Sequential Therapy for *Helicobacter pylori*: A Worthwhile Effort for Your Patients

Sequential therapy for *Helicobacter pylori* refers to the idea of adding more antibiotics to the treatment regimen but giving them in sequence rather than giving all 4 drugs together. Typically, this involves an initial 5-day therapy with a benign combination (for example, pantoprazole, 40 mg, with amoxicillin, 1 g, twice daily) followed by 5 days of 2 further antibiotics plus a proton-pump inhibitor (PPI) (for example, clarithromycin, 500 mg, and tinidazole, 500 mg, plus pantoprazole, 40 mg, twice daily), as shown below:

	Pantoprazole (40 mg twice daily) + amoxicillin (1 g twice daily)				
Day	1	2	3	4	5

	Pantoprazole (40 mg twice daily) + clarithromycin (500 mg twice daily) + tinidazole (500 mg twice daily)				
Day	6	7	8	9	10

In a large, prospective, controlled study in 2007, Vaira and colleagues (1) showed a 90% cure rate for this "new" treatment versus 80% for the "old." In this issue, Jafri and colleagues (2) perform a meta-analysis of clinical trials of sequential therapy. This review convincingly confirms the efficacy of sequential therapy. There are several reasons why this therapeutic strategy makes sense.

First, after a decade of clarithromycin-based treatments and continued widespread use of long-acting macrolides in general practice, 10% to 15% of *H. pylori* strains are resistant de novo to clarithromycin (3). As a result, the failure rate is around 20% for triple combination therapy (PPI plus amoxicillin plus clarithromycin), which was so effective when it was first evaluated 10 years ago (4, 5). Because persistent *H. pylori* in patients with ulcer can cause continuing ulcer complications, a failure rate of 20% also means that everyone needs follow-up proof of cure. In addition, the 20% of patients with persistent *H. pylori* warrant repeated attempts at eradication with ever-decreasing success.

Second, staggering the treatment with multiple antibiotics does not increase side effects but still eradicates almost all *H. pylori* isolates, the exceptions being doubly resistant isolates. Thus, sequential therapy combines the initial and the repeated therapy in 1 treatment sequence, for the same cost and with the same side effect profile as those of the present standard therapy.

Third, adherence to a complicated treatment is better the first time it is given, when patients are likely to be well-motivated. It is disappointing for the clinician and the patient when they have adhered to therapy but the post-treatment urea breath test result is still positive.

The how and why of sequential therapy are based on nearly 20 years of experience treating *H. pylori*. In the stomach, the bacterium occupies several very different microenvironments. Deep in the antral glands, with acid far away in the lumen, pH is probably in the 6 to 8 range. In the corpus of the stomach, however, acid-secreting glands nearby are likely to keep the pH far lower so that the bacterium must rely on urea hydrolysis to generate ammonia and maintain a viable internal environment pH of around 5.5. Thus, antibiotic therapy must attend to a slow-growing organism (less susceptible to penicillin) that dwells both in a low-pH environment on the surface and at a neutral pH deep in the glands. In addition, some *H. pylori* might even persist within epithelial cells. A single antibiotic will not penetrate all these locations, and in vitro sensitivity results notoriously fail to predict in vivo outcomes.

Allowing that the goal of modern therapy is to cure at least 80% of patients at the first attempt, the first breakthrough came with triple therapy consisting of bismuth plus tetracycline plus metronidazole given for 14 days (6, 7). The addition of an H_2-blocker or a PPI in recent years has boosted this regimen and is still widely used in the United States. The pharmacokinetics of these complicated multiagent therapies are poorly understood, except that the bismuth and tetracycline may chelate and act directly in the mucus layer rather than by diffusion of drug through the mucosa from the bloodstream. Of interest, the metronidazole in this combination still often overcomes the antibiotic resistance present in around 30% of *H. pylori* isolates. Cure rates for this first "bismuth triple therapy" remain around 80%, and the therapy continues to have an advantage for patients with penicillin allergy.

The next major breakthrough came from the recognition that PPIs, initially omeprazole, could increase the effectiveness of amoxicillin. By rendering the gastric pH neutral, PPIs stripped the *H. pylori* of its protection, allowing in vitro susceptibility to amoxicillin to predict its in vivo efficacy. Cure rates with 2 drugs only (such as PPI and amoxicillin) ranged from 50% to 80% depending on how thoroughly gastric acid was suppressed. The lesson for PPIs in this role was that "more is better." By adding clarithromycin, an acid-stable macrolide with a long half-life and an inherent cure rate of 40% when given as a single agent, cure rates of 80% to 90% were achieved in 7 to 14 days (8). However, these success rates were performed on a low background of clarithromycin resistance, typically 3% to 6%. Nowadays, most Western countries see macrolide re-

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sistance in 10% to 15% of *H. pylori* isolates and higher failure rates as a result.

In sequential therapy, the first 5 days of amoxicillin and PPI no doubt results in an 8- to 10-log reduction of *H. pylori* and even its eradication in at least 50% of patients. At this stage, the second part of the regimen (clarithromycin and tinidazole) acts to eradicate a rather small residual population of viable organisms. The weakness of clarithromycin is that random mutations in the *H. pylori* 23S ribosome gene can prevent binding of the antibiotic so that it is no longer effective. Through reduction of the *H. pylori* population before it is exposed to clarithromycin, such mutations are statistically much less likely. Similarly, nitroimidazoles become ineffective when a random mutation inactivates the *rdxA* gene so that the antibiotic is no longer metabolized to its bacteria-toxic form (5). Once again, low numbers of bacteria minimize the probability of a mutation. By combining 2 dissimilar agents (that is, clarithromycin and tinidazole), high cure rates are possible.

Finally, let's consider duration of therapy. Many studies have evaluated treatment duration varying upward from 3 days. In brief, 3 days is too short for *H. pylori*, 5 days is the minimum, 7 days is difficult to beat, 10 days is about optimal for patient adherence and cure rate, and treatment never needs to exceed 14 days. Therefore, the sequential therapy of 5 days plus 5 days seems a wise choice, with good clinical data to back it up. My only concern is that patients who miss a dose or 2 during days 5 to 6 could escape suppression, so I ask them to take the PPI–amoxicillin combination for 1 extra day, allowing 12 to 24 hours when all 4 components are on board.

How should one implement this regimen when all these drugs are generic? Because the sequential therapy seems so cost-effective, prescribers could make up special individual patient packs to enhance adherence. Sequential treatment may initially take some extra physician time, but it will be well-invested because fewer patients need second and third attempts.

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