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PERSPECTIVES IN CLINICAL GASTROENTEROLOGY AND HEPATOLOGY

Rational *Helicobacter pylori* Therapy: Evidence-Based Medicine Rather Than Medicine-Based Evidence

David Y. Graham,[*] Yi–Chia Lee,[‡] and Ming–Shiang Wu[‡]

[*]Department of Medicine, Michael E. DeBakey VA Medical Center, and Baylor College of Medicine, Houston, Texas;
[‡]Department of Internal Medicine, College of Medicine, National Taiwan University, Taipei, Taiwan

This article has an accompanying continuing medical education activity on page e13. Learning Objective—At the end of this activity, the successful learner will be able to reliably interpret the available data regarding therapies for *H pylori* infection, to be able to identify the regimen(s) suitable for empiric use in a region, as well as how modify those choices to identify the regimen for a specific patient that has the greatest chance of achieving a cure.

Data are available such that choice of *Helicobacter pylori* therapy for an individual patient can be reliably predicted. Here, treatment success is defined as a cure rate of 90% or greater. Treatment outcome in a population or a patient can be calculated based on the effectiveness of a regimen for infections with susceptible and with resistant strains coupled with the knowledge of the prevalence of resistance (ie, based on formal measurement, clinical experience, or both). We provide the formula for predicting outcome and we illustrate the calculations. Because clarithromycin-containing triple therapy and 10-day sequential therapy are now only effective in special populations, they are considered obsolete; neither should continue to be used as empiric therapies (ie, 7- and 14-day triple therapies fail when clarithromycin resistance exceeds 5% and 15%, respectively, and 10-day sequential therapy fails when metronidazole resistance exceeds 20%). Therapy should be individualized based on prior history and whether the patient is in a high-risk group for resistance. The preferred choices for Western countries are 14-day concomitant therapy, 14-day bismuth quadruple therapy, and 14-day hybrid sequential-concomitant therapy. We also provide details regarding the successful use of fluoroquinolone-, rifabutin-, and furazolidone-containing therapies. Finally, we provide recommendations for the efficient development (ie, identification and optimization) of new regimens, as well as how to prevent or minimize failures. The trial-and-error approach for identifying and testing regimens frequently resulted in poor treatment success. The described approach allows outcome to be predicted and should simplify treatment and drug development.

Keywords: Helicobacter pylori; Treatment; Quadruple Therapy; Review; Treatment Success; Concomitant Therapy; Sequential Therapy; Bismuth; Clarithromycin; Tetracycline; Metronidazole; Amoxicillin; Proton Pump Inhibitors; Evidence Based.

Similar to other infectious diseases, the factors responsible for effective antimicrobial therapy of a *Helicobacter pylori* infection as well as those responsible for treatment failure are both straightforward and easily discoverable. Poorly designed or executed regimens rarely produce good results. Treatment success depends on the details of the regimen including choice of drugs, doses, formulations, duration of therapy, administration in relation to meals, number of administrations/day, the use of adjuvants such as antisecretory drugs or mucolytics, and so forth.[1] Results can be defined in terms of treatment success.[2,3] For exploratory studies the primary outcome generally is expressed per protocol (PP), which controls for compliance and other variables and thus provides an indication of the potential maximum success of the regimen in clinical practice.[1] For the information to be useful and to be used to predict success in other groups, regions, and populations, the results also should be provided as the outcomes with both susceptible and resistant strains (see later). In addition, the data also should be expressed as both modified intention to treat (MITT) (which is the outcome of all who received a dose and for whom an outcome measure is available), and as intention to treat (ITT), in which those lost to follow-up evaluation typically are scored as treatment failures. ITT and MITT provide estimates of a regimen's actual success in clinical practice. PP and MITT are the most useful for the development of new regimens, whereas for large multicenter randomized comparisons most authorities prefer ITT.[4]

Considering that *H pylori* is a common infectious disease and 100% success is obtainable, outcome (eg, PP or ITT) also is scored in terms of efficacy (ie, as excellent, good, borderline acceptable, or unacceptable) because efficacy is the most important measure for patient care. For evaluating new therapies we score success (PP with susceptible strains) as excellent ($\geq$95% success), good ($\geq$90 success), borderline acceptable (85%–89% success), or unacceptable ($<$85% success). The most common causes for reliably good or excellent regimens to fail

Abbreviations used in this paper: ITT, intention to treat; MITT, modified intention to treat; PP, per protocol; PPI, proton pump inhibitor.

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are the presence of organisms resistant to one or more of the antimicrobials used, poor compliance with therapy, or both. A number of studies have suggested a variety of miscellaneous factors that might be important including age, presentation (eg, nonulcer dyspepsia vs duodenal ulcer), and CagA status.[5–7] However, these candidates typically have been discovered in data-dredging studies in which resistance was not assessed, and most of the studies lacked biologic plausibility. Although some of these factors (eg, nonulcer dyspepsia vs duodenal ulcer) have proven to be surrogates for differences in the prevalence of resistant strains,[8,9] none of the clinical correlates other than resistance and compliance has proven to be important in studies in which compliance and resistance have been assessed.

Therapy Choice

Similar to other infectious diseases, treatment results are best when reliably excellent regimens are used to treat patients with organisms susceptible to the antimicrobials chosen. Pretreatment susceptibility testing, either by culture of the organism or indirectly by molecular testing of stools of infected patients or fluorescent in-situ hybridization using paraffin-embedded gastric biopsy specimens, allows one to select a regimen tailored by antimicrobial susceptibility (ie, tailored therapy).[3] However, in many instances, one must choose therapy empirically and, in this instance, the best approach is to use regimens that have been proven to be reliably excellent locally.[2] That choice should take advantage of knowledge of resistance patterns obtained from local or regional antimicrobial surveillance programs and/or based on local clinical experience with regard to which regimens are effective locally. Finally, the history of the patient's prior antibiotic use and any prior therapies will help identify which antibiotics are likely to be successful and those for which resistance is probable (Figure 1).

All other things being equal, data from any area or region regarding the effects of resistance on outcome can be used reliably to predict outcome in any other area. Thus, strains with similar patterns of resistance in Italy, the United States, Iran, China, and so forth should be expected to respond alike such that, if one knows the results with susceptible and with resistant strains in one place, one reasonably can predict the outcome of therapy anywhere.

Using Available Data to Predict Treatment Success

An optimized regimen is defined as one that reliably achieves 95% or greater cures in patients with susceptible organisms. Although the effectiveness of any regimen can be undermined by antimicrobial resistance, the effect of resistance is not random and the effect of any particular level of resistance can be estimated based on studies with that combination elsewhere, for example, use of the

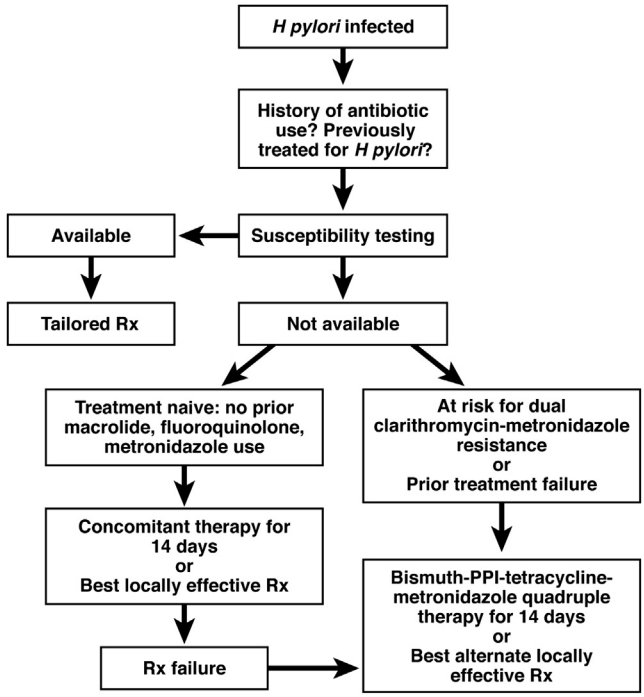

Figure 1. Recommended approach to treatment of *H pylori* infections. Rx, treatment.

optimized regimen (14-day concomitant therapy, consisting of a proton pump inhibitor [PPI], clarithromycin, metronidazole, and amoxicillin, given twice a day for 14 days).[10] The regimen contains 4 drugs, but for the purpose of understanding the effects of resistance can best be considered as the simultaneous administration of 2 triple therapies plus a dual therapy (eg, a PPI–amoxicillin-clarithromycin plus a PPI–amoxicillin-metronidazole plus a PPI-amoxicillin dual therapy). Both triple regimens individually will reliably achieve 95% or greater success PP with susceptible strains whereas the dual component will achieve approximately 50% success with clarithromycin- and metronidazole-resistant strains (ie, the strains are only susceptible to amoxicillin). If resistance to clarithromycin or metronidazole was not present, there would be no indication to use the 4-drug regimen. However, when resistance results in unacceptably low treatment success rates when either is used empirically, the 4-drug combination might be considered.

Unless there is an interaction between the antibiotics, the treatment population can be visualized as 4 separate subgroups: one group with organisms susceptible to all antibiotics, one group with only clarithromycin-resistant organisms, another group with only metronidazole-resistant organisms, and the final group with organisms resistant to both (here, we assume an absence of resistance to amoxicillin). The subgroups without resistance and those resistant to a single drug will each receive an optimized triple therapy for their infection and most will be cured, and the overall success thus will depend entirely on the success of the PPI-amoxicillin therapy for those with dual clarithromycin-metronidazole resistance.