

***Helicobacter pylori's* resistance to antibiotics**

Alberto Rodríguez Varón, MD.¹

¹ Tenured Professor of Internal Medicine and Gastroenterology, Pontificia Universidad Javeriana, Bogotá, Colombia.

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The effectiveness of eradication treatments against *Helicobacter pylori* (*H. pylori*) has been decreasing in recent years. This is not only our perception drawn from unquantified clinic experience, but rather is something we encounter more and more in the results studies which have alerted us to the fact that the standard triple therapy (STT) traditionally used to eradicate *H. pylori* has lower rates of success than it originally had. Its success rate is now lower than the 80% rate recommended by the Maastricht Consensus Report as the minimum acceptable number for usage as a first-line therapy (1-7).

The main factors involved in the effectiveness of an eradication treatment are local resistance to antibiotics and acceptance of the treatment. For several years the average level of resistance to metronidazole has been 30% to 40% with even higher resistance rates in Latin American countries such as Colombia. Although different methods of measuring resistance may explain the diverse numbers reported among our studies, all of them are over what is found in other populations and are higher than the maximum tolerated limit. For this reason the various treatment guides in Colombia have not included metronidazole in the recommended scheme for eradication of *H. pylori* for several years (8-9).

The traditional triple scheme recommended and used by our team, includes a proton pump inhibitor (PPI) combined with amoxicillin and clarithromycin. With this scheme, we used to obtain eradication numbers higher than 90%. Nevertheless, in the recent years we have consistently found information showing that the eradication rate obtained had decreased to between 70% and 80%. Because of these numbers it has become unacceptable to continue using this method systemically (1, 3, 5, 6).

If we consider that the difficulties of accepting this triple scheme do not seem to have changed in recent years and that resistance to amoxicillin is below 1%, and that the resistance to clarithromycin has increased to over 20% according the latest reports, and that, in some populations including Colombia's, the real resistance rate may be even higher (9, 10), then this fact could be the main factor specifically affecting the effectiveness of the triple scheme.

Progressive diminution of the effectiveness of STT has motivated the evaluation of new alternative methods which include the bismuth tetra-conjugate scheme, the use of quinolones like levofloxacin to replace clarithromycin, and sequential therapy.

Studies comparing tetra-conjugate scheme (PPI+ Bismuth+ Metronidazole+ Tetracycline) with STT have found significantly higher eradication rates for the tetra-conjugate scheme than for STT (93.3% versus 69.6%), even though the tetra-conjugate

scheme had traditionally been considered a second-line treatment. These results draw attention not only to the performance of the tetra-conjugate, but also to the low rates of eradication achieved with STT. Although the tetra schemes may have lower acceptance, it is important to mention that this difference in eradication rates remains analysis by intention to treat (79.8% versus 55.4%) (11, 12).

Since triple schemes in which clarithromycin is replaced with levofloxacin show an approximately 80% total eradication rate (81% by protocol and 77% by intention to treat), they also can be considered as ideal alternatives (13).

Sequential therapy has been used as an alternative to triple therapy primarily to diminish the impact of resistance to clarithromycin. The pharmacological basis of sequential therapy proposes that during the first 5 days of treatment amoxicillin debilitates the bacterial cell wall. This prevents the formation of channels which block the entrance of clarithromycin and induce resistance to the antibiotic. Studies in which sequential therapy and triple therapy have been compared show higher eradication rates for sequential therapy which have been sustained even after clarithromycin was replaced with other antibiotics such as levofloxacin. With its initial good results for eradication, sequential therapy was expected to become more popular. Nevertheless this has not been so evident due to difficulties in acceptance of the treatment given the greater complexity of the scheme. On the other hand, increasing resistance to clarithromycin and its association with metronidazole could give rise to resistance in the second phase of the scheme. Recent studies have shown that the effectiveness of sequential therapy has been decreasing in recent years from the levels of over 90% reported in the initial Italian studies (14-16).

Following what has been adapted as standard practice, in this issue of the magazine an article evaluates the local effectiveness of eradication treatments against *Helicobacter pylori*. Titled "Comparison of Sequential Therapy for Eradication of *Helicobacter Pylori* with Standard Triple Therapy," the authors of the article performed a randomized clinical study to compare the obtain rates of eradication from these two schemes. They found that both therapies have similar effectiveness in terms of intention to treat: 63.75% for ST and 62% for STT. The important and troubling result is that both schemes have eradication rates below the minimum acceptable rate for consideration as suitable schemes for eradication of *H. pylori*. Although this work does not determine the causes of these results, if we take into consideration bias due to patients dropping out of the study related to acceptance of the treatment and the fact that secondary effects were

similar in both groups, we might infer that resistance to antibiotics is possibly an important factor in these results.

The discouraging clinical results of this study are consistent with studies of other populations and constitute an additional element of local experience. They add to previous Colombian publications which have shown the resistance of *H. pylori* to antibiotics. This is an important and increasing problem in our environment that is most likely having a negative impact in the effectiveness of the eradication schemes that we are using (8-10, 17, 18).

Several years ago when the etiological role of *Helicobacter pylori* in multiple gastrointestinal pathologies became accepted, it was believed that its eradication would lead to a change in natural history and the management of these pathologies. Throughout the world researchers started a systematic search for the best therapeutic alternative for treating this new infectious disease. At that moment, double therapy was the treatment of choice, but – as often happens in the history of treatments of all the infectious diseases - paradigms change. Once the poor effectiveness of the dual scheme had been confirmed, we accepted the standard triple scheme as the new paradigm. It was not easy to make this change at all the different levels of medical attention, and nowadays we still find found patients who are being treated with the inadequate dual scheme. Unfortunately, just when we felt comfortable with STT, the evidence from various populations including our own, began to show us that the paradigm of standard triple therapy must also change.

We do not yet have sufficient evidence to recommend a new ideal scheme, but should consider the recommendation of Doctor Graham above the consensus and other recommendations: doctors must use what works well locally. Clinical and demographic results of studies undertaken in Colombia, including the one published in this issue of the magazine, must motivate different groups in our country to do research to confirm the real local level of resistance and the factors that underlie this resistance. Once that has been done we will be able to evaluate the effectiveness of the schemes that we are using. We need to make this evaluation based on research combined with our daily clinical research in order to be able to promote the use and evaluation of alternative schemes. We might suggest quadruple therapy and sequential therapy plus antibiotics with low rates of resistance. Ideally, the use of these new schemes should be performed under well-designed research protocols which would allow us to gather solid local evidence with which to make recommendations for more effective schemes in Colombia. Then we would truly have our new paradigm for the eradication of *Helicobacter pylori*.

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