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EDITORIAL

The rise of antibiotic resistance to *Helicobacter pylori* in Mexico: Is azithromycin plus levofloxacin the answer?☆

El incremento en la resistencia al antibiótico de *Helicobacter pylori* en México: ¿son la azitromicina más levofloxacina la respuesta?

Helicobacter pylori (*H. pylori*) infection is an important causal factor in chronic gastritis, peptic ulcer disease, gastric mucosa-associated lymphoid tissue lymphoma (MALT tumor), and gastric cancer.[1] Thus, scientific societies recommend eradicating the ''bug'' in well-defined clinical situations. The standard triple therapy of a proton pump inhibitor (PPI), amoxicillin, and clarithromycin administered for [7–14] days has been used for many years. However, the efficacy of that regimen has decreased to values below 80% in many countries due to an increase in the prevalence of clarithromycin resistance. Therefore, clarithromycin-based triple therapy is not currently recommended, unless a resistance rate to clarithromycin below 15% is documented.[2–5]

On the other hand, levofloxacin-based triple therapy, combined with a PPI and amoxicillin, has been reported as an effective first-line alternative, as well as being considered an option for salvage therapy.[6,7] However, the primary resistance rate to levofloxacin has increased in many countries due to its generalized use.[8–10] More recent studies, including one conducted in Mexico, have shown that the efficacy of triple therapy with fluoroquinolones varies widely, from 70 to 90%, limiting its efficacy with respect to initial reports.[11–13]

The authors of a meta-analysis reported eradication rates of 80% for levofloxacin-based therapy and of 77% for clarithromycin-based therapy, showing no significant differences between the two regimens.[14] In a more recent meta-analysis of 178 studies from 68 countries, fluoroquinolone resistance rates were reported at above 15% in all the regions, with a significant reduction in parallel with the *H. pylori* eradication rate, with the exception of Europe (11%, 95% CI: 9-13). In that same study, clarithromycin resistance rates above 15% were reported in all the regions, except Southeast Asia and the Americas.[15] In a word, the efficacy of that triple therapy is below 80% in many countries, and so its empiric use should not be recommended when the levofloxacin resistance rate is above 5-10%.[12]

The analyzed use of azithromycin has been reported as an effective alternative. Nevertheless, studies have shown that eradication rates vary widely, from 22 to 93%.[16–18] That disparity may be partially due to alterations in azithromycin absorption and to the cross-resistance of azithromycin with other macrolides.[19,20] In a meta-analysis of 14 studies, Dong et al. reported an eradication rate of 80% for therapy with azithromycin, with an acceptable frequency of adverse effects. Even though those rates are barely satisfactory, it should be stated that most of the studies included are from regions with a prevalence of clarithromycin resistance above 15%.[15,20] In a recent Italian randomized clinical trial, therapy based on azithromycin and levofloxacin for 7 days was compared with standard triple therapy with clarithromycin for 7 days, obtaining eradication rates of 70% and 76%, respectively. Both values are below acceptable figures and no difference in treatment adherence was observed. We should clarify that the results are from an area in which prevalence of resistance to clarithromycin is above 15% and levofloxacin resistance is from 10-15%.15,21 That information underlines the difference in resistance rates by geographic region, its impact on eradication, and the difficulty in selecting an adequate empiric regimen, emphasizing the need for decisions to be based on an analyzed local resistance pattern.[21]

Given those arguments, we believe the publishing of the results of an experimental clinical trial conducted in Mexico

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in this issue of the *Revista de Gastroenterología de México* is opportune. The trial compared a triple regimen based on azithromycin and levofloxacin with the standard triple therapy with clarithromycin, searching for a non-inferiority contrast in the cure rate between the two regimens, both of which were administered for 10 days. The study had an adequate number of subjects (n = 227) and eradication rates of 63% in the azithromycin/levofloxacin group and 58.5% in the clarithromycin/amoxicillin group were reported. The authors corroborated the elevated clarithromycin resistance rate in Mexico, which was 28.2% in their cohort. Unfortunately, they did not characterize azithromycin resistance. The only difference between the study groups was in the adverse effect rate, which was higher in the clarithromycin group at 86%, compared with 65% in the azithromycin group (p = 0.001).[22]

Regrettably, both eradication rates were below that suggested in the current clinical guidelines and were similar to results reported in other recent studies.[15,22–25] As with the standard triple therapy with clarithromycin, the inference is that azithromycin-based triple therapy should not be used in areas with clarithromycin resistance above 15%. Mexico is such an area, with rates on the rise. Said resistance can be explained by the fact that macrolides are the most frequently prescribed antibiotics in the United States, and perhaps in Mexico as well.[26] Thus, we suggest that it is essential to implement local surveillance networks that provide the information for appropriately selecting more effective eradication regimens in each region.

Mexico is a heterogeneous country with limited infrastructure and access in many zones, making that type of research very difficult to carry out. Therefore, we believe it is relevant to point out another option. That alternative could be to replicate the recently published experience of a group of researchers from Taiwan who compared the efficacy of therapy guided by the genotypic resistance pattern of *H. pylori* with empiric therapy based on the history of previous antibiotic exposure, in a group of patients in whom 2 or more eradication regimens had failed.[27] The therapy based on the resistance pattern achieved a cure in 78% of the patients, whereas the cure rate was 72% in the empiric treatment group, with no statistically significant difference. Those results suggest that empiric management based on the history of medications used in the past could be a practical and effective alternative, as well as a cost-efficient and accessible option.

Conclusions

- *H. pylori* resistance to antibiotics has reached alarming levels worldwide, which has a great effect on treatment efficacy. Local surveillance networks are required to select appropriate eradication regimens for each region.
- Clarithromycin-based triple therapy is not recommended unless the local clarithromycin resistance rate is below 15%.
- Empiric first-line therapy should be a 14-day course of bismuth or antibiotic-based quadruple therapy.
- The efficacy of levofloxacin-based triple therapy has been lower than 80% in many countries and is not recommended when levofloxacin resistance is higher than 5-10%.
- However, a properly designed empiric therapy, based on medication history, is an acceptable alternative to genotypic resistance-guided therapy for the eradication of refractory *H. pylori* infection after considering accessibility, cost, and patient preference.
- Second-line therapy should be determined in relation to the first-line therapy that failed.

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Conflict of interest

The authors declare that there is no conflict of interest.

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