylori*, it will release labeled CO_2, which can be collected and measured in the exhaled breath.

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The ^{14}C-urea test takes only 20 minutes to perform and is likely to be widely available in the near future. However, ^{14}C-urea is radioactive and thus restricted to nonpregnant adults. The ^{13}C-urea breath test is nonradioactive, but it takes longer to perform (20 to 60 minutes). Also, it requires expensive technology and so will probably remain less accessible.

Breath testing is an effective way to demonstrate the presence of an active *H pylori* infection and to document bacterial eradication after treatment. It does not provide an assessment of upper gastrointestinal (GI) pathology, however.

Serologic Testing

Serologic testing has received attention as potentially the most widely available test of *H pylori* infection. Commercial testing kits are flourishing,[2] and they certainly represent the least expensive and simplest diagnostic tool in patients not undergoing endoscopy. Serologic assays detect an IgG antibody against an outer membrane protein of *H pylori*. The antibody is frequently present in high titer, since the infection (hence the antigen stimulation) is chronic. Thus, a positive test may indicate only an infection at some point in the recent past.

By no means does a positive serologic test for *H pylori* indicate an upper GI lesion that merits investigation or an infection that merits therapy. Furthermore, this test is of limited utility in following the results of therapy, since it takes months to years for a positive titer to fall after successful eradication of infection.[16]

TREATMENT

When to Treat *H pylori* Infection

As with any infectious disease, the haphazard and indiscriminate use of antibiotics in the treatment of *H pylori* infection is to be shunned. The treatment of asymptomatic infected individuals is not recommended.

For patients with upper GI symptoms, *H pylori* infection should be treated only in the presence of duodenal ulcer disease that is a significant management problem (ie, requiring either continuous medication or consideration of surgery) or that has been complicated by bleeding or perforation.[17] This recommendation has not yet been

revised to incorporate the new data about *H pylori*–positive gastric ulcers. For the time being, the treatment of *H pylori* infection in the setting of gastric ulcer or nonulcer dyspepsia should be reserved for research studies and referral centers.

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Spouses and other close family members of infected patients do not need to be tested or treated, since reinfection of the patient is the exception rather than the rule, with an apparent reinfection rate of about 3% at 1 year in our patients at the University of Virginia.[18] Symptomatic spouses will usually request treatment, and their complaints should be appropriately investigated. Table 1 summarizes treatment recommendations.

Table 1

When to Treat *Helicobacter pylori* Infection

Disease	*H pylori* Treatment?
Gastritis	Not recommended, except in research settings
Uncomplicated duodenal ulcer (no bleed/perforation, good response to H_2-blocker)	Not required, but relapse rate can be dramatically lowered after *H pylori* eradicated
Complicated duodenal ulcer (status post-bleed/perforation, excessive H_2-blocker requirement, surgical therapy contemplated)	Recommended
Gastric ulcer	Not yet recommended, except in research settings
Nonulcer dyspepsia	Not recommended, except in research settings

Treatment Obstacles

The treatment of *H pylori* infection presents some unique obstacles and involves variations on the usual practices of antibiotic therapy.

First, the organism is found mainly beneath and within the mucous layer on the surface of the gastric epithelium. It adheres to but rarely invades the epithelium. However, it seems to find sanctuary within the gastric glands and pits. This would suggest, as has been borne out, that agents with primarily luminal or topical activity given as monotherapy will usually fail to eradicate the organism, although temporary suppression is easily achieved. In fact, temporary suppression of the infection is so thorough that true eradication (or "cure") is operationally defined by a negative diagnostic test for *H pylori* no earlier than 1 month after completion of therapy.[17] In our experience, even three to four doses of an antibiotic can suppress the infection enough to render a breath test faslely negative for up to 2 weeks. Antibiotics with topical activity against *H pylori* include amoxicillin/ampicillin, erythromycin, tetracycline, and the bismuth compounds—bismuth subsalicylate (Pepto-Bismol and others) and colloidal bismuth subcitrate (DeNol; not available in the United States).

Second, the gastric environment is a hostile one for many antibiotics that are not acid stable. Third, *H pylori* has a propensity to rapidly acquire resistance to several classes of antibiotics after exposure to the agent as monotherapy. These antibiotics include the fluoroquinolones (ofloxacin [Floxin], ciprofloxacin [Cipro], norfloxacin [Noroxin]); the nitroimidazoles (metronidazole, tinidazole [Fasigyn, Simplotan]); the macrolides (erythromycin, clarithromycin [Biaxin Filmtabs], clindamycin); and rifampin (Rifadin, Rimactane).[17]

These last two points may explain the failure of several systemically active antibiotics to achieve in vivo eradication of *H pylori* even when the drugs are effective in vitro and capable of achieving high concentrations in the gastric mucosa.[19] *H pylori* has not yet shown resistance to the β-lactams, the bismuth salts, or tetracycline.

Metronidazole resistance can be reduced when the drug is given in combination with either amoxicillin[20] or bismuth.[21,22] Although overly broad spectrum antibiotics can have undesirable consequences in the treatment of infection at other sites, the stomach is apparently not subject to superinfection with other bacterial organisms.

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Monotherapy

It is of historical interest that Sir William Osler himself may have been among the first physicians to treat *H pylori*. He sometimes gave bismuth subnitrate lozenges for acute and chronic gastritis.[23] Unfortunately, effective monotherapy for *H pylori* does not yet exist. A variety of antibiotics have been tested in vivo based on *H pylori* susceptibility in vitro. Only a few (bismuth, tetracycline, metronidazole, amoxicillin, and ofloxacin) produced any response, with eradication rates of between 5% and 27%.[17]

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Dual Therapy

Dual-antibiotic therapies are generally more effective than monotherapies but are still only modestly successful, with eradication rates of between 30% and 60%. These rates seem to reflect an additive effect of the monotherapies.

There is one notable exception: bismuth combined with metronidazole achieves an eradication rate of 75% in unselected patients, suggesting a synergism that so far has been noted only between these two agents. The eradication rate is more than 90% when this combination is used in patients infected with metronidazole-sensitive *H pylori*, but it falls to 13% in patients with metronidazole-resistant *H pylori*.[24,25] In developed countries, about 75% of *H pylori* isolates are metronidazole sensitive.[26] However, in many third-world countries, where common parasitic infections are treated with metronidazole, sensitive isolates are in the minority.[27] The clinical utility of metronidazole sensitivity testing before attempting *H pylori*–eradicative therapy has not been fully evaluated.

Interestingly, there are other forms of dual therapy that do not strictly involve two antibiotics. The combination of high-dose omeprazole (Prilosec) (40 to 80 mg/d) with amoxicillin (500 mg qid) has recently been reported to achieve an 82% eradication rate, and it appears to be a well-tolerated though not inexpensive therapy.[28] Also, the combination of high-dose omeprazole with clarithromycin (500 mg/tid) has recently been shown to result in an 80% eradication rate.[29]

Table 2

Triple Therapy and Some Alternatives

Standard therapy		
Bismuth subsalicylate (Pepto-Bismol and others)	2 tab qid	Day 1–14
Metronidazole	250 mg qid	Day 1–14
Tetracycline	500 mg qid	Day 1–14
Modified standard therapy (if intolerant of tetracycline)		
Bismuth subsalicylate	2 tab qid	Day 1–14
Metronidazole	250 mg qid	Day 1–14
Amoxicillin	500 mg tid	Day 1–14
Second-line therapy (for metronidazole-resistant strains)		
Bismuth subsalicylate	2 tab qid	Day 1–14
Tetracycline	500 mg qid	Day 1–14
Erythromycin base	500 mg qid	Day 1–14
Omeprazole (Prilosec)	40 mg qd	Day 1–14
Second-line therapy (if intolerant of all of the above)		
I. Amoxicillin	500 mg qid	Day 1–14
Omeprazole	40 mg bid	Day 1–14
Omeprazole	20 mg qod	Day 15–42
II. Clarithromycin	500 mg tid	Day 1–14
Omeprazole	40 mg qd	Day 1–14

Triple Therapy

The officially recommended therapy for *H pylori* infection is commonly referred to as "triple therapy." This originally consisted of a 2-week course of bismuth subsalicylate (one tablet qid), tetracycline (500 mg qid), and metronidazole (500 mg tid).[17] In the Western literature, most studies examining the effect of *H pylori* eradication on the natural history of peptic ulcer disease have used this triple therapy with slight modifications, often in combination with an H_2-blocker. Modification of the standard triple therapy involves doubling the bismuth dose to two tablets qid and reducing the metronidazole dose to 250 mg qid.

The eradication rate with triple therapy is between 80% and 90%. Failure of therapy has been reported to correlate most closely with patient compliance, with eradication rates of 96% in patients who took more than 60% of the prescribed therapy, compared with 69% in those who took less.[30] Amoxicillin (500 mg qid) may be substituted for tetracycline in allergic patients without compromising efficacy.

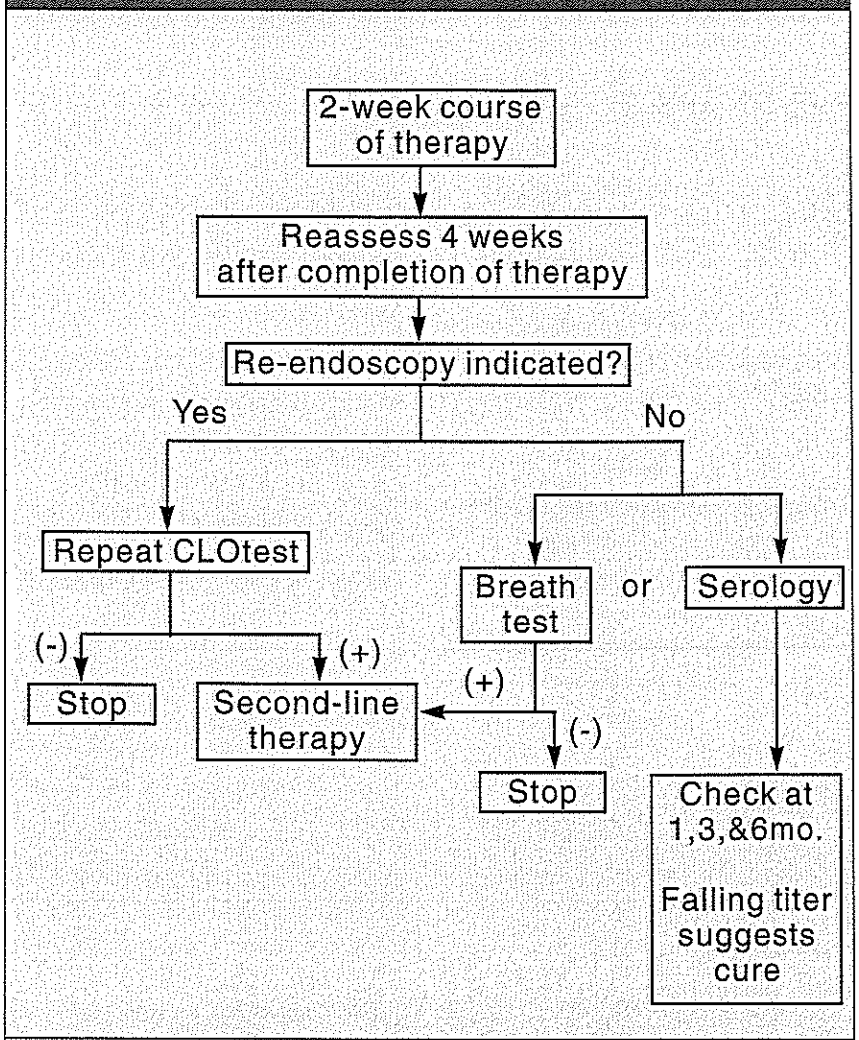
In cases of known metronidazole resistance, we substitute erythromycin base and an acid-suppressing medication for metronidazole as a second-line therapy.

In cases of known metronidazole resistance, we substitute erythromycin base and an acid-suppressing medication for metronidazole as a second-line therapy. This approach has resulted in a cure rate of 70%.[18] Interestingly, erythromycin base appears to be more effective than the acid-stable erythromycin prodrugs, erythromycin stearate and erythromycin ethylsuccinate.

Table 2 provides prescribing information on triple therapy and alternatives to be considered in the case of drug allergy, metronidazole resistance, or initial therapeutic failure.

Figure 2

Follow-up management of *H pylori* therapy



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Side Effects

Many patients cannot tolerate the side effects of multiple antibiotic therapy. In general, side effects include malaise, nausea, diarrhea, sore mouth, and fungal infections, but each antibiotic has its own profile of side effects. Bismuth is perhaps the most benign medication, often causing only darkened stools. In rare instances, excessive bismuth ingestion in a patient with poor renal function may lead to toxic bismuth levels and consequent reversible encephalopathy.[31]

Metronidazole may cause a metallic taste, may have a disulfiram-like effect, and should be avoided in pregnancy. Penicillin allergy and pseudomembranous colitis may complicate therapy with amoxicillin, although in our experience pseudomembranous colitis is not seen when the patient is receiving cotherapy with metronidazole.

Alternative Regimens

The frequent intolerance of triple therapy has prompted attempts to establish gentler variations on this theme. The addition of omeprazole or an H_2-blocker to the antibiotic therapy seems to help reduce

symptoms. These medications would be indicated anyway in the treatment of acute peptic ulcer disease. A reduced dose of metronidazole (250 mg qid) may be more tolerable and equally efficacious. Shorter courses of therapy (7 days) are probably adequate *if full compliance can be ensured.* The combination of high-dose omeprazole with amoxicillin or clarithromycin is certainly well tolerated, but further evaluation and confirmation of their therapeutic efficacy are needed before it can be recommended as a first-line therapy.

Follow-up

The patient must be followed carefully after therapy. The success of *H pylori* eradication is established 1 month after the completion of treatment. If repeat endoscopy is indicated at that time, a CLOtest can be obtained. If repeat endoscopy is not clinically indicated, a breath test can be used. If the breath test is not available, *H pylori* serology can be checked at 1, 3, and 6 months after therapy. A falling titer is evidence of cure. In the event of therapeutic failure, alternative therapies are available (Table 2). Figure 2 outlines a management scheme for the follow-up of *H pylori* therapy.

IN CONCLUSION

A decade of investigation has established that H pylori *plays a clear role in the pathogenesis of active chronic gastritis and duodenal ulcer disease. Although a variety of diagnostic methods are available to detect this infection, its treatment should be limited to cases of duodenal ulcer disease that has been complicated by bleeding, perforation, or difficult management. The role of* H pylori *in patients with nonulcer dyspepsia or gastric ulcer is still being explored, and treatment of the infection in these situations should be handled under protocol by research or referral centers. The standard triple therapy can be modified in several ways to improve tolerance to metronidazole, overcome tetracycline allergy, and treat metronidazole-resistant strains.*

References

1. Von Haunalter G, Chandler W. Cost of ulcer disease in the United States. Stanford Research Institute Project 5894. In: Sleisenger MH, Fordtran JS, eds. *Gastrointestinal Disease.* Philadephia, Pa: WB Saunders; 1989:814–878.
2. Buccino L. New study corroborates *H pylori* as cause of most peptic ulcers. *Advance News Magazine for Medical Laboratory Professionals.* June 22, 1992:10.
3. Soll AH. Pathogenesis of peptic ulcer and implications for therapy. *N Engl J Med.* 1990;322:909.
4. Drugs for treatment of peptic ulcer. *Med Lett Drugs Ther.* 1991;33:858.
5. Paull G, Yardley JH. Pathology of *C pylori*–associated gastric and esophageal lesions. In: Blaser MJ, ed. Campylobacter pylori *in Gastritis and Peptic Ulcer Disease.* New York, NY: Igaku-Shoin; 1989:73–97.
6. Blaser MG, Brown WR. Campylobacters and gastroduodenal inflammation. *Adv Intern Med.* 1989;34:21.
7. Strickland RG, Fenoglio-Preiser CM. Gastritis: classification then and now. In: Marshall GJ, McCallum RW, Guerrant R, eds. Helicobacter pylori *in Peptic Ulceration and Gastritis.* Cambridge, Mass: Blackwell Scientific Publications; 1991:1–18.
8. Dooley CP. *Helicobacter pylori* and duodenal ulcer. In: Marshall BJ, McCallum RW, Guerrant R, eds. Helicobacter pylori *in Peptic Ulceration and Gastritis.* Cambridge, Mass: Blackwell Scientific Publications; 1991:129–138.
9. O'Riordan T, Mathai E, Tobin E, et al. Adjuvant antibiotic therapy in duodenal ulcers treated with colloidal bismuth subcitrate. *Gut.* 1990;31:999.
10. Graham DY, Lew GM, Evans DG, et al. Effect of triple therapy (antibiotic plus bismuth) on duodenal ulcer healing. *Ann Intern Med.* 1991;115:266.
11. Rauws EA, Tytgat GN. Cure of duodenal ulcer associated with eradication of *H pylori.* *Lancet.* 1990;335:1233.
12. Seppala K, Pikkarainen P, Karvonen AL, et al. The role of *Helicobacter pylori* in gastric ulcer healing and relapse. *Gastroenterology.* 1992;102(4, part 2):abstract 1043.
13. Graham DY, Lew GM, Klein PD, 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.
14. Parsonnet J, Friedman GD, Vandensteen DP, et al. *Helicobacter pylori* infection and the risk of gastric carcinoma. *N Engl J Med.* 1991;3 25:1127.
15. Nomura A, Stemmermann GN, Chyou PH, et al. *Helicobacter pylori* infection and gastric carcinoma among Japanese Americans in Hawaii. N *Engl J Med.* 1991;325:1132.
16. Marshall BJ. Practical diagnosis of *Helicobacter pylori.* In: Marshall BJ, McCallum RW, Guerrant R, eds. Helicobacter pylori *in Peptic Ulceration and Gastritis.* Cambridge, Mass: Blackwell Scientific Publications; 1991:139–159.
17. Axon ATR. *Helicobacter pylori* therapy: effect on peptic ulcer disease: V. Working Party Report of the World Congress of Gastroenterology, 1990. *J Gastroenterol Hepatol.* 1991;6:131.
18. Marshall BJ. Treatment of *Helicobacter pylori.* In: Marshall BJ, McCallum RW, Guerrant R, eds. Helicobacter pylori *in Peptic Ulceration and Gastritis.* Cambridge, Mass: Blackwell Scientific Publications; 1991:160–186.
19. McNulty CA, Dent JC, Ford GA, et al. Inhibitory antimicrobial concentrations against *Campylobacter pylori* in gastric mucosa. *J Antimicrob Chemother.* 1988;22:722–738.
20. Burette A, Glupczinski U, Deprez C. Evaluation of two short term amoxicillin/tinidazole regimens for eradication of *H pylori. Gastroenterology.* 1990;98:A27.
21. Goodwin CS, Marshall BJ, Blincow BJ, et al. Prevention of nitroimidazole resistance in *Campylobacter pylori* by coadministration of colloidal bismuth subcitrate: clinical and in vitro studies. *J Clin Pathol.* 1988;41:207–210.
22. Mathai E, O'Riordan T, Tobin A, et al. Drug resistance in *Campylobacter pylori. Klin Wochenschr.* 1989;67(suppl 18):46.
23. Osler W. *The Principles and Practice of Medicine.* New York, NY: Appleton; 1920.
24. Marshall BJ, Dye KR, Plankey M, et al. Eradication of *Campylobacter pylori* infection with bismuth subsalicylate and antibiotic combinations. *Am J Gastroenterol.* 1988;83:1035. Abstract.
25. Marshall BJ, Barrett LJ, McCallum RW, et al. *C pylori* therapy: is in vitro disc testing with metronidazole worthwhile? Poster presentation, Fifth International Workshop on Campylobacter Infections. Puerto Vallarta, Mexico, February 1989.
26. McNulty CA, Dent JC. Susceptibility of clinical isolates of *Campylobacter pylori* to twenty-one antimicrobial agents. *Eur J Clin Microbiol Infect Dis.* 1988;7:566–569.
27. Glupczynski Y, Burette A, De Koster E, et al. Metronidazole resistance in *Helicobacter pylori. Lancet.* 1990;335:976–977. Letter.
28. Bayerdorffer E, Mannes GA, Sommer A, et al. High dose omeprazole treatment combined with amoxicillin eradicates *H pylori. Gastroenterology.* 1992;102(4, part 2):A38.
29. Logan RPH, Gummett PA, Hegarty BT, et at. Clarithromycin and omeprazole for *H pylori. Lancet.* 1992;340:239. Letter.
30. Graham DY, Lew GM, Malaty HM, et al. Factors influencing the eradication of *Helicobacter pylori* with triple therapy. *Gastroenterology.* 1992;102:493–496.
31. Playford RJ, Matthews CH, Campbell MJ, et al. Bismuth induced encephalopathy caused by tripotassium dicitrato-bismuthate in a patient with chronic renal failure. *Gut.* 1990;31:359–360