# The Toronto *Helicobacter pylori* Consensus in Context

Guideline development uses a formal series of steps that are time, resource, and labor intensive to produce recommendations that are likely to be trustworthy.[1] The authors of the Toronto Consensus for the Treatment of *Helicobacter pylori*, published in this issue of *Gastroenterology*,[2] followed such a rigorous process for producing their recommendations. Lack of important stakeholders (eg, primary care, infectious disease) on the panel was a shortcoming. In addition, systematic reviews were restricted to studies published from 2008 onward. Although the restriction was used to avoid relying on older eradication data when resistance rates may have been lower, studies providing useful information on achievable eradication rates with different *H pylori* regimens may have been missed and a formal assessment of change in outcomes over time could not be done. Nevertheless, the process produced recommendations that should impact practice.

The consensus panel made strong recommendations that first-line therapy should be a 14-day course of quadruple therapy—either traditional bismuth-containing therapy or non–bismuth-containing "concomitant" therapy. The panel also strongly recommended that proton pump inhibitor triple therapy, currently the most widely used regimen, should not be used unless physicians know that the clarithromycin resistance is <15% or the eradication rate is >85% in their local population. They cite the increase in clarithromycin resistance and the dramatically lower eradication rates with triple therapy in patients with clarithromycin-resistant vs clarithromycin-susceptible strains as reasons to restrict triple therapy. The consensus panel also strongly recommended that the choice of first-line therapy consider local antibiotic resistance patterns and eradication rates, citing a systematic review revealing eradication rates with susceptibility-based therapy of 90%–95% by intention-to-treat analysis and 97%–98% by per-protocol analysis in 4 of the 5 component studies—significantly higher than eradication rates with triple therapy and no susceptibility testing.[3]

The last 2 recommendations lead to a conundrum for clinicians. Unlike most infectious diseases, culture, and susceptibility testing for *H pylori* is rarely performed in standard practice and reliable recent data about susceptibility are generally not available. This may be due to several factors, including that gastroenterologists rather than infectious disease physicians "own" *H pylori* and concerns about the time and the difficulty required for *H pylori* culture versus other standard bacterial cultures. Given the very limited data on current resistance rates for many parts of the world, including individual populations in the United States, physicians often have little local information to guide their choice of therapy other than their anecdotal experience with current therapies.

## Toronto *H pylori* Consensus Recommendations in Context

Considered as an infectious disease, *H pylori* is conceptually easy to treat. Treatment success requires (1) use of antimicrobials to which the organism is susceptible; (2) use of antimicrobials that reach all the niches occupied by the organism; (3) depending on the antimicrobial, adjuvants to increase the pH so that the antimicrobial becomes more effective and so that resting organisms divide; and (4) established details of the regimen, including drugs, doses, formulations, frequency of administration, administration in relation to meals, and duration of therapy. The most common causes of treatment failure are antibiotic resistance and lack of patient adherence to the regimen. Because not only do *H pylori* strains vary, but so too do the humans receiving treatment (eg, CYP2C19 polymorphisms, allergies, medication-induced symptoms, antibiotic history), the optimal regimen for an individual or population may also vary in relation to drugs and doses of drugs used.

*H pylori* may be the only common disease that gastroenterologists treat with medications for which there is no placebo response. For infectious diseases, studies designed to confirm that a new therapy achieves a prespecified threshold of success (eg, ≥95%) do not require a comparator.[4] Comparative studies are done as noninferiority trials to ensure that new regimens are not worse than the best current regimen.[4]

Infectious disease therapy is fundamentally susceptibility based. Population eradication rates may vary widely depending on resistance rates in the study populations. The lack of susceptibility data in published *H pylori* "trial and error" treatment studies provides population mean results that reflect the sum of treatment success with susceptible infections plus the treatment success with resistant infections.[4] Figure 1 illustrates how the eradication rates of a specific regimen such as triple therapy vary widely across different populations based on underlying antibiotic susceptibility, despite no change in efficacy in eradicating susceptible and resistant *H pylori* strains. Given an expected 95% eradication rate for individuals with susceptible strains and 15% with resistant strains, the population eradication rate changes markedly across populations based solely on the proportion with resistant strains: from 95% with no resistance to 75% with a 25% resistance rate to 55% with a 50% resistance rate (Figure 1).

Thus, comparison of a treatment regimen across studies is problematic and eradication rates likely represent differences in the resistant rates of the population studied rather than differences in the underlying efficacy of a regimen. Aggregating studies as required in meta-analyses may not be

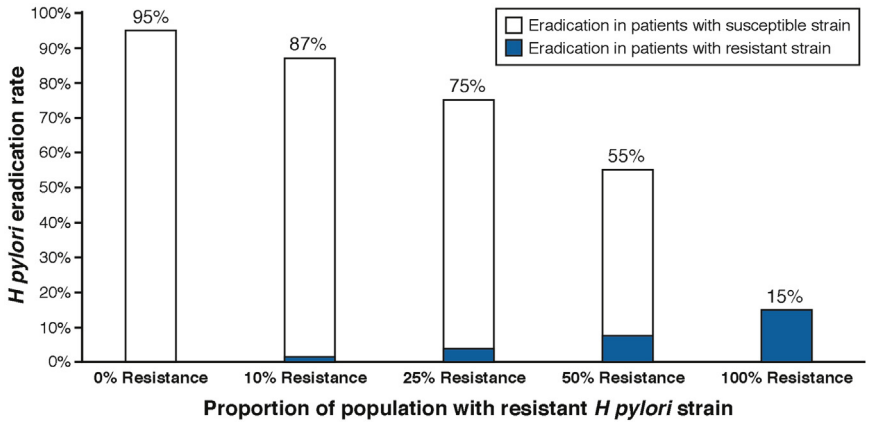


**Figure 1.** *Helicobacter pylori* eradication rates with proton pump inhibitor triple therapy in populations with varying proportions of clarithromycin resistance. Based on a theoretical population where the cure rate is 95% with susceptible infections and 15% with resistant infections.

useful in determining the efficacy of the regimen itself. Rather, pooled estimates of eradication rates and the precision around the estimates vary greatly based on the variation in resistance rates in the component studies of the meta-analysis. If marked variation in resistance rates exists across component studies, heterogeneity in study results potentially may be so great that aggregating the data to provide a pooled estimate is of questionable utility. For example, using data in Figure 1, if one-half of the component studies in a meta-analysis of triple therapy had near zero clarithromycin resistance (eradication rate of 95%) and one-half the component studies had around 50% resistance (eradication rate of 55%), the pooled eradication rate of 75% would provide limited guidance in choosing an *H pylori* therapy.

There are now sufficient data regarding treatment outcomes in relation to susceptibility that one can predict the eradication rate of a therapy based on susceptibility data.[4,5] The details are well-described in the recent literature, which also includes the formulas, a web site, and a decision model and sensitivity analysis based on the effectiveness in relation to antibiotic susceptibility.[5–7] A number of different regimens when prescribed to patients with susceptible infections will reliably achieve near 100% cure rates among those who adhere to the regimen.[8] The susceptibility-based approach helps to explain why treatments succeed and fail and has been reported to be cost saving.[9] Given high rates of antibiotic-resistant strains in children, susceptibility-based therapy has also been suggested in the pediatric population.[10,11]

The 14-day regimens of concomitant and bismuth quadruple therapy recommended by the Toronto Consensus are appropriate as empiric therapies in the absence of information on susceptibility testing. It is important to note that use of 4-drug non-bismuth quadruple therapies promotes overprescribing of antibiotics because those with susceptible strains receive an antibiotic that is not required to achieve eradication. For example, if only 20% of patients who receive concomitant therapy have clarithromycin resistance, then 80% will receive metronidazole unnecessarily. Figure 2 is an example of how using susceptibility to guide therapy could reduce or eliminate the need to prescribe unnecessary antimicrobials.

The reason for success with concomitant therapy is that it is undermined only by dual metronidazole-clarithromycin resistance, which occurs in <5% of treatment-naïve patients in the United States.[8,12] Bismuth quadruple therapy also performs well as an empiric therapy because in vitro metronidazole resistance does not appear to markedly reduce efficacy, at least when given for 14 days with ≥1500 mg of metronidazole.[5,13–16] In addition, resistance to tetracycline, the other antibiotic in bismuth quadruple therapy, is <1% in most of the world.[14,15] However, the details of the optimum bismuth regimen remain unclear. For example, is bismuth twice a day equivalent to 4 times daily? Is tetracycline twice a day equivalent to 4 times daily? Is 800 mg of metronidazole twice daily equal to 400 mg 4 times daily? Is metronidazole resistance actually overcome or is the benefit owing to bismuth killing the remaining metronidazole-resistant organisms? Finally, tetracycline is unavailable currently in many countries, and agents such as doxycycline cannot substitute effectively. Tetracycline is available in a combination product of bismuth, tetracycline, and metronidazole (PYLERA, Aptalis Pharma US, Birmingham, AL), although this product is approved and packaged for only 10-day therapy and is expensive (approximately $600 for 14 days).

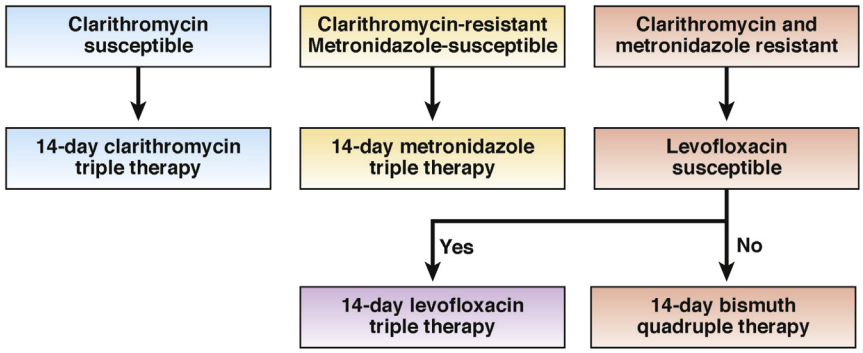


**Figure 2.** Example of one possible set of recommendations for susceptibility-based first-line *Helicobacter pylori* therapy. This example is based on the premises that it is preferable to minimize the use of unnecessary antibiotics and that proton pump inhibitors, amoxicillin, and third drug triple therapies are usually better tolerated than bismuth quadruple therapy.