

## Improving *Helicobacter pylori* Eradication Regimens

**H***elicobacter pylori* colonization has known costs to humans, including increased risk for peptic ulcer disease (1), gastric adenocarcinoma (2), and gastric lymphoma (3). The finding that elimination of *H. pylori* changes the natural history of peptic ulcer disease (4) and gastric mucosa-associated lymphoid tissue lymphoma (5) has led to the development of successful strategies to clear the organism from persons with these disorders. Over the past 20 years, regimens that use acid-suppressing agents in conjunction with several antibiotics (in particular, clarithromycin [6]) have been highly successful for *H. pylori* eradication (7). However, recent reports detail decreasing efficacy of these combination therapies (8). Why is this happening, and what can be done to improve therapies to eradicate *H. pylori*?

Some of the decrease in treatment efficacy has been due to increasing resistance of *H. pylori* to clarithromycin (9). This trend, now being observed in many industrialized countries, partly reflects the growing use of second-generation macrolides, which has increased 388% in the United States from 1992 to 2000 (10) and has probably been increasing since. Even a short course of clarithromycin selects for resistance within the persistent, indigenous microbiota, including *Enterococcus* and *Staphylococcus* species, in which resistant organisms may persist for years in the intestinal tract or in the skin, respectively, without any further selective pressure (11). The persistence of resistant bacteria is an important but largely overlooked consequence of antibiotic use. The same phenomenon seems to affect *H. pylori* (12). To address the problem of diminished efficacy of *H. pylori* eradication regimens, Zullo and colleagues (13) recently evaluated a sequential course of treatment that consisted of 5 days of therapy with a proton-pump inhibitor and amoxicillin followed by 5 days of the proton-pump inhibitor with clarithromycin and tinidazole (a nitroimidazole similar to metronidazole). The authors reported higher eradication rates with the sequential regimen than with the standard regimen (13).

In this issue, De Francesco and colleagues (14) extend Zullo and colleagues' study by reporting a post hoc analysis of 156 individuals selected consecutively from 377 *H. pylori*-positive participants of a larger Italian multicenter randomized eradication trial. The subgroup consisted of 75 patients randomly assigned to standard therapy (7-day therapy with rabeprazole, clarithromycin, and amoxicillin twice daily) and 81 patients randomly assigned to sequential therapy (rabeprazole and amoxicillin twice daily for the first 5 days followed by rabeprazole, clarithromycin, and tinidazole twice daily for the next 5 days). The authors wanted to elucidate the effect of 3 different point mutations (A2142C, A2142G, and A2143G) encoding clarithromycin resistance on eradication rates and to evaluate the efficacy of sequential and standard therapy in patients

with these mutations (14). Using a validated, real-time polymerase chain reaction method to detect point mutations, the authors found that the prevalence of pretreatment clarithromycin resistance was 24% in their cohort, similar in magnitude to that of another recent study (15). They report the novel finding that persons with *H. pylori* 23S ribosomal RNA genotype A2143G have lower eradication rates than those with strains mutated at position 2142 (45% vs. 93%). The study also showed that sequential therapy was superior to standard therapy in eradicating both susceptible and resistant *H. pylori* strains.

The limiting factors for De Francesco and colleagues' study include the post hoc design, small sample size, restrictions on multivariate analyses, and lack of in vitro results with which to correlate genotypes. Nevertheless, the apparent superiority of sequential therapy in treating both susceptible and resistant strains of *H. pylori* is an important observation that must be confirmed in larger and better controlled studies. The reasons that sequential therapy performs better than standard therapy remain speculative. Currently, these questions remain to be clarified by other studies, and we turn to a pressing clinical question.

Noninvasive testing for *H. pylori* and, if results are positive, treatment has been recommended as the initial approach to patients younger than 45 years of age who present with persistent dyspepsia, who are not receiving nonsteroidal anti-inflammatory drugs, and who do not have reflux or alarm symptoms (weight loss, bleeding, anemia, or dysphagia), since the risk for gastric cancer in this age group is low (16). How can we use the data currently in hand to think about this strategy, which some U.S. and European guidelines recommend? We discuss 3 perspectives.

First, the supporting evidence for eradication of *H. pylori* is strongest for peptic ulcer disease and for gastric mucosa-associated lymphoid tissue lymphoma. The actual benefit of eradication in the setting described in the guidelines is questionable, given a less than 10% symptom improvement rate at 3 to 12 months after treatment (17). Therefore, many patients who are "tested and treated" are unnecessarily exposed to antibiotics.

Second, every antibiotic exposure selects for resistance, not only among the high-grade pathogens, such as *S. pneumoniae* (18), which is bad enough, but also the "silent majority," the persistent indigenous microbiota, including *H. pylori* (19). On the basis of current antimicrobial agent-prescribing trends, macrolide resistance will continue to grow as a clinical problem that will limit therapeutic options for physicians and patients, since clarithromycin is part of recommended first-line *H. pylori* eradication regimens. This observation highlights the importance of having a treatment option, such as sequential therapy, that may overcome the adverse effect of resistance on treatment

success. Assuming that future studies confirm the superiority of sequential therapy in treating both susceptible and resistant strains of *H. pylori*, its use in the clinical setting will depend on the background rate of clarithromycin resistance in the population that is being treated, anticipated cure rate with the standard “triple therapy” regimen in practice, and costs associated with re-treatment.

Finally, is performing antimicrobial susceptibility testing in the usual candidate for *H. pylori* eradication useful? The preliminary results of sequential therapy suggest that most patients can be cured, regardless of genotype. Which agents would be effective in the patient whose initial anti-*H. pylori* therapy fails? One recommendation for second-line treatment is quadruple therapy with a proton-pump inhibitor, colloidal bismuth subcitrate, metronidazole, and tetracycline (16). Routine pretreatment genotyping or susceptibility testing, although not currently recommended, may be useful for individuals whose second-line treatment has failed since it may help direct the selection of an appropriate rescue regimen. In particular, one must consider the therapeutic approach to individuals with the A2143G mutation whose attempts at eradication have failed, since this group is less likely to respond to sequential therapy.

In summary, given the current trends in antibiotic resistance, De Francesco and colleagues' (14) results of the enhanced efficacy of sequential therapy is a timely advance for patients with peptic ulcer disease or mucosa-associated lymphoid tissue lymphoma, in whom *H. pylori* eradication is clearly indicated. A larger question, not addressed by the study, is whether the relatively indiscriminate practice of “test and treat” for *H. pylori* treats the patient or the physician. In their zeal to remedy many ailments with antibiotics, including those in which antibiotics are no more effective than placebo (20), physicians are contributing to new problems of antibiotic resistance and to changing human microecology.

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