Treatment of *Helicobacter pylori* Infection

Julio A. Salcedo, MD; Firas Al-Kawas, MD

Since acceptance of the association between *Helicobacter pylori* and peptic ulcer disease, eradication of *H pylori* has become the standard of care in the treatment of peptic ulcer disease. Unfortunately, eradication therapy is no easy task, especially when one is faced with a myriad of drug combinations with varying degrees of efficacy and tolerability. The following is a review of the literature regarding the drugs and drug combinations used to eradicate *H pylori* and their effectiveness both as single agents and in combination.

Arch Intern Med. 1998;158:842-851

ERADICATION REGIMENS

Single Agents

Amoxicillin. *Helicobacter pylori* is very sensitive to amoxicillin both in vivo and in vitro. Unlike other penicillins, amoxicillin works by inhibition of bacterial cell wall synthesis, leading to cell death. Amoxicillin has topical intraluminal activity at the level of the gastric mucosa, as well as systemic activity. Unlike ampicillin, amoxicillin is actively secreted into the gastric juices from the blood stream. Despite being secreted into the gastric juice and mucosa during oral therapy, amoxicillin by itself achieves less than a 20% eradication rate of *H pylori*. More than 2 g a day of amoxicillin does not increase its eradication rate of *H pylori* when used as a single agent. However, when it is given in combination with omeprazole, the concentration of amoxicillin in the gastric juice and its eradication efficacy increase significantly. It is hypothesized that this eradication enhancement comes about by omeprazole decreasing gastric secretions, thus increasing the intragastric concentration of amoxicillin to more than the minimal inhibitory concentration (MIC) of *H pylori*, as well as decreasing the MIC of amoxicillin by increasing the gastric pH. The advantage of using amoxicillin is that *H pylori* does not develop resistance to it, and, therefore, it can be used again in another antibiotic regimen.
Tetracycline. Tetracycline has been used primarily in combination with other antibiotics for the eradication of *H pylori*. It is stable at a low pH and, like amoxicillin, has activity against *H pylori* as a topical agent, achieving concentrations in the gastric juice and mucosa much greater than the published MIC of *H pylori*. Used alone, tetracycline is unable to eradi cate *H pylori* infection; however, *H pylori* resistance has not been reported. This regimen cannot be used in children or pregnant women, because it causes permanent staining of developing teeth.

Metronidazole. Metronidazole is a nitroimidazole used primarily for the treatment of anaerobic and parasitic infections. In the past decade, it has become a mainstay in the treatment of *H pylori* infection. In Western countries where metronidazole use is very low, more than 70% of *H pylori* isolates are sensitive to metronidazole; however, *H pylori* eradication is rarely achieved when it is given as a single agent. In fact, in developing countries where metronidazole use is more common, there have been reports that more than 80% of *H pylori* isolates are metronidazole resistant. Therefore, metronidazole is always given in combination with 1 or more antibiotics. Metronidazole resistance is attributed to a mutation resulting in a strain of *H pylori* with defective nitroreductase. Metronidazole is stable at a low pH and is actively secreted into the gastric juice. Active secretion of metronidazole is diminished when it is given with a proton pump inhibitor. It has a half-life of 8 to 12 hours. The most common adverse effects of metronidazole are a metallic taste in the mouth, nausea, and epigastric discomfort. Metronidazole has been reported to produce a disulfiramlike reaction when taken in combination with alcohol.

Bismuth Salts. Bismuth salts have been used for medicinal purposes for more than 200 years. Bismuth acts topically and as an antimicrobial agent against *H pylori* by disrupting the organism’s cell wall. In addition, bismuth may also interfere with adhesion of *H pylori* to the gastric epithelium, as well as inhibiting the organism’s urease, phospholipase, and proteolytic activity. Frequent doses of bismuth are required since adequate antibacterial gastric mucosal concentrations only last for 2 hours. Bismuth is only available in the United States as bismuth subsalicylate (BSS; Pepto-Bismol [an upset stomach remedy]). Colloidal bismuth subcitrate (CBS; De-Nol [an upset stomach remedy]) is the other form of bismuth that is available in the rest of the world. According to Marshall and colleagues, BSS is less effective against *H pylori* than CBS when given as a single agent, having an approximately 10% eradication rate, compared with a 40% eradication rate with CBS. In combination with 1 or more antibiotics, the mean eradication rate rises dramatically, with rates greater than 80% when given in combination with 2 antibiotics.

Clarithromycin. Clarithromycin is a new generation macrolide antibiotic, which is acid stable and well absorbed from the gut. It has a longer half-life than erythromycin—3 to 4 hours for clarithromycin, compared with 1 to 2 hours for erythromycin. Its antibacterial activity is similar to that of erythromycin, but it is clearly more effective against *H pylori*. In addition, it is broken down in the liver to a hydroxylated compound that is also active against *H pylori*. Clarithromycin is unique in that as a single agent it by far has the best activity against *H pylori*, achieving between 40% to 60% eradication rates. Clarithromycin achieves the best eradication rate when given frequently and in larger doses. Unfortunately, as with metronidazole, when clarithromycin is given as monotherapy, resistance can develop. Clarithromycin can alter the taste sensation, producing a bitter metallic taste that results in noncompliance.

Azithromycin. Azithromycin is one of the newer orally administered macrolide antibiotics. Like clarithromycin, it too is acid stable. Azithromycin is well absorbed from the gastrointestinal tract and extensively distributed in tissues and reaches concentrations much greater than the MICs of common infectious pathogens. The elimination half-life of azithromycin increases with time after the dose, and with each subsequent dose the elimination half-life increases. After an initial oral dose of 1000 mg, followed by 500 mg/d for 5 days, the elimination half-life has been reported to be 57 hours. Azithromycin has excellent in vitro activity against *H pylori*. It is not effective as a single agent because of acquired resistance. However, when it is used in combination with other antibiotics, improved eradication rates are achieved.

Ranitidine Bismuth. Ranitidine bismuth citrate (RBC) is a bismuth compound with histamine2-receptor–antagonist (H2RA) activity formed by the reaction of ranitidine with bismuth citrate and is precipitated as an amorphous compound. The agent has been developed for the treatment of patients with duodenal ulcer with or without infection with *H pylori*. The agent is freely soluble in water, whereas an equimolar admixture of ranitidine and bismuth citrate forms an almost insoluble suspension. Even at a pH of 2, the solubility of RBC is still 2-fold better than the admixture. The RBC has antipepsin activity and enhanced antibacterial activity against *H pylori* that is not observed with the admixture of ranitidine and bismuth citrate. It is hypothesized that the greater solubility of RBC is what confers these added properties. When given alone, RBC has been shown to suppress *H pylori*. This effect is enhanced by taking RBC with food rather than on an empty stomach. As a single agent, however, RBC achieves a 20% eradication rate. A combination of RBC with clarithromycin has resulted in eradication rates in the range of 72% to 80%, comparable to those of triple antibiotic therapy.

Dual Antibiotic Therapy

Bismuth Plus 1 Antibiotic. The eradication rate of CBS and amoxicillin is dependent on both the total daily dose of amoxicillin and how frequently it is given.
tion rate after 28 days of this dual therapy increased from 33% in one study to 70% in another, when the dose of amoxicillin was increased from 500 mg twice a day to 500 mg 4 times a day. The eradication rates of CBS plus metronidazole have been variable with no consistent trend to suggest that more frequent or larger doses of metronidazole are required to improve eradication efficacy. Results with BSS and another antibiotic have been disappointing, requiring several weeks of therapy to achieve eradication rates slightly greater than 50%. A meta-analysis by Chiba et al dem-

strates that the mean eradication rate for dual therapy composed of bismuth plus another antibiotic, primarily amoxicillin or metronidazole, is approximately 50%. Because of its variable results, as well as low rate of eradication, bismuth plus a single antibiotic is not considered adequate therapy for eradication.

Amoxicillin Plus a Proton Pump Inhibitor. Axon reviewed several studies examining the eradication of H pylori using either omeprazole or lansoprazole with amoxicillin and found the results to be variable. Early studies, primarily from Germany, reported eradication rates of 80% to 85% with omeprazole (20 mg twice a day) and at least 1 g of amoxicillin twice a day. However, these results have not been replicated in similar trials. A meta-analysis by Chiba et al showed that, independent of the dose given or duration of therapy of omeprazole and amoxicillin, the overall eradication rate using this dual therapy is approximately 60%. Some trials have suggested that giving a total daily dose of 40 mg or more of omeprazole in divided doses or larger doses of amoxicillin, usually more than 2 g/d for at least 2 weeks, enhance the efficacy of the amoxicillin-omeprazole combination. This was not the case in a recent study by Malaty et al, where only a 34.9% eradication rate was observed in H pylori–infected patients who were treated with a 14-day course of a large dose of a proton pump inhibitor (either omeprazole [40 mg twice daily] or lansoprazole [60 mg twice daily]) and amoxicillin [750 mg twice daily]). Omeprazole pretreatment prior to the addition of amoxicillin has been demonstrated to reduce the efficacy of this combination significantly. Because the efficacy data of this combination are so variable, amoxicillin combined with a proton pump inhibitor is no longer considered an adequate first choice for eradication.

Clarithromycin Plus a Proton Pump Inhibitor. Recently, the Food and Drug Administration has approved the marketing of clarithromycin and omeprazole for concurrent use in the treatment of duodenal ulcers associated with H pylori. In the study by Logan et al, 2 weeks of clarithromycin (500 mg 3 times a day) plus omeprazole (40 mg/d) followed by 2 additional weeks of omeprazole achieved an eradication rate of 83%. In 2 US studies using the same regimen, the eradication rates were lower, 74% and 64%. Chiba demonstrated that reducing the dose of clarithromycin to 250 mg twice a day in this regimen lowers the eradication rate (62.1%). Studies that used a lower dose of omeprazole, usually less than 40 mg/d, also had lower eradication rates. Comparable results have been described with lansoprazole and clarithromycin. An eradication rate of 72.4% was attained with lansoprazole (30 mg twice a day) and clarithromycin (400 mg twice a day) administered for 2 weeks; however, when a lower dose of lansoprazole (30 mg/d) was used with the same dose of clarithromycin, the eradication rate declined to 50%. The effectiveness of this dual regimen is dependent on the dose of the proton pump inhibitor and clarithromycin. Although frequent adverse effects have been reported with this dual therapy (approximately 45%), in general, this regimen has been well tolerated with most of the adverse reactions being mild. Taste perversion is the most common complaint, and this is likely related to the clarithromycin. In the US studies mentioned above, 3.5% of the patients enrolled discontinued the regimen because of adverse events. Both omeprazole and lansoprazole directly inhibit the growth of H pylori in vitro; therefore, using larger doses may possibly result in better eradication rates. In addition, a beneficial pharmacokinetic drug interaction exists between omeprazole and clarithromycin where the area under the curve for both drugs’ clearance is increased when the 2 drugs are given concomitantly. This also results in higher concentrations of clarithromycin in the gastric mucosa and gastric mucus. These pharmacokinetic interactions probably enhance the antisecretory effects of omeprazole as well as the antibacterial effect of clarithromycin, explaining in part why this combination is more effective when given together.

Clarithromycin Plus RBC. This combination was recently approved by the Food and Drug Administration. As mentioned earlier, the combination of RBC with clarithromycin has been shown to be effective in eradicating H pylori infection. In a multicenter randomized, double-blind, placebo-controlled trial of 205 patients with an active duodenal ulcer, the group treated with RBC (400 mg twice a day) for 4 weeks and clarithromycin (500 mg 3 times a day) during the first 2 weeks of therapy was associated with an 82% eradication rate at 4 weeks. Only 36% of the group that received clarithromycin alone cleared their infection. These findings are consistent with previous studies using similar doses and duration of treatment. The number of patients that left the study because of adverse reactions was similar between the treatment and placebo groups.

Triple Antibiotic Therapy

Bismuth Triple Therapies. The early regimens used to eradicate H pylori used bismuth as the cornerstone of triple therapy. The most effective treatments consisted of bismuth plus 2 antibiotics—usually metronidazole and tetracycline or metronidazole and amoxicillin. Pooled data have demonstrated that those bismuth-based regimens using tetracycline instead of amoxicillin in combination with metronidazole are more efficacious with a mean eradi-
cation rate of 87%, compared with 72%. Recently, Tefera et al80 conducted a study using a triple therapy consisting of bismuth subcitrate (150 mg 4 times a day), oxytetracycline (500 mg 4 times a day), and metronidazole (400 mg 3 times a day) for 10 days. This regimen resulted in an eradication rate of 91%. In the arm of the study that used metronidazole placebo, the eradication rate dropped to 9%. This implies that the efficacy of this regimen is highly dependent on metronidazole. Another recent trial81 demonstrated a similar eradication rate with a comparable regimen of bismuth, metronidazole, and tetracycline. Fifty-five infected patients received a 14-day course of tetracycline (250 mg), metronidazole (250 mg), and CBS (120 mg), 4 times a day. This regimen yielded a 96.3% eradication rate, which is consistent with previous studies. Of the 55 patients, 8 had H pylori isolates that were metronidazole resistant. Seven of these 8 patients were tested for treatment efficacy, and all but 1 had cleared their infection using this triple antibiotic regimen. The implication is that this regimen is still quite effective for patients with metronidazole-resistant strains of H pylori, and this has been shown to be the case in several other trials.82 Another trial83 used a large dose of the same antibiotic combination (bismuth subcitrate [120 mg], tetracycline [500 mg], and metronidazole [400 mg] 4 times a day) in 55 patients with duodenal ulcer and H pylori infection. Treatment was for only a week. An eradication rate of 83.7% was achieved; however, compliance was fair to poor in 45% of the patients enrolled. The most common adverse effects reported were nausea, dizziness, malaise, metallic taste, and anorexia. Six of the 55 patients enrolled could not complete the study because of the adverse effects of this combination. Therefore, despite an acceptable rate of eradication, the higher doses of tetracycline and metronidazole in this regimen make it difficult to tolerate.

Because of metronidazole-resistant strains of H pylori, investigators have substituted either clarithromycin or azithromycin for metronidazole in the standard bismuth-based triple therapies in an effort to overcome this problem. Al-Assi et al84 studied the combination of clarithromycin (500 mg 3 times a day), tetracycline (500 mg 4 times a day), and BSS (2 tablets [151 mg per tablet] 4 times a day) in 30 infected patients. The combination was administered for 14 days. At 4 weeks, 93% of the patients were cured of their infection, including 3 patients who had previously failed therapy containing metronidazole. This combination is very effective against H pylori and may be an alternative treatment in those patients who are infected with metronidazole-resistant isolates.

As mentioned, azithromycin is a new macrolide antibiotic that is very active against H pylori and achieves excellent tissue penetration with a long half-life. In one study,85 30 patients with H pylori infection were treated with 1 of 2 regimens: 2 tablets of BSS (each tablet contained 151 mg of bismuth) 4 times a day, tetracycline hydrochloride (500 mg 4 times a day), and either azithromycin (250 mg twice a day in one group [18 patients] or 250 mg 3 times a day in the other [12 patients]) for 2 weeks. The overall eradication rate in both groups was 50%. The group receiving azithromycin 3 times a day (750 mg/d) achieved a significantly higher eradication rate of 83%; however, two thirds of this group also experienced frequent and troublesome adverse effects, which included diarrhea (most common), stomatitis, dysgeusia, and facial and tongue swelling. Despite a comparable eradication rate to other effective bismuth-based triple therapies, this triple therapy is limited because its efficacy relies on high doses of azithromycin, which produce much too high a rate of adverse effects to make this regimen practical.

Another trial86 studied the combination of azithromycin, metronidazole, and bismuth. Fifty-six patients infected with H pylori received bismuth subcitrate (120 mg 4 times a day for 14 days) along with azithromycin (500 mg daily for the first 3 days) and metronidazole (250 mg 4 times a day for the first 7 days). The eradication rate for this regimen was 58.9%. Only 3 patients in this group experienced an adverse event; however, all were able to complete treatment. Although the adverse-effect profile improved by decreasing the dose and frequency of azithromycin administration, the eradication rate was significantly lowered, making this regimen impractical.

Most studies regarding bismuth-based triple therapy have been conducted using CBS, but more recent trials suggest that BSS can achieve similar eradication rates in the same combinations.87 To date, the bismuth-based triple therapies are the most effective and least costly treatments for the eradication of H pylori, because they have high cure rates even in those patients infected with metronidazole-resistant strains. Unfortunately, compliance is poor with these regimens because of the large number of tablets and frequent adverse effects. Adverse effects are seen in approximately 30% of patients and include diarrhea, dizziness, headache, nausea, paraesthesia, and a disulfiram-like reaction when metronidazole and alcohol are taken concurrently.88 Compliance is the single most important factor that affects the eradication rate of this regimen. Graham et al89 demonstrated that for those patients who took less than 60% of bismuth-based triple therapy the eradication rate dropped from 96% to 69%. Still, the search for therapies that are more effective than bismuth-based regimens is ongoing.

Proton Pump Inhibitors as a Component of Triple Therapy. In an attempt to find more tolerable triple drug regimens, proton pump inhibitors have been studied in combination with 2 other antibiotics. The most studied has been omeprazole in combination with either metronidazole and amoxicillin or metronidazole and clarithromycin. Both regimens possess eradication rates greater than 85%.84 In a recent randomized controlled trial86 of 183 patients with an active duodenal ulcer and histologically proven H pylori gastric infection, omeprazole (20 mg/d for 4 weeks) plus amoxicillin (1 g 3 times a day) and metronidazole (250 mg 4 times a day) during the second and third week was associated with a 90%
eradication rate. Another trial treating 22 patients using the same combination (omeprazole [40 mg/d], amoxicillin [500 mg 3 times a day], and metronidazole [250 mg 4 times a day]) for 2 weeks achieved a similar eradication rate of 86.4%. More recently, in a randomized trial, 31 patients were treated with a 1-week course of this omeprazole-antibiotic combination. After receiving omeprazole (20 mg twice a day), amoxicillin (1 g twice a day), and metronidazole (500 mg twice a day), only 79% of the infected patients had cleared their infection 4 to 6 weeks after completing treatment. This implies that perhaps it is necessary to treat patients with this regimen longer to achieve a higher eradication rate.

A smaller study evaluated the efficacy of triple therapy using metronidazole, omeprazole, and clarithromycin. Thirty-three patients with documented *H pylori* infection received omeprazole (20 mg twice a day), clarithromycin (250 mg twice a day), and metronidazole (500 mg twice a day) for 2 weeks. *Helicobacter pylori* was eradicated in 88% of the patients. Moreover, 90% (18/20) of those patients who had failed prior eradication therapy achieved a cure with this regimen. A similar eradication rate (93.3%) was achieved in another trial using the same 2-week regimen of metronidazole, omeprazole, and clarithromycin in 30 patients. This regimen has also been shown to retain its efficacy when given for only a week. In an international multicenter, double-blind randomized placebo-controlled trial, 105 of 111 patients receiving a 7-day course of omeprazole (20 mg twice a day), metronidazole (400 mg twice a day), and clarithromycin (250 mg twice a day) cleared their infection (95%) as proven by carbon 13–urea breath test 4 weeks after the completion of treatment.

In this same study, the combination of omeprazole (20 mg twice a day), clarithromycin (500 mg twice a day), and amoxicillin (1000 mg twice a day) for 7 days was also shown to be effective in 106 of 110 patients, with a 96% eradication rate. However, when the dose of clarithromycin was decreased to 250 mg twice a day, the eradication rate decreased to 84%, suggesting that the efficacy of this combination is dependent on the dose of clarithromycin. Additionally, the efficacy of this therapy is also dependent on the length of time that it is given. In a small randomized trial, patients received omeprazole (20 mg twice daily), clarithromycin (500 mg twice daily), and amoxicillin (1 g twice daily) for 7, 10, or 14 days. The rate of cure was greater in the group who received 10 or more days of treatment (eradication rate of 88% after 10 days and 100% after 14 days). Lansoprazole, another proton pump inhibitor, has been shown to be just as effective as omeprazole in triple antibiotic therapy. In a multicenter trial conducted in the United Kingdom and Ireland, patients with either duodenal ulcer or gastritis and *H pylori* infection were randomized to 1 of 4 1-week regimens: lansoprazole (30 mg twice a day) plus clarithromycin (250 mg twice a day) with either amoxicillin (1 g) or metronidazole (400 mg) twice daily or amoxicillin (1 g) plus metronidazole (400 mg twice a day) with either lansoprazole (30 mg) or omeprazole (20 mg) twice a day. The combination of lansoprazole, amoxicillin, and clarithromycin and lansoprazole, clarithromycin, and metronidazole had eradication rates of 89.7% and 90.4%, respectively. The eradication rates of the lansoprazole, amoxicillin, and metronidazole and omeprazole, amoxicillin, and metronidazole therapies were 72.5% and 81.7%, respectively. Therefore, lansoprazole when used in combination with clarithromycin and either amoxicillin or metronidazole for 1 week is still as effective as omeprazole in the same combination, retaining a 90% eradication rate.

**Histamine-2-Receptor Antagonists in Triple Antibiotic Therapy.** Histamine-2-receptor antagonists (H2RAs) have been used in combination with 2 antibiotics for the eradication of *H pylori* with good success. Hentschel et al. in a randomized, double-blind trial, achieved an 89% eradication rate using metronidazole, amoxicillin, and ranitidine for 12 days, followed by 30 additional days of ranitidine. A similar rate of eradication (86%) was achieved in patients with peptic ulcer disease with a 10-day regimen of ranitidine (600 mg before bedtime [which was continued for a total of 6 weeks to ensure ulcer healing]), amoxicillin (750 mg 3 times a day), and clarithromycin (500 mg 3 times a day).

The addition of ranitidine enhances the eradication rate of dual antibiotic therapy. In a randomized, double-blind, multicenter trial, 156 patients were randomized to either metronidazole (250 mg 3 times a day) and tetracycline (500 mg 4 times a day) with either ranitidine (150 mg 4 times a day) or placebo. Eradication in the group receiving ranitidine was significantly enhanced with an eradication rate of 66.7%, compared with 36% in those receiving placebo. The minimal dose of ranitidine required in combination with dual antibiotics to achieve maximal eradication efficacy has been shown to be at least 600 mg/d.

A recent meta-analysis by Holtmann et al suggests that eradication of *H pylori* with H2RAs in combination with antibiotics is similar to proton pump inhibitor combinations. In a study by Powell et al, 2 weeks of ranitidine (300 mg/d) combined with metronidazole (400 mg 3 times a day) and amoxicillin (500 mg 3 times a day), compared with the same antibiotic regimen using omeprazole (40 mg/d) instead of ranitidine, was similar in efficacy in eradicating metronidazole-sensitive *H pylori* strains (96% vs 98%). However, in those patients with metronidazole-resistant isolates, the omeprazole-containing regimen was superior to the ranitidine combination (76% vs 50%). Thus, omeprazole has an advantage over ranitidine with respect to antibiotic resistance. This may be omeprazole’s intrinsic antibacterial activity against *H pylori*, which ranitidine and other H2RAs do not possess.

**Quadruple Antibiotic Therapy**

Quadruple antibiotic therapies have consisted of traditional bismuth-based triple therapy with the addition of an antisecretory agent, either an H2RA or a proton pump
inhibitor, to achieve close to complete eradication. These regimens have consistently achieved high eradication rates. In a randomized placebo-controlled trial, 108 consecutive patients with peptic ulcer disease and biopsy-proven H. pylori infection were randomized to 7 days of triple therapy with or without omeprazole (20 mg twice a day) or placebo. Triple antibiotic therapy consisted of CBS (120 mg 4 times a day), tetracycline hydrochloride (500 mg 4 times a day), and metronidazole (500 mg 3 times a day). Ninety-eight percent of patients (53/54 patients) treated with omeprazole had their infection eradicated, compared with 83.3% (45/54 patients) who did not receive omeprazole (P = .02). Addition of omeprazole to this traditional triple therapy enhanced its efficacy.

In another trial, 72 addition of either omeprazole or famotidine to triple antibiotic therapy was studied to see if the efficacy of triple antibiotic therapy could be improved. This prospective, randomized study enrolled patients with symptoms of dyspepsia and confirmed H. pylori infection. Patients received a 12-day course of CBS chewable tablets (108 mg) 4 times a day, tetracycline (250 mg 4 times a day), and metronidazole (200 mg 4 times a day) in addition to either omeprazole (20 mg twice daily) or famotidine (40 mg at bedtime). One-hundred twenty two of the 125 (97.6%) patients who completed the study achieved eradication whereas only 110 of 124 (89%) of those patients who were receiving famotidine had cleared their infection. The pretreatment prevalence of metronidazole-resistant strains was greater in the group receiving omeprazole (24%), compared with the group receiving famotidine (21%). Again, addition of a proton pump inhibitor resulted in enhanced eradication efficacy despite a greater prevalence of metronidazole-resistant isolates.

**ANTIBIOTIC RESISTANCE**

Antibiotic resistance with regard to H. pylori eradication has become a growing problem both here in the United States and in developing countries. In some countries, the prevalence of metronidazole-resistant strains approaches 70% and is associated with prior exposure to metronidazole. Some of the most effective regimens against H. pylori include metronidazole; however, there have been reports that their efficacy is diminished when isolates are metronidazole resistant. Several research groups have demonstrated a 30% to 60% reduction in the eradication rate of standard bismuth-based triple therapy when given to individuals with metronidazole-resistant strains compared with patients with metronidazole-sensitive organisms. Yet others have found no reduction in eradication rates using standard bismuth-based triple therapy in areas where the prevalence of metronidazole-resistant strains are between 20% and 40%. This conflict has prompted researchers to find regimens that can be used reliably against metronidazole-resistant strains. Recent studies have demonstrated that triple drug regimens that contain both metronidazole and clarithromycin are able to maintain their efficacy against H. pylori despite metronidazole resistance. In a randomized multicenter trial of 230 patients with H. pylori infection, 1 of the 3 following 10-day regimens was administered: (1) omeprazole (20 mg), metronidazole (400 mg), and clarithromycin (250 mg) twice daily; (2) omeprazole (20 mg), amoxicillin (750 mg), and metronidazole (400 mg) twice daily; or (3) bismuth subcitrate (240 mg), clarithromycin (250 mg), and metronidazole (400 mg) twice a day. The eradication rates for the metronidazole-omeprazole-amoxicillin, metronidazole-omeprazole-clarithromycin, and bismuth subcitrate-clarithromycin-metronidazole groups were 95%, 91%, and 95%, respectively, with no statistical difference among the groups. Metronidazole resistance was found in 29% of the patients. None of the isolates were resistant to clarithromycin. When those patients with the metronidazole-resistant isolates were analyzed separately, eradication rate for the metronidazole-omeprazole-amoxicillin group was 77% (17/22 patients), compared with 100% (23/23 patients) for the bismuth subcitrate-clarithromycin-metronidazole group and 94% (17/18 patients) for the metronidazole-omeprazole-clarithromycin group.

Similar results were obtained in a randomized controlled trial using omeprazole (20 mg), metronidazole (400 mg), and clarithromycin (250 mg) twice daily for 1 week. Of the 64 patients enrolled, only 59 had successful culture and antibiotic sensitivity testing of their H. pylori infection. Twenty-five patients (42%) were found to have H. pylori isolates that were metronidazole resistant, including 1 patient whose isolate was also clarithromycin resistant. Still, 61 (95%) of 64 patients achieved successful eradication of their infection. The 3 patients who failed therapy all had isolates that were resistant to metronidazole, including the patient who had the isolate that was clarithromycin resistant. Again, these 2 studies demonstrate that, in those patients with only metronidazole-resistant isolates, triple therapy with metronidazole, clarithromycin, and omeprazole is still effective eradication therapy.

Although clarithromycin is one of the newer agents used in the eradication of H. pylori, resistant strains are emerging. Compared with metronidazole resistance, clarithromycin resistance is of relatively low prevalence here in the United States (approximately 4%); however, in Belgium and France, where macrolide use is high, the prevalence is close to 10%. Unfortunately, a study by Cayla has shown that exposure to clarithromycin without successful eradication of H. pylori results in a clarithromycin-resistant strain in approximately two thirds of eradication failures. Therefore, with greater use of clarithromycin in regimens to eradicate H. pylori, there is a high likelihood that the prevalence of resistant strains will continue to increase. This supports the view that clarithromycin-containing regimens should be avoided in those patients with prior exposure to the drug. For patients who have failed treatment...
with clarithromycin-containing regimens, effective alternative antibiotic combinations should be given.

**TREATMENT RECOMMENDATIONS**

Choosing a single regimen from the myriad of regimens offered in the literature can be a bewildering experience; however, after careful analysis of the data, these can be narrowed to a select few. The **Figure** outlines the algorithm we use for patients identified with a peptic ulcer and concurrent infection with *H pylori*. The **Table** lists the most effective regimens found in the literature. Based on the data reviewed, our first choice of treatment for eradication would be the metronidazole-omeprazole-clarithromycin regimen (omeprazole [20 mg], clarithromycin [500 mg], and metronidazole [500 mg] twice a day) for at least 7 to 10 days. As mentioned earlier, several studies have demonstrated that this regimen carries an eradication rate of 90% or more and is well tolerated by most patients, resulting in good patient compliance. In addition, preliminary data seem to indicate that metronidazole resistance does not appear to reduce the efficacy of this regimen, suggesting that it can still be used in areas where metronidazole resistance is frequent; however, studies to directly address this issue still need to be conducted.

Where eradication therapy becomes difficult is in those patients who fail initial treatment with metronidazole omeprazole clarithromycin. At this stage, we suggest that these patients receive the highly effective bismuth-based triple therapy (bismuth-metronidazole-amoxicillin or bismuth-metronidazole-tetracycline) plus a proton pump inhibitor for at least 2 weeks. These regimens consistently achieve eradication rates greater than 95%; however, compliance is diminished because of the number of pills required and the associated adverse effects. We feel patients with *H pylori* infection who develop recurrent ulcers, have symptoms or bleeding, and have failed initial *H pylori* eradication therapy would be more inclined to comply with treatment, especially if the clinician stresses the importance of completing therapy and its impact on long-term outcome.

Subsequent eradication failures become more difficult to manage. At this point, the clinician should attempt to culture the organism and obtain antibiotic sensitivities. This is not commonly done and requires a laboratory that specializes in *H pylori* antibiotic sensitivity testing. Once this information is in hand, an appropriate regimen with at least an 80% eradication rate can be tried.

**CONCLUSIONS**

It is clear that eradication of *H pylori* is important in ulcer disease; however, the confusion comes with which regimen to choose. From our review of the literature on eradication, it has become clear that 7- to 14-day regimens containing a proton pump inhibitor in combination with metronidazole and clarithromycin are highly efficacious and well tolerated. Unfortunately, as more and more patients receive eradication therapy, antibiotic resistance will become a growing problem, especially as the prevalence of clarithromycin resistance increases. As a result, antibiotic sensitivity testing will play a greater role in the future of eradication therapy. Still, there are presently very effective regimens against *H pylori*; however, the search for improved treatments requiring fewer pills and shorter courses continues.

**Accepted for publication September 11, 1997.**

Reprints: Firas Al-Kawas, MD, Department of Gastroenterology,
Most Effective Regimens for the Eradication of *Helicobacter pylori*

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Dose</th>
<th>Duration of Course</th>
<th>Eradication Rate, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ranitidine bismuth citrate*3</td>
<td>Ranitidine bismuth citrate, 400 mg twice daily; and clarithromycin, 500 mg 3 times daily</td>
<td>Ranitidine bismuth citrate, 4 wk; and clarithromycin, 2 wk</td>
<td>82</td>
</tr>
<tr>
<td>Omeprazole and clarithromycin*3-40</td>
<td>Omeprazole, 40 mg daily; and clarithromycin, 500 mg 3 times daily</td>
<td>Omeprazole, 4 wk; and clarithromycin, 2 wk</td>
<td>64-83</td>
</tr>
<tr>
<td>Lansoprazole and clarithromycin*5</td>
<td>Lansoprazole, 30 mg twice daily; and clarithromycin, 400 mg twice daily</td>
<td></td>
<td>72.4</td>
</tr>
</tbody>
</table>

**Bismuth-Based Triple Therapy**

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Dose</th>
<th>Duration of Course</th>
<th>Eradication Rate, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bismuth, metronidazole, and tetracycline (BMT)*3</td>
<td>Colloidal bismuth subcitrate, 120 mg 4 times daily; metronidazole, 250 mg 4 times daily; and tetracycline, 250 mg 4 times daily</td>
<td>14 d</td>
<td>96.3</td>
</tr>
<tr>
<td>Bismuth, metronidazole, and tetracycline (BMT)*3</td>
<td>Colloidal bismuth subcitrate, 120 mg 4 times daily; metronidazole, 250 mg 4 times daily; and tetracycline, 500 mg 4 times daily</td>
<td>7 d</td>
<td>83.7</td>
</tr>
<tr>
<td>Bismuth, metronidazole, and amoxicillin (BMA)*3</td>
<td>Bismuth subsalicylate, 302 mg 4 times daily**; metronidazole, 500 mg 3 times daily; and amoxicillin, 500 mg 3 times daily</td>
<td>14 d</td>
<td>84</td>
</tr>
<tr>
<td>Bismuth, clarithromycin, and tetracycline (BCT)*3</td>
<td>Bismuth subsalicylate, 302 mg 4 times daily**; clarithromycin, 500 mg 3 times daily; and tetracycline, 500 mg 4 times daily</td>
<td>14 d</td>
<td>93</td>
</tr>
</tbody>
</table>

**Quadruple Therapy**

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Dose</th>
<th>Duration of Course</th>
<th>Eradication Rate, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bismuth, tetracycline, metronidazole, and omeprazole*3</td>
<td>Colloidal bismuth subcitrate, 120 mg 4 times daily**; tetracycline, 500 mg 4 times daily; metronidazole, 500 mg 3 times daily; and omeprazole, 20 mg twice daily</td>
<td>7 d</td>
<td>98</td>
</tr>
<tr>
<td>Bismuth, tetracycline, metronidazole, and omeprazole*5</td>
<td>Colloidal bismuth subcitrate, 108 mg 4 times daily**; tetracycline, 250 mg 4 times daily; metronidazole, 200 mg 4 times daily; and omeprazole, 20 mg twice daily</td>
<td>12 d</td>
<td>97.6</td>
</tr>
</tbody>
</table>

* Bismuth subsalicylate available in 151-mg tablets as Pepto Bismol. Dose is 2 tablets. Colloidal bismuth subcitrate is available as De-Nol outside the United States. The dose is as chewable tablets.

**REFERENCES**

9. Bell GD, Powell KU, Burridge SM, et al. Short report: omeprazole plus antibiotic combinations for the eradication of *Campylobacter pyloridis*-resistant *Helico-


