 0889–8553/93 $0.00 + .20

TREATMENT STRATEGIES FOR *HELICOBACTER PYLORI* INFECTION

Barry J. Marshall, MD, MBBS, FRACP, FACG

In 1983, when *Helicobacter pylori* and peptic ulceration were first associated,[36] the only therapy that healed duodenal ulcer and also inhibited *H. pylori* in vitro was colloidal bismuth subcitrate (CBS). Unfortunately, bismuth caused only suppression of *H. pylori*, so patients suffered relapse of the infection a few weeks after therapy ended, and duodenal ulcer relapse rates were only slightly lower than those seen with H_2 receptor antagonists.[43]

Early investigators often made the mistake of equating a negative biopsy at the end of therapy with cure, thus leading to unrealistic claims for some therapies and subsequently disappointing results when many infections relapsed. The addition of metronidazole or amoxicillin to bismuth regimens in 1984 led to the first permanent eradication of *H. pylori* and opened the way for investigators to study the clinical effects of such eradication.[19] Tedious empiric clinical trials were necessary because the effect in vitro of antibacterial agents did not predict their effect in vivo on the new bacterium. After 8 years of experimentation, we now have several safe and effective therapies to cure *H. pylori* infection. Some of them may be suitable for prospective double-blind clinical studies and ultimately for general use.

RULES FOR DETERMINING ERADICATION OF *H. PYLORI*

Proof of *H. pylori* eradication must be based on a follow-up biopsy performed more than 28 days after therapy is completed. The test used

From the Division of Gastroenterology, University of Virginia Health Sciences Center, Charlottesville, Virginia

to prove eradication should detect the bacterium rather than an immunologic response. Currently, biopsy of the gastric mucosa for histology is still the most sensitive means of detecting *H. pylori*. At least two biopsy specimens should be tested by histologic staining. As a noninvasive test for cure, the urea breath test may be used.[35] If these methods are unavailable, serial antibody titers (IgG) that show a consistent fall 3 and 6 months after treatment are circumstantial evidence of cure.[50] Figure 1 shows a time line of treatment (triple therapy) and follow-up after therapy.

CONSIDERATIONS IN THE THERAPY OF *H. PYLORI* INFECTION

Luminal or Systemic Antibiotics?

Healthy *H. pylori* organisms can often be seen in the gastric mucus layer or antral mucus glands, within phagocytic cells, and even inside canaliculi of parietal cells. Gastric juice also has been shown to contain viable *H. pylori* organisms, even when the pH is below 3.0. These gastric luminal bacteria are transiently attacked with oral antibiotics but are probably best treated by drugs that are secreted in gastric juice or saliva. The pH near the lumen of the stomach is maintained at 2.0, whereas the cell-mucus interface is more alkaline, with a pH of approximately 6.0. Few antibiotics are active in both these pH extremes. Oral agents reach very high concentrations in gastric mucus,[45] but levels quickly fall as the stomach empties after a meal.[30] As a consequence, dosing schedules of three or four times daily may allow *H. pylori* to multiply between doses. The low eradication rates achieved with bismuth salts and tetracyclines suggest that luminally active agents do

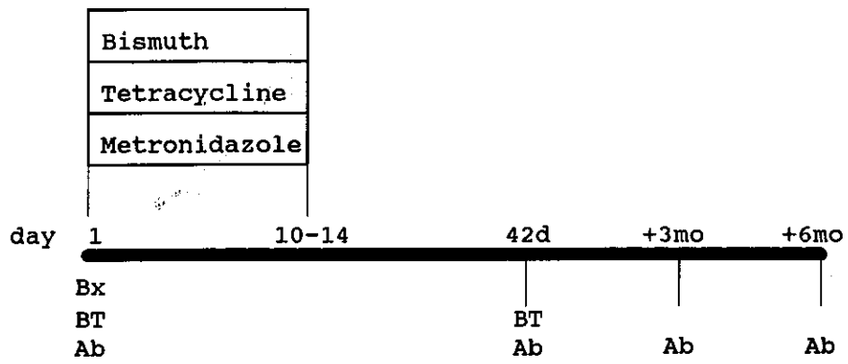

Figure 1. Time line of therapy for *H. pylori* infection. Bismuth—8 tablets/d (Pepto-Bismol) or 4 tablets/d (De-Nol); tetracycline—8 tablets/d (250 mg); metronidazole—4 tablets/d (250 mg). Bx = biopsy; BT = urea breath test; Ab = serology.

not achieve adequate concentrations in the deep mucus-secreting glands of the antrum, which often harbor many *H. pylori* organisms.

Is Acid Protective for *H. pylori*?

Several observations suggest that acid may protect *H. pylori* from antibiotics. In patients with achlorhydria due to pernicious anemia, the prevalence of *H. pylori* infection is usually less than that of the background population.[15] The usual explanation for this observation is heightened immunity in these patients or decreased virulence of *H. pylori* in the absence of acid. Alternatively, *H. pylori* may be far more easy to eradicate in the absence of acid, allowing ordinary courses of common antibiotics to eradicate the bacterium. As an example, the eradication rate of amoxicillin alone is not more than 20%, yet far higher rates of *H. pylori* cure were observed when amoxicillin was given in combination with omeprazole, a proton pump inhibitor.[54]

Are There Sequestered Organisms?

H. pylori organisms can be found in several very different regions of the upper gastrointestinal tract, including dental plaque,[28] islands of gastric metaplasia in the esophagus,[4] and Barrett's epithelium of the lower esophagus.[3] All three of these locations actually are outside the body and are only imperfectly contacted by the extracellular fluid. Systemic therapies may therefore be ineffective in these locations, in which drugs that are chewed (De-Nol chewable tablets) or secreted in saliva (metronidazole, clarithromycin) may be preferred. Sequestration of *H. pylori* in dental plaque or periodontal tissues may also be a factor contributing to its prevalence among lower socioeconomic groups.[23]

Can in vitro Studies Predict in vivo Effects?

Many antibacterial agents that have not proved successful in vivo have merely exceeded the minimal inhibitory concentration (MIC) of *H. pylori*, perhaps leaving quiescent but viable forms in the gastric mucosa. Whereas phagocytic cells should be capable of killing such organisms, *H. pylori* may be relatively resistant to phagocytic eradication because of its catalase activity.[25] In phagocytic cells, catalase destroys lysosomal hydrogen peroxide before it can generate the oxygen radicals necessary for a bactericidal effect.[1, 53] Antibacterial agents may have to exceed the minimal bactericidal concentration (MBC) to eradicate *H. pylori*.[44]

ACTIVITY OF ANTIBIOTICS ON *H. PYLORI*

H. pylori is a microaerophilic gram-negative organism related to *Campylobacter jejuni* and with a similar antibiogram. In the following

Table 1. AGENTS THAT ALWAYS INHIBIT *H. PYLORI* AND NEVER LEAD TO ANTIBIOTIC RESISTANCE*

Drug	Cure Rate as Single Agent (%)	Usage
Colloidal bismuth subcitrate (De-Nol)	30–40	1 tablet qid or 2 tablets bid†‡
Bismuth subsalicylate (Pepto-Bismol)	5–10	1 tablet 8 times per day or 2 tablets qid†‡; this dose contains 1 g salicylate per day
Amoxicillin or ampicillin	15	500 mg qid†‡§ 1 g bid‡§
Tetracycline	5	500 mg qid†‡‖
Doxycycline	5	200 mg daily; acts systemically, excreted in bile, convenient administration possible in some difficult-to-treat vomiting patients‖
Furazolidone	20–40	100 mg tid or qid†‡¶
Nitrofurantoin	10–15	100 mg tid or qid†‡

qid = four times daily; bid = twice daily; tid = three times daily.
*These agents may be used more than once in the same patient.
†More frequent dosing is preferred (every 3 hours) because of the short half-life in gastric mucosa.
‡Use in combination therapy.
§Higher cure rates if used in combination with acid-reducing therapy.
‖May cause photosensitivity.
¶70% cure rate in one study; poor results in other studies.

discussion, the action of various antibiotics on *H. pylori* is classified by the in vivo efficacy of the drug and the ability of *H. pylori* to develop in vitro antibiotic resistance. This information is summarized in Tables 1 and 2.

Table 2. AGENTS THAT INHIBIT *H. PYLORI* IN VITRO AND IN VIVO BUT CAUSE ANTIBIOTIC RESISTANCE*

Drug	Cure Rate as a Single Agent (%)	Usage
Metronidazole	5	1–1.5 g daily (20 mg/kg)†
Tinidazole	5	1 g daily†
Erythromycin base	15	2 g daily in divided doses‡§‖¶
Clarithromycin	40–60	1.5 g daily for 14 days
Ciprofloxacin (ofloxacin, norfloxacin, etc.)	10	500 mg daily†**; vary doses for other quinolones

*Therefore, they should be used only once. If antibiotic susceptibility is available, it should be used as a guide to therapy.
†Never use as a single agent.
‡More frequent dosing is preferred (every 3 hours) because of the short half-life in gastric mucosa.
§Use in combination therapy.
‖Do not use pro-drug forms such as erythromycin ethylsuccinate, because they are inactive in the stomach.
¶Higher cure rates if used in combination with acid-reducing therapy.
**Last-resort therapy to be used in combination with multiple other agents.

Agents That Always Inhibit *H. Pylori* and Never Lead to Antibiotic Resistance—They May Be Re-used in the Same Patient

Amoxicillin

Amoxicillin has been widely used to treat *H. pylori* because of its dosing convenience rather than for its efficacy. Although all isolates of *H. pylori* are sensitive to amoxicillin in vitro, treatment results in vivo have been disappointing. Ampicillin is likely to be at least as effective as amoxicillin (and possibly cheaper), but no direct comparisons of the two drugs have been performed. Because *H. pylori* does not produce penicillinase, there is no advantage to using combinations such as amoxicillin and clavulanic acid (Augmentin).

High concentrations of amoxicillin are obtained in gastric juice and mucosa during oral therapy,[45] but the *H. pylori* eradication rate is low, usually less than 20%.[50, 52] Higher amoxicillin doses, as much as 4 g daily, have been tried at the University of Virginia but have been no better than the 2-g dose (Marshall BJ: unpublished). Amoxicillin is mostly used in a dose of 500 mg four times daily in combination therapies (see later discussion). Frequent dosing with amoxicillin—for example, 250 mg of suspension every three hours—is well tolerated and may be used for initial suppression of *H. pylori* in patients with severe nausea and vomiting.

A disadvantage of amoxicillin is a 5% incidence of *Clostridium difficile* colitis, which may be prevented by combining the drug with metronidazole. Such therapy has been advocated as a 7-day treatment by Logan et al.[33] Amoxicillin may also be more effective if given in combination with omeprazole. Although the amoxicillin-bismuth-metronidazole combination has been used by several investigators, it does not eradicate metronidazole-resistant *H. pylori*. In this respect, therefore, tetracycline is a more active component of triple therapy (see later discussion).

One-Week Therapy. Logan et al[33] reported a 1-week triple therapy for *H. pylori* using CBS, four tablets; amoxicillin, 2 g; and metronidazole, 1 g daily. Therapy was given for only 7 days, and 74% eradication was achieved. In metronidazole-sensitive strains, the eradication rate was 93%, but in resistant strains, eradication was less than 50%. Although the brevity of this therapy is commendable, it appears that Logan et al did not really see a cure rate greater than that with bismuth and metronidazole alone (74%), with similar respective cure rates for metronidazole-resistant and -sensitive organisms.[40] Thus, the addition of amoxicillin to bismuth-metronidazole appears to be of marginal benefit and at first glance does not seem to give the reported synergism that is seen with tetracycline. As discussed in letters to the *Lancet*,[27] further studies are required to sort out the present controversy.

Pediatric Therapy. In children, in whom bismuth is difficult to administer and tetracycline is contraindicated, amoxicillin-tinidazole therapy has been used. Oderda et al[50] report an eradication rate of 75%

with a 6-week course. The dose of tinidazole was 20 mg/kg/d, and that of amoxicillin was 50 mg/kg/d. In the United States, metronidazole may be used in the same dose as tinidazole. In retrospect, it is likely that compliance with the therapy described by Oderda et al was poor and that a 7- to 14-day therapy would have been equally efficacious.[18]

Does Omeprazole Enhance Antibiotic Effect? Unge et al[54] observed eradication in 60% to 70% of patients given combination therapy with amoxicillin, 500 mg four times daily, and omeprazole, 40 mg daily. The rationale for this use was that lack of efficacy with amoxicillin alone was due to *H. pylori* sequestered in the parietal cells. It was proposed that omeprazole would enhance antibiotic penetration into a location now rendered pH neutral. Bayerdorffer et al[3] recently reported preliminary results from a larger study, using omeprazole 40 mg twice daily, and amoxicillin, 1 g twice daily. The *H. pylori* cure rate was 80% in the antibiotic-treated group, a far higher cure rate than has been reported elsewhere with this combination. As expected, ulcer relapse was virtually nonexistent in the patients from whom *H. pylori* had been eradicated. At the University of Virginia, we have had disappointing results with this type of therapy but have used it only in refractory patients in whom the cure rate has been less than 50%. We prefer to use combinations of omeprazole and erythromycin instead (see subsequent discussion of triple therapy).

Tetracycline

The main use of tetracycline is as a component of triple therapy (see later discussion). Tetracycline is acid stable and active at acid pH,[45] achieves high concentrations in the mucosa, and exceeds the MIC of *H. pylori* for several hours. Tetracycline by itself is ineffective at eradicating *H. pylori* but is useful as a single agent for prolonged suppression in a dose of 250 mg every 3 hours for 4 weeks in patients who are not able to take other medications. Tetracycline is also very cheap.

Tetracycline in combination with bismuth is not curative but causes substantial suppression of *H. pylori* as evidenced by breath test. For most infections, bismuth and tetracycline would not be given together lest they chelate and not be absorbed. In the case of *H. pylori* infection, this reaction may be beneficial, perhaps resulting in prolonged retention of both drugs in the gastric mucus. The only other tetracycline with potential use is doxycycline, which is secreted in bile and is active (but not curative) in patients who have *H. pylori* in a gastric remnant (e.g., after Billroth II partial gastrectomy).[47]

Nitrofurantoin and Furazolidone

Nitrofurans retain their in vitro activity against *H. pylori* and may have some use as topical agents for the gastric mucosa. Graham et al[21] have demonstrated that frequent low-dose furazolidone suspension

(7 mg seven times daily) suppresses *H. pylori* in most patients as assessed by ^{13}C urea breath test. This finding suggests that it may be used as a gastric luminal antibacterial agent, supplementing the actions of bismuth, tetracycline, and amoxicillin.

The ulcer-healing action of furazolidone had been observed in China even before the discovery of *H. pylori*.[56] Later reports by Morgan et al[48] and by Börsch et al[7] have shown that both furazolidone and nitrofurantoin are relatively ineffective as single agents in doses as high as 400 mg daily. In addition, gastric side effects made clinical response very difficult to assess. Morgan et al[48] found that *H. pylori* was suppressed in most patients but eradicated in only 20%. In a surprising study, Xiao et al[55] claimed a 75% eradication rate for furazolidone, 100 mg three times daily for 3 weeks, in Chinese patients with symptomatic gastritis. So far, this cure rate has not been duplicated by other investigators.

Bismuth Salts

Bismuth and other heavy metals have been used to treat gastritis for more than 200 years. In electron microscope studies, bismuth can be seen to precipitate in and around *H. pylori* organisms in the gastric mucus layer, to collect beneath the cell wall of *H. pylori*, to cause detachment of the organism from the mucosa, and to lead to bacterial lysis of most gastric mucosal *H. pylori* within 2 hours of ingestion.[37] Bismuth therapy for diarrheal disease and *H. pylori* has been the subject of several recent reviews.[20, 34]

Colloidal Bismuth Subcitrate (De-Nol). The first bismuth drug used specifically for *H. pylori* therapy was CBS (De-Nol, Gist-Brocades Nederland, Rijswijk, Netherlands). The initial formulation of CBS was an unpleasant alkaline liquid, but it was reformulated into a pleasant spray-dried chewable tablet in 1979 and more recently into a swallowable tablet.[34] Current formulations of CBS are to be taken as two tablets twice daily for duodenal and gastric ulcer disease. Ulcer-healing rates are equal to those seen with H_2-receptor antagonists, and probably because of *H. pylori* suppression, CBS is especially useful in healing ulcers refractory to H_2-receptor antagonists.

Bismuth Subsalicylate (BSS). In the acid environment of the stomach, BSS disassociates into bismuth oxychloride and salicylate. Salicylate is absorbed and excreted in the kidneys, with approximately 1 g salicylate released from the recommended dose of eight BSS tablets (or spoonsful of regular-strength Pepto-Bismol) per day. BSS is less effective than CBS for *H. pylori*, resulting in a single-agent cure rate of only 10%. As with CBS, the drug is best used in combination therapy, usually with metronidazole and tetracycline. Failure of BSS to eradicate *H. pylori* is probably related to both its unpalatability (leading to poor compliance) and its poor solubility.

In a double-blind study at the University of Virginia, only 5% of *H. pylori* infections were cured during BSS therapy given as 512 mg four times daily.[42] In the case of CBS, long-term *H. pylori* eradication

rates of 40% have repeatedly been achieved.[12, 40] Logically, therefore, bismuth therapy alone is not expected to affect the long-term outcome of patients with *H. pylori*. Because of its short half-life in gastric mucus,[30] bismuth should be administered frequently. As an example, although the ulcer-healing rate is not obviously enhanced, dosing four times daily with CBS appears to suppress *H. pylori* better than does three-times-daily dosing (73% versus 42%).[11]

Other Bismuth Salts. Bismuth subnitrate (Roter tablets), subgallate (Devrom), and subcarbonate have activity similar to that of BSS and CBS, with an MIC of 12 to 25 mg/L for most *H. pylori* isolates.[37] The effect of three bismuth preparations was recently described by Pounder et al,[51] who acutely dosed several volunteers and tested for *H. pylori* suppression with the urea breath test. As shown in Figure 2, all three compounds showed equal efficacy in vivo, with none giving useful long-term eradication of the organism.

Agents That May Cause Antibiotic Resistance and Therefore Should Be Used Only Once (or as Indicated by Susceptibility Testing)

Erythromycin

Erythromycin is available as erythromycin base, erythromycin stearate, erythromycin ethylsuccinate (EES), and erythromycin estolate. Erythromycin stearate and EES, although acid stable, must be metabolized to the active drug after absorption, which may result in less activity for gastric infections. McNulty et al[46] found that EES by itself eradicated less than 20% of *H. pylori* infections, suggesting that serum activity was ineffective at clearing the gastric mucosa. This poor effect in vivo is in striking contrast to the very low MIC seen for *H. pylori* with erythromycin in vitro. When mucosal levels of erythromycin were studied, McNulty et al found 1 to 5 mg/L, about twice the serum level, to be present, easily exceeding the MIC (0.1–1.0 mg/L).

Erythromycin increases gut motility by stimulating motilin receptors in the stomach. Abdominal cramping, gnawing, nausea, and diarrhea are all common with erythromycin therapy, often limiting its use. Erythromycin is secreted in bile so may be more effective in patients with duodenogastric bile reflux.

Alternatives to locally inactive acid-stable formulations are enteric-coated erythromycin base delivered as small granules within a capsule (ERYC, Parke-Davis) and erythromycin-base film-coated tablets (Erythromycin Base Filmtabs, Abbott). To achieve gastric dissolution and local action of enteric-coated granules, the stomach should be rendered neutral with either high-dose H_2-receptor antagonists or omeprazole, and the erythromycin should be given as 250-mg tablets every 3 hours. This regimen ensures good absorption (ante cibum doses) and prolonged gastric retention (post cibum doses). Quadruple therapy with omeprazole, 40 mg daily; Pepto-Bismol, 8 tablets daily; tetracycline,

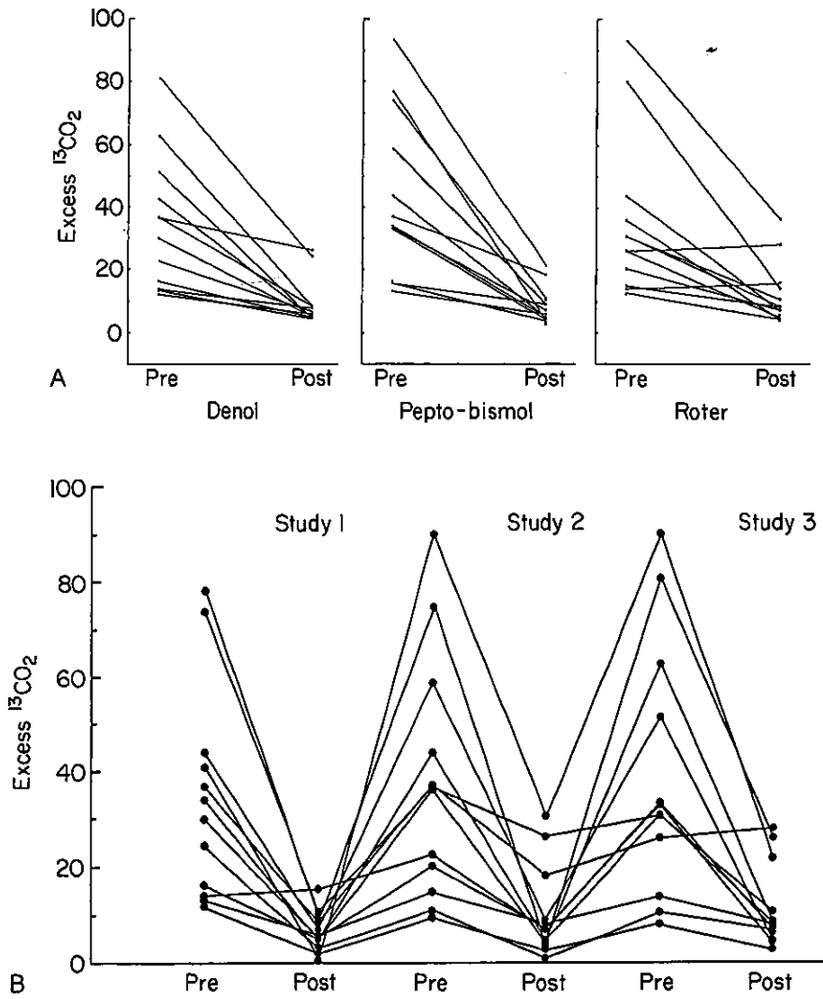

Figure 2. Graphs showing initial suppression (*A*) of gastric urease with subsequent resurgence (*B*) weeks after ceasing therapy with three bismuth compounds. (*From* Prewett EJ, Luk WY, Fraser AG, et al: Comparison of one-day oral dosing with three bismuth compounds for the suppression of *H. pylori* assessed by the ^{13}C-urea breath test. Alimentary Pharmacology and Therapeutics 6:97–102, 1992; with permission.)

250 mg × 8 daily; and ERYC, 250 mg × 8 daily, has given a cure rate of 80% at the University of Virginia.[41] Therapy is given for 14 days, and the cure rate is not affected by previous therapy with metronidazole.

Other Macrolides (Clindamycin, Azithromycin, Clarithromycin)

Clindamycin has been studied both as monotherapy and in combination with BSS by Westblom (Westblom U: personal communica-

tion). Low eradication rates were achieved, suggesting that this is not a useful therapy. Azithromycin, an acid-stable macrolide with a very long half-life, was also found to be ineffective for treating *H. pylori* infection. Glupczynski et al[16] found that 10 of 12 patients had persistent *H. pylori* during 7 days of azithromycin monotherapy and that the infection relapsed in the remaining 2 patients. In most cases a resistant strain developed, tolerant also to erythromycin, clindamycin, and other macrolides. Similarly poor results were seen with josamycin,[32] which has been found to cause resistant *H. pylori* strains to emerge in vitro.[24] As with metronidazole and quinolones, a small proportion of *H. pylori* organisms seem to carry inherent macrolide resistance and emerge as the dominant strain when exposed to the drug. Thus, macrolides are best used in combination therapy rather than alone.

Clarithromycin (Biaxin, Abbott). Clarithromycin, a new-generation macrolide, is acid stable, with a longer half-life than that of erythromycin. The MIC to *H. pylori* is low, and the drug is metabolized to an active metabolite that is also active against *H. pylori*. In limited clinical studies, cure rates of 40% to 60% have been achieved with use of clarithromycin as a single agent,[49] making clarithromycin unique in being the only agent with such activity when given alone. The dose is 1 to 1.5 g daily for 7 to 14 days (dose range not yet determined for this indication). The major side effect is a bad taste in the mouth. Unfortunately, when clarithromycin treatment fails, *H. pylori* often becomes erythromycin resistant, so as with the other new macrolides, clarithromycin can be used only once, or therapy should be guided by in vitro sensitivity results.

Quinolones (Ciprofloxacin, Norfloxacin, Ofloxacin)

Quinolones inhibit *H. pylori* in vitro but have had limited success when used in vivo. Bayerdorffer et al[2] reported that ofloxacin enhanced duodenal ulcer healing when used in addition to ranitidine. This effect was noted even though *H. pylori* could not be eradicated by the combination. When persistent *H. pylori* isolates were examined in vitro after therapy, they were found to be resistant to all quinolone drugs. Thus, quinolones cannot be used as monotherapy, but they may have an adjuvant role in patients with resistant infections. Ciprofloxacin is secreted in bile at 5 to 10 times the serum concentration.[29] Ofloxacin is secreted in saliva at concentrations equal to those in serum. We have used ciprofloxacin, 1 to 1.5 g daily, as a supplementary agent to triple therapy in a few patients in whom other therapies have failed. Quinolone combination therapies are expensive and currently unproven.

Metronidazole and Tinidazole

Nitroimidazoles are used mainly for the treatment of anaerobic infections and parasites such as *Giardia* and *Trichomonas*. They are secreted in saliva and differ from each other only in dosage and half-life. Tinidazole is usually given as a single daily dose of 1 g, whereas metronidazole is given as 250 to 500 mg three times daily.

In Western countries, about 75% of *H. pylori* isolates are sensitive to metronidazole.[19] Nevertheless, if metronidazole is given as a single agent, *H. pylori* is rarely eradicated, and resistance to metronidazole develops in almost all cases. Thus, nitroimidazoles must always be given as components of combination therapy rather than as single agents. In Africa, this advice may be irrelevant because long-term use of metronidazole for parasites (*Ameba* and *Giardia*) seems to have rendered most *H. pylori* isolates resistant to metronidazole; therefore, the drug is useless, alone or in combination, for *H. pylori* infections in that region.[17]

Resistance to nitroimidazoles does not usually develop if a second antimicrobial drug is given concurrently. This was first observed with tinidazole-bismuth therapy[19] but appears to hold true if the bismuth is replaced with amoxicillin or tetracycline. Successful therapies for *H. pylori* infection are based on a broad-spectrum agent that acts luminally to cause extreme suppression of the bacterium. Such agents are bismuth, tetracycline, amoxicillin, ampicillin, and furazolidone. In this scenario, a second agent acting both topically and systemically is more efficacious and less likely to cause selection of a resistant isolate.

TRIPLE THERAPY

Triple therapies have the advantage of luminal activity and systemic activity. Luminally active agents are bismuth, tetracycline, amoxicillin or ampicillin, and, perhaps, furazolidone.[21] Combining two luminally active agents causes marked suppression of *H. pylori* and may have an inherent cure rate of 10% to 40%. In addition, these agents do not appear to cause resistance, so they may be used in repeated courses and in various combinations.

The combination of bismuth, tetracycline, and metronidazole seems to be particularly effective. Borody and colleagues[5, 6] in Australia claim a 90% cure rate, suggesting that at least half the metronidazole-resistant forms are eradicated by this triple therapy. Supporting this is a recent comparison of various therapies for resistant organisms, in which the cure rate exceeded 50% even if *H. pylori* infection was re-treated with the same triple therapy containing metronidazole.[5, 6] Because the cure rate with tetracycline-bismuth is very low, it appears that synergism exists between metronidazole and the other two drugs. Our own experience is that 90% of patients with sensitive isolates are cured by dual therapy with bismuth and metronidazole. The extra benefit seen in triple therapy (over dual therapy) is thus about 10%, with side effects of occasional tetracycline allergies. If antibiotic sensitivity testing is unavailable, triple therapy is a practical first choice for *H. pylori* eradication.

Resistant Infections

Most triple therapies contain a nitroimidazole, usually metronidazole, and this drug appears to be the most active component provided

that suppression of *H. pylori* with the other agents has occurred. There is now good evidence that the presence of bismuth somehow affects the ability of *H. pylori* to resist metronidazole, and about 50% of metronidazole-resistant isolates can be eradicated by using the triple therapy described earlier. In patients in whom triple therapy fails, my second choice is the quadruple therapy with erythromycin (ERYC) described earlier. A viable second or third option appears to be high-dose amoxicillin-omeprazole therapy[3] or clarithromycin-omeprazole therapy, recently described by Logan et al.[33]

COMPLIANCE AND ERADICATIVE THERAPY

In a double-blind trial of ulcer therapy in which ranitidine was compared with ranitidine plus triple therapy, Graham et al[12] monitored drug compliance and correlated it with the eradication rate. He found that patients who took more than 60% of their medication had 96% eradication of *H. pylori*, compared with a cure rate of only 69% in those who were noncompliant. Unfortunately, metronidazole sensitivity was not tested prior to therapy, so it is not certain that compliance was the real factor involved. Patients without *H. pylori* eradication may have had more gastrointestinal symptoms and been less compliant with (ineffective) medication. If compliance is a major factor, it could explain why longer courses of therapy do not offer any advantage over 14-day treatments. It may even be better to have good compliance over 7 days than mediocre compliance over 14 days. For this reason, several investigators have tried to eradicate *H. pylori* with short courses of combination therapy, even going as far as single-day therapy. So far, therapies shorter than 7 days have been less effective than 10- to 14-day therapies, but the optimal duration of therapy is still undecided.

OTHER (NEW) THERAPIES

Table 3 lists recent developments in the field of combination therapies for *H. pylori*. These provide useful alternative options for eradication of *H. pylori* in patients with metronidazole resistance, allergies, and compliance problems.

Coelho et al[10] have reported 83% eradication of *H. pylori* in patients treated with a regimen of furazolidone, 100 mg; amoxicillin, 500 mg; and metronidazole, 250 mg, three times daily for 5 days. It should be noted that, as with 7-day therapy (described earlier), the value of furazolidone in this successful triple-therapy regimen remains unproven because high cure rates are also obtained with dual therapy using amoxicillin and metronidazole.[50] It is worthy of note, however, that 5 days seems to have been an adequate duration of therapy. In a follow-up study of these patients, Coelho et al[10] report a reinfection rate of only 15% after 1 year. This relatively low rate is very encouraging for those who wish to treat *H. pylori* in areas where environmental sources of infection exist, such as Brazil.

Table 3. LATE-BREAKING DATA ON *H. PYLORI* THERAPY (MAY 1992)

Therapy	Days	Cure Rate (%)	n	Comment	Reference
CBS, 1 tablet qid; metronidazole, 250 mg qid; amoxicillin, 500 mg qid	14	Sensitive = 95; resistant to metronidazole = 63	65	If organism is metronidazole sensitive, omit bismuth	8
Amoxicillin, 1g bid; omeprazole, 40 mg daily	10	82	56	No ulcer relapse in DU patients rendered *H. pylori* negative; minimal side effects	3
Amoxicillin, 500 mg qid; omeprazole, 40 mg daily	7	0	—	Conflicts with above report; actual cure rate somewhere between 0% and 80%	14
CBS, 1 chewable tablet; metronidazole, 200 mg; tetracycline, 250 mg 5 times daily	14	96; >70 cure on second try	250	Add omeprazole, 40 mg, and repeat this therapy if the initial treatment fails	5, 6
Metronidazole, 250 mg tid; furazolidone, 200 mg tid; amoxicillin, 500 mg tid	5	75	150	Follow-up at 1 year shows low (15%) recurrence rate in Brazil	9
Omeprazole, bismuth, metronidazole	7	95	70	Metronidazole resistance not determined, so may differ from results in United States	26
Omeprazole (O), 20 mg, or ranitidine (R), 300 mg; amoxicillin, 2 g; tinidazole, 1 g daily	10	81(R)–86(O)	49	Use of ranitidine and omeprazole does not seem to make any difference to this therapy; similar cure rates without acid reduction in other studies	31

qid = four times daily; bid = two times daily; tid = three times daily.

References

1. Babiour BM: Oxygen dependent killing by phagocytes. N Engl J Med 298:659–668, 1978
2. Bayerdorffer E, Kasper G, Pirlet T, et al: Ofloxacin in the therapy of *Campylobacter pylori* positive duodenal ulcer: A prospective randomised study. Dtsch Med Wochenschr 11:1407–1411, 1987
3. Bayerdorffer E, Mannes GA, Sommer A, et al: High dose omeprazole treatment combined with amoxicillin eradicates *H. pylori*. Gastroenterology 4102:A38, 1992
4. Borhan-Manesh F, Farnhum JB: Does *Campylobacter pylori* infect the heterotopic gastric mucosa (HGM) at the upper esophageal sphincter (UES)? Gastroenterology 98 (5 suppl 2):A23, 1990
5. Borody TJ, Brandl S, Andrews P, et al: *H. pylori* eradication failure (EF)—further treatment possibilities. Gastroenterology 102:A43, 1992
6. Borody TJ, Brandl S, Andrews P, et al: High efficacy, low dose triple therapy (TT) for *Helicobacter pylori* (HP). Gastroenterology 102:A44, 1992
7. Borsch G, Mai U, Muller KM: Monotherapy or polychemotherapy in the treatment of *Campylobacter pylori*–related gastroduodenal disease. Scand J Gastroenterol Suppl 142:101–106, 1988
8. Burette A, Glupczynski Y, Deprez C: Two weeks triple therapy overcomes metronidazole resistance: Results of a randomized double blind study. Gastroenterology 102:A46, 1992
9. Coelho LGV, Passos MCF, Chausson Y, et al: One-week $12.00 therapy heals duodenal ulcer and eradicates *H. pylori*. Gastroenterology 102:A51, 1992
10. Coelho LGV, Passos MCF, Queiroz DMM, et al: Five days triple therapy and 15 days double therapy of *C. pylori* eradication [abstract]. Klin Wochenschr 67(suppl XVIII):11, 1989
11. Coghlan J, Hutchinson L, Gilligan D, et al: Dosage of colloidal bismuth subcitrate in duodenal ulcer healing and clearance of *Campylobacter pylori*. Alimentary Pharmacology and Therapeutics 4:49–54, 1990
12. Coghlan JG, Gilligan D, Humphries H, et al: *Campylobacter pylori* and recurrence of duodenal ulcers—a 12-month follow-up study. Lancet 2:1109–1111, 1987
13. De Giacomo C, Fiocca R, Villani L, et al: Barrett's ulcer and *Campylobacter*-like organisms infection in a child. J Pediatr Gastroenterol Nutr 7:766–768, 1988
14. de Koster ED, Nyst JF, Deprez C, et al: *Helicobacter pylori* treatment: Double vs. triple therapy: Who needs bismuth? Gastroenterology 102:A58, 1992
15. Fong TL, Dooley CP, Dehesa M, et al: *Helicobacter pylori* infection in pernicious anemia: A prospective controlled study. Gastroenterology 100:328–332, 1991
16. Glupczynski Y, Burette A: Failure of azythromycin to eradicate *Campylobacter pylori* from the stomach because of acquired resistance during treatment [letter]. Am J Gastroenterol 85:98–99, 1990
17. Glupczynski Y, Burette A, de Koster E, et al: Metronidazole resistance in *Helicobacter pylori* [letter]. Lancet 335:976–977, 1990
18. Glupczynski Y, Labbe M, Vanderlinden MP, et al: Lack of antibiotic compliance in patients treated for *Campylobacter pylori*–associated gastritis [letter]. Am J Gastroenterol 84:1125–1126, 1989
19. Goodwin CS, Marshall BJ, Blincow ED, et al: Prevention of nitroimidazole resistance in *Campylobacter pylori* by co-administration of colloidal bismuth subcitrate: Clinical and in vitro studies. J Clin Pathol 41:207–210, 1988
20. Gorbach SL: Bismuth therapy in gastrointestinal diseases. Gastroenterology 99:863–875, 1990
21. Graham DY, Klein PD, Opekun AR, et al: In vivo susceptibility of *Campylobacter pylori*. Am J Gastroenterol 84:233–238, 1989
22. Graham DY, Lew GM, Malaty HM, et al: Factors influencing the eradication of *Helicobacter pylori* with triple therapy. Gastroenterology 102:493–496, 1992
23. Graham DY, Malaty HM, Evans DG, et al: Epidemiology of *Helicobacter pylori* in an asymptomatic population in the United States: Effect of age, race, and socioeconomic status. Gastroenterology 100:1495–1501, 1991

24. Hardy DJ, Hanson CW, Hensey DM, et al: Susceptibility of *Campylobacter pylori* to macrolides and fluoroquinolones. J Antimicrob Chemother 22:631–636, 1988
25. Hazell SL, Evans DJ Jr, Graham DY: *Helicobacter pylori* catalase. J Gen Microbiol 137:57–61, 1991
26. Hosking SW, Ling T, Yung MY, et al: One week of therapy is sufficient to eradicate *Helicobacter pylori*—a randomized trial. Gastroenterology 102:A85, 1992
27. Katelaris P: Eradicating *Helicobacter pylori* [letter]. Lancet 1:54, 1992
28. Krajden S, Fuksa M, Anderson J, et al: Examination of human stomach biopsies, saliva, and dental plaque for *Campylobacter pylori*. J Clin Microbiol 27:1397–1398, 1989
29. Kucers A, Bennett NM: The Use of Antibiotics, ed 4. Philadelphia, JB Lippincott, 1987, pp 1249–1268
30. Lambert JR, McLean A: Pharmacology of colloidal bismuth subcitrate ("DeNol") and use in non-ulcer dyspepsia. *In* Marshall BJ, McCallum, Guerrant RL (eds): *Helicobacter pylori* in Peptic Ulceration and Gastritis; Boston, Blackwell, 1991, pp 201–209
31. Lamouliatte H, Bernard PH, Cayla R, et al: Controlled study of omeprazole-amoxicillin-tinidazole vs. ranitidine-amoxicillin-tinidazole in *Helicobacter pylori* associated duodenal ulcers (DU): Final and long-term results. Gastroenterology 102:A106, 1992
32. Lamouliatte H, Mégraud F, DeMascarel A, et al: Etude controlée de la josamycine dans les gastrites associées au *Campylobacter pylori* [abstract]. Gastroenterol Clin Biol 12:A156, 1988
33. Logan RP, Gummett PA, Misiewicz JJ, et al: One week eradication regimen for *Helicobacter pylori*. Lancet 338:1249–1252, 1991
34. Marshall BJ: The use of bismuth in gastroenterology: The ACG Committee on FDA-Related Matters: American College of Gastroenterology. Am J Gastroenterol 86:16–25, 1991
35. Marshall BJ, Surveyor I: Carbon-14 urea breath test for the diagnosis of *Campylobacter pylori* associated gastritis. J Nucl Med 29:11–16, 1988
36. Marshall BJ, Warren JR: Unidentified curved bacilli in the stomach of patients with gastritis and peptic ulceration. Lancet 1:1311–1315, 1984
37. Marshall BJ, Armstrong JA, Francis GJ, et al: Antibacterial action of bismuth in relation to *Campylobacter pyloridis* colonization and gastritis. Digestion 37:16–30, 1987
38. Marshall BJ, Barrett LJ, McCallum RW, et al: *C. pylori* therapy: Is in vitro disc testing with metronidazole worthwhile? [poster] Presented at the Vth International Workshop on Campylobacter Infections, Puerto Vallarta, Mexico, February 1989
39. Marshall BJ, Dye KR, Plankey M, et al: Eradication of *Campylobacter pylori* infection with bismuth subsalicylate and antibiotic combinations [abstract]. Am J Gastroenterology 83:1035, 1988
40. Marshall BJ, Goodwin CS, Warren JR, et al: A prospective double-blind trial of duodenal ulcer relapse after eradication of *Campylobacter pylori*. Lancet 2:1437–1442, 1988
41. Marshall BJ, Guerrant RL, Hoffman SR, et al: Eradication of metronidazole resistant *H. pylori* [abstract]. Am J Gastroenterol 86(9):100, 1991
42. Marshall BJ, Valenzuela JE, McCallum RW, et al: A placebo controlled clinical trial of bismuth subsalicylate for the treatment of *Helicobacter pylori*–associated gastritis [abstract]. Presented at the American Gastroenterological Association Meeting, 1989
43. Martin DF, Hollanders D, May SJ, et al: Difference in relapse rates of duodenal ulcer after healing with cimetidine or tripotassium dicitrato bismuthate. Lancet 1:7–10, 1981
44. McKinley AW, Milne K, Mowat NAG, et al: *H. pylori* eradication: Why do in vitro antibiotic sensitivity tests have poor predictive power? [abstract] Gut 33:S67, 1992
45. McNulty CA, Dent JC, Ford GA, et al: Inhibitory antimicrobial concentrations against *Campylobacter pylori* in gastric mucosa. J Antimicrob Chemother 22:729–738, 1988
46. McNulty CA, Gearty JC, Crump B, et al: *Campylobacter pyloridis* and associated gastritis: Investigator-blind, placebo-controlled trial of bismuth salicylate and erythromycin ethylsuccinate. Br Med J 293:645–649, 1986
47. Meshkinpour H, Thrupp LD, Shiffler P, et al: Reflux gastritis syndrome: Role of upper gastrointestinal microflora. Arch Surg 116:1148–1152, 1981
48. Morgan D, Kraft W, Bender M, et al: Nitrofurans in the treatment of gastritis associated with *Campylobacter pylori:* The Gastrointestinal Physiology Working Group

of Cayetano Heredia and The Johns Hopkins Universities. Gastroenterology 95:1178–1184, 1988
49. Neri M, Susi D, Bovani I, et al: Omeprazole bismuth and clarythromycin: A new approach to the treatment of *H. pylori* related gastritis. Gastroenterology 102:A134, 1992
50. Oderda G, Vaira D, Holton J, et al: Amoxycillin plus tinidazole for *Campylobacter pylori* gastritis in children: Assessment by serum IgG antibody, pepsinogen I, and gastrin levels. Lancet 1:690–692, 1989
51. Prewett EJ, Luk WY, Fraser AG, et al: Comparison of one-day oral dosing with three bismuth compounds for the suppression of *H. pylori* assessed by the ^{13}C-urea breath test. Alimentary Pharmacology and Therapeutics 6:97–102, 1992
52. Rauws EAJ, Langenberg W, Houthoff HJ, et al: *Campylobacter pyloridis*–associated chronic active antral gastritis: A prospective study of its prevalence and the effects of antibacterial and antiulcer treatment. Gastroenterology 94:229–238, 1988
53. Roos D, Weening RS, Wyss SR, et al: Protection of human neutrophils by endogenous catalase. J Clin Invest 65:1515–1522, 1980
54. Unge P, Gad A, Gnarpe H, et al: Does omeprazole improve antimicrobial therapy directed towards gastric *Campylobacter pylori* in patients with antral gastritis? A pilot study. Scand J Gastroenterol Suppl 167:49–54, 1989
55. Xiao SD, Liu WZ, Xia DH, et al: The efficacy of furazolidone and metronidazole in the treatment of chronic gastritis associated with *Helicobacter (Campylobacter) pylori*—a randomized double-blind placebo-controlled clinical trial. Hepatogastroenterology 37:503–506, 1990
56. Zheng ZT, Wang ZY, Chu YX, et al: Double-blind short-term trial of furazolidone in peptic ulcer [letter]. Lancet 1:1048–1049, 1985

Address reprint requests to

Barry J. Marshall, MD, MBBS, FRACP, FACG
Division of Gastroenterology
University of Virginia Health Sciences Center
Charlottesville, VA 22908