

Cartas al editor

Which should be the first-line treatment for *Helicobacter pylori* in Colombia? A lesson from a recent study

Turin, August 30th, 2019

Dear Editor,

In the last decades, the recommended regimens for *Helicobacter pylori* eradication have included the combination of a proton-pump inhibitor (PPI) and two or more antibiotics (1). Among the latter, clarithromycin is widely used to treat *H. pylori* infection, due to its low minimal inhibitory concentration. However, due to a steady increase in *H. pylori* resistance to clarithromycin, this drug has become progressively less efficacious worldwide.

To highlight the concerns caused by the increasing resistance of this bacterium to antibiotics, the World Health Organization inserted *H. pylori* with high priority for clarithromycin resistance, in the priority list for research and development of new antibiotics (2). A European multicentre study, published in 2013, showed that the resistance rate of *H. pylori* in Europe was 34.9% for metronidazole, 17.5% for clarithromycin, 14.1% for levofloxacin, 1.1% for rifabutin, 0.9% for tetracycline, and 0.7% for amoxicillin (3).

The dominant mechanisms underlying the development of clarithromycin resistance are several point mutations in domain V of the 23S ribosomal RNA (*rRNA*) gene, which result in decreased affinity and in absence of clarithromycin binding to the 50s ribosome subunit, and thus, failure to influence protein synthesis.

It is well-known that clarithromycin resistance may originate from the previous consumption of macrolides. There are essential point mutations, which can occur at the nucleotide positions 2142 (A2142G and A2142C), 2143 (A2143G) and 2144 (A2144G) in the peptidyl transferase loop of the 23S *rRNA* gene. These mutations result in conformational change leading to decreased efficacy of the drug (4).

In a recent interesting article, Roldán, *et al.*, reported the frequency of A2143G and A2142G mutations in patients with previous unknown *H. pylori* status, admitted for dyspepsia in an endoscopic unit in Medellín, Colombia. They found a prevalence of 44.2% of *H. pylori* infection with A2143G and A2142G mutations in the 18.8% of them (5). These results must be considered together with the data regarding the high rate (78%) of RdxA nitroreductase mutations (associated with metronidazole resistance) shown in *H. pylori* strains in Colombia (6).

Considering that beyond its involvement in several gastro-duodenal diseases, *H. pylori* is recognized as a necessary but insufficient cause of gastric cancer, it is possible that eradication at a population level may lead to the future decline of this malignancy, especially in countries where it represents a severe burden. Hence, it is crucial to optimize the treatment in each country.

These findings indicate that also in Colombia should be appropriate to treat patients with new therapeutic options, in particular the formulation with bismuth subcitrate potassium, metronidazole, and tetracycline contained in a single capsule (three-in-one). Due to its efficacy the International Guidelines recommended this regimen as first line and second line therapies in regions where clarithromycin resistance has resulted in low-cure rates (7).

Very truly yours,

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Medellín, October 31st., 2019

Dear Dr. Pellicano,

We would like to thank you for your interest and comments about our manuscript, which we found extremely useful (1). Since Colombia is a country with a high gastric cancer incidence we agree with your observation: “The *Helicobacter Pylori* eradication could lower the morbidity rate for this cancer. However, this rate diminution has been shown to have a dramatic downward trend because of the antibiotic resistance” (2). Therefore, we must implement optimal eradication regimens according to the pertinent antibiotics.

Worldwide (with rare exceptions) the use of clarithromycin regimens are no longer appropriate because of the low eradication rates (<80%) (3,4). Even more concerning, the alternative levofloxacin therapies (quadruple, sequential, concomitant and triple therapies) efficacy has decreased (5,6). While the resistance increases, the standard triple therapy success has decreased below 60% (2,7–11), The *H. pylori* empirical treatment has contributed to the misuse of antibiotics. Although the latest international consensus reports suggest selection of treatment according to local resistance patterns (12–20) *H. pylori* sensitivity test is rarely performed.

The standard triple therapy is no longer use in Europe, and the quadruple therapy is now used instead (12). Nevertheless, since there is not consensus with this treatment a random combination is used worldwide, especially in regions with high resistance rates leading to the increase of quinolones and rifabutin resistance (21).

Unfortunately, in our experience most of the patients with failure treatment have shown multiple concurrent clarithromycin and metronidazole resistance, or even a triple resistance to clarithromycin, metronidazole, and fluoroquinolone (according to the culture susceptibility test) (7). As a result of antibiotics misuse, concomitant quadruple therapy is rapidly losing its efficacy.

Since 2015, Kioto’s *H. pylori* consensus defined it as an infectious disease regardless of the symptoms and complications (22). Maastricht’s V Consensus recommended that after the second-line treatment failure, *H. pylori* treatment should be guided according to the sensitivity tests (12). If the correct antibiotics are chosen for the first therapy the success rate is higher, while after first therapy failure the bacteria will probably develop antibiotic resistance and it would be harder to eliminate.

Bismuth is a medicament very effective to treat *H. pylori* infection and most of the consensuses recommend it because resistance against it has not been described yet (12,15,19,20). However, since bismuth is not absorbed it is not effective against intracellular and pericellular bacteria. Therefore, bismuth should be used in combination with additional medicaments to successfully eradicate the infection. Dore, *et al.*, demonstrated that adding bismuth to the triple therapy could increase the curation rate against resistant strains, but bismuth is rarely added to the first-line *H. pylori* triple treatment (23).

In our practice, as second-line therapy and increasingly more frequent as first-line therapy, the proton pump inhibitors (PPI), amoxicillin, levofloxacin and bismuth combined treatment achieve over 90% success rates in clinical trials performed since 2010 (24). We are currently working on a project trying this therapy with our patients because *H. pylori* will not become resistant to bismuth and it could prevent *Clostridium difficile* complications.

Besides choosing the correct antibiotics according to the sensitivity tests, the acid gastric inhibition plays a key role in treatment success. Therefore,

Conflicts of interest:

The authors do not have any conflict of interest.

choosing the correct PPI with the higher effectiveness over the acid and a lower influence for the host's CYP2C19 polymorphisms (rabeprazole and esomeprazole) could improve the cure rate (21). Maastricht's V Consensus establishes that a high PPI dose controls better the gastric pH, thus increasing the therapy efficacy (12). Since the acid inhibition power differs in different PPI, duplicating the standard dose of any of these PPI would provide a better outcome (25).

As a summary, *H. pylori* is an infectious disease and its eradication can be achieved ($\geq 95\%$ cure rate) with well-designed therapies based not only in antibiotic selection (precise selection) according to the antimicrobial sensitivity tests and cultures, but also with the patient's adherence to the treatment and the correct PPI dose. Due to the high resistance, gastroenterologists must handle it as an infectious disease and change the empirical treatment model for a precision therapy guided by antimicrobial susceptibility tests. The treatment program needs to be applied in the local, regional and national environment to track the *H. Pylori* resistance patterns to antibiotics.

Sincerely yours,

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