

Sequential Therapy for *Helicobacter pylori* Time to Consider Making the Switch?

Nimish Vakil, MD

Dino Vaira, MD

HELICOBACTER PYLORI INFECTION REMAINS AN IMPORTANT cause of morbidity and mortality worldwide. Attempts at developing a vaccine have failed, and the current focus for clinicians is the treatment of the infection. Eradication of *H pylori* has been shown to prevent recurrent peptic ulcer disease, to cure some localized gastric mucosa-associated lymphoid tissue lymphomas, and to prevent nonsteroidal anti-inflammatory drug (NSAID)-related ulcers in patients who are initiating long-term NSAID therapy.¹ In recent years, the rate of treatment failure associated with established drug regimens has increased at a rapid rate.²

Antibiotic Delivery and Antimicrobial Resistance

Helicobacter pylori is uniquely adapted to life in the stomach. Its location in the gastric mucus, where it does not invade the gastric epithelium, provides the organism with protection from the host immune mechanisms and results in several challenges for delivery of antimicrobial agents to eradicate *H pylori* infection. For example, clarithromycin, a key component of many treatment regimens used to eradicate *H pylori*, is particularly sensitive to degradation in an acidic environment and has a half-life of less than 1 hour in the stomach if the pH level is 2 or lower.² The gastric mucus layer acts as a mechanical barrier that limits the delivery of antimicrobials, and gastric emptying limits retention of the antibiotics in the stomach.²

A multistate monitoring program in the United States reported that clarithromycin resistance was present in 10% to 12% of patients infected with *H pylori* and that metronidazole resistance was present in 25.1% during the period from 1999 through 2002.³ Culture and antimicrobial sensitivity testing of *H pylori* is not widely available and, when it is available, may not translate into clinical benefit. For example, although *H pylori* is highly susceptible to ampicillin in vitro, this drug is ineffective in vivo. In contrast, amoxicillin is effective in vivo and the organism rarely develops amoxicillin resistance despite widespread use of this drug for other infections. In vitro susceptibility testing does reliably predict if clarithromycin-based treatments will fail but

is less likely to predict if a metronidazole-containing regimen will fail.²

Treatment Strategies for *H pylori* Infection

Currently Used Treatments. The most widely used treatment for *H pylori* in the United States and Europe, referred to as proton pump inhibitor (PPI) triple therapy, is a 7- to 10-day course of a PPI plus clarithromycin and amoxicillin (BOX).^{1,4} Recent studies have shown high treatment failure rates with triple therapy. In a large US randomized trial, the eradication rate with 10-day PPI triple therapy was 78% (95% confidence interval [CI], 72%-84%).⁵ Attempts to increase the duration of therapy and therefore prolong exposure to antibiotics have not resulted in measurable benefit.⁶

A less frequently used regimen is quadruple therapy, consisting of bismuth plus metronidazole, tetracycline, and a PPI administered for 10 days. It has been suggested as an alternative to PPI triple therapy. The most recent US study of quadruple therapy, performed in 1999 and published in 2003, used a single-capsule preparation containing bismuth, tetracycline, and metronidazole. The *H pylori* eradication rate was 87.7% (n=138; 95% CI, 82.2%-93.2%) and the results were not significantly different from the eradication rate with PPI triple therapy.⁷ With changes in resistance rates, these data may not be valid almost a decade later.

Sequential Therapy. Sequential therapy is a novel approach for *H pylori* treatment and consists of 10 days of treatment with a PPI, plus amoxicillin for the first 5 days and a combination of clarithromycin and tinidazole for the second 5 days (Box).⁸ Sequential therapy is based on observations made when 2-drug therapies (PPI plus amoxicillin) were the standard of care for treating *H pylori*.⁹ The combination of PPI and amoxicillin led to many treatment failures and the eradication rate achieved with a therapeutic strategy of initially administering 14-day dual therapy (PPI plus amoxicillin) followed by 7-day triple therapy in individuals in whom the original therapy failed was significantly greater than the reverse sequence (7-day triple therapy as an initial strategy with 14-day dual therapy for failures).⁹ In a study involving 300 patients with *H pylori* infection who were randomized to sequential therapy or triple therapy, the

Author Affiliations: University of Wisconsin School of Medicine and Public Health, Madison (Dr Vakil); and University of Bologna, Bologna, Italy (Dr Vaira).

Corresponding Author: Nimish Vakil, MD, Aurora Medical Center, 945 N 12th St, Room 4040, Milwaukee, WI 53233 (nvakil@wisc.edu).

Box. Treatment Regimens for *Helicobacter pylori*

Proton pump inhibitor (PPI) triple therapy: PPI (standard dose twice daily) + amoxicillin (1 g twice daily) + clarithromycin (500 mg twice daily) for 7 to 10 days

Quadruple therapy: PPI (standard dose twice daily) + metronidazole (500 mg 3 times daily) + tetracycline (500 mg 3 times daily) + bismuth (dose depends on preparation) for 10 days

Sequential therapy: PPI (standard dose twice daily) + amoxicillin (1 g twice daily) for 5 days followed by PPI (standard dose twice daily) + clarithromycin (500 mg twice daily) + tinidazole (500 mg twice daily) for 5 days

Levofloxacin triple therapy: PPI (standard dose twice daily) + amoxicillin (1 g twice daily) + levofloxacin (500 mg twice daily) for 10 days

Rifabutin triple therapy: PPI (standard dose twice daily) + amoxicillin (1 g twice daily) + rifabutin (150-300 mg daily) for 10 days

eradication rate with the sequential regimen was statistically significantly greater than with the standard treatment regimen for the intention-to-treat analysis: 89% (95% CI, 83.6%-93.7%) vs 77% (95% CI, 70.6%-84.0%; $P = .01$).¹⁰ A series of randomized controlled trials from Italy have shown that eradication rates are high with this approach.⁸ A recent meta-analysis of 10 trials found an eradication rate of 93.4% (95% CI, 91.3%-95.5%) with sequential therapy compared with an eradication rate of 76.9% (95% CI, 71%-82.8%) with PPI triple therapy, despite publication bias.¹¹

Preliminary data from open-label studies in Spain¹² ($n = 139$; eradication rate, 84.2%; 95% CI, 77%-90%) and Taiwan¹³ ($n = 129$; eradication rate, 89% [95% CI not provided]) appear to confirm the results of previous studies.⁸⁻¹⁰ A noteworthy finding is that the sequential therapy regimen appears to be effective in patients with documented clarithromycin resistance. In the largest trial reported to date ($n = 300$), the eradication rate was 89% in patients with *H pylori* infection that was resistant to clarithromycin who were treated with sequential therapy ($n = 9$) compared with 29% among those treated with triple therapy ($n = 21$).¹⁰ Adverse effects were comparable with the 2 treatment regimens (17% in both), and the cost of the new treatment regimen was lower than triple therapy because clarithromycin was used for a shorter period and the other antimicrobials are available as generics.¹⁰ The complexity of the sequential therapy regimen is a potential disadvantage, but adherence in clinical trials and routine clinical practice was comparable with triple therapy.^{10,12}

Other Treatment Strategies. Two other antimicrobials have been suggested as potential agents for treatment of *H pylori* infections when initial therapy fails (salvage strat-

egies). These are levofloxacin and rifabutin. Levofloxacin has been used in triple therapy (in combination with a PPI and amoxicillin) as a salvage regimen when conventional therapy fails.¹⁴ Resistance develops rapidly, however, and recent reports suggest that resistance rates may already be high, limiting the potential use of levofloxacin as a front-line treatment.² Rifabutin has a role as a salvage agent among patients in whom eradication therapy with other regimens has failed and who have multidrug-resistant strains.¹⁵

Conclusion

Traditional therapies for *H pylori* infection are failing as resistant strains of *H pylori* become more prevalent. Sequential therapy is a novel treatment approach that deserves consideration as a treatment strategy for *H pylori* infection.

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