Strategies for *Helicobacter pylori* eradication in the year 2020

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During the last two decades, several multidrug regimens consisting of a proton pump inhibitor (PPI) and two or three antibiotics, have been used to treat *Helicobacter pylori* (*H. pylori*) infection.[1]

However, over time, an increased failure rate of standard eradication treatment, in particular for clarithromycin-based regimens, has been reported worldwide with eradication rates falling to unacceptable levels.[2] To highlight the concerns caused by the increasing resistance of *H. pylori* to antibiotics, in particular to clarithromycin, the World Health Organization added this microorganism in the priority list for research and development of new antibiotics.[3]

Mechanistically, we have learned that the bacteria develop four main barriers to antibiotics that are prevention of cell penetration, modification of the target, enzymatic inactivation of the antibiotic, and elimination via efflux pumps. Modification of the target is the main mechanism of *H. pylori* resistance to macrolides and quinolones, and this bacterium becomes resistant as the consequence of chromosomal mutations.[4]

As a consequence of the unsatisfactory pharmacological armamentarium, it is currently accepted that the optimal regimen to cure *H. pylori* infection should be decided regionally based on local antibiotic resistance and data obtained in clinical practice. According to internatipnal guidelines, in countries with low clarithromycin resistance rates (<15%), an empiric clarithromycin-based regimen can be used, while in regions with high clarithromycin resistance rates, a bismuth-containing quadruple therapy (with metronidazole and tetracycline) should be the first choice.[5] Encouraging data are reported, both in the first and in the rescue treatments, with the use of the new formulation with bismuth subcitrate potassium, metronidazole, and tetracycline contained in a single capsule (called the single three-in-one capsule).[6] This formulation, in packages for 10 days regimen, requires 3 tablets to be taken 4 times a day, accompanied by a PPI twice daily. The efficacy of alternative regimens or the usefulness of adding probiotics, prebiotics, or symbiotics to standard regimens to ameliorate *H. pylori* eradication rate remain to be defined.[7]

Two articles published in this issue of the Journal evaluated the possibility of improving the *H. pylori* eradication rate with the three-in-one formulation in Saudi Arabia[8] and the potential improvement, in terms of effectiveness, by adding probiotics to a standard regimen in China.[9]

In Saudi Arabia, there is great interest in evaluating the antibiotic resistance pattern due to the high failure rates of anti-*H.pylori* standard therapy.[10] In some regions, metronidazole and clarithromycin resistance rates of 48% and 28%, respectively, have been reported.[11] Hence, there is a need to evaluate the benefits induced by the new antibiotics available on the market. In a prospective, open-label, non-randomized trial, conducted in a tertiary care teaching hospital in Alsohaibani, *et al.* evaluated the treatment efficacy of the new bismuth-based quadruple therapy contained in a single capsule (three-in-one). *H. pylori* eradication was obtained in 78.3% and 87.8% of patients in the intention-to-treat (ITT) analysis and in per-protocol (PP) analysis, respectively. The efficacy did not change considering naïve patients (66 out of 82) or those who have failed previous treatments (16 out of 82). Poor compliance or adverse events occurred in 7 and 3 patients, respectively.[8] The eradication rates in this study, the first published in Saudi Arabia with the three-in-one based regimen, although lower than those reported in other countries,[12] show improvement with respect to those reported in recent years in the same country.[11] On the other hand, the results reported by the multitude of studies performed worldwide using this formulation are not homogeneous. In an Italian study, *H. pylori* eradication was achieved in 92.7% of naïve patients, and this rate was not different from those obtained in previously treated patients (96%, $P = 0.383$).[12] Similar results were reported by Delchier *et al.* who, in a multicenter, open-label, single-arm study, conducted in France, Germany, Italy, and Spain, treated *H. pylori*-positive patients who had failed ≥1 previous course of triple clarithromycin-based therapy, with the bismuth-based three-in-one capsule. Using the three-in-one regimen, *H. pylori* eradication rates ranged from 93.2% to 93.8% in the ITT analysis, and from 94.7%

to 95.0% in the PP analysis.[13] In contrast, in Lebanese patients with peptic ulcer, 14-days sequential therapy was superior to bismuth-containing quadruple therapy (80% *versus* 50%; $P = 0.015$).[14]

In a retrospective study conducted in Shanghai, China, Liu *et al.* evaluated the efficacy of a two-week probiotic treatment with *Lactobacillus acidophilus*, *Streptococcus fecalis,* and *Bacillus subtilis* followed by a 10-day quadruple regimen with esomeprazole, bismuth potassium citrate, tetracycline, and furazolidone in patients with at least two previous *H. pylori* eradication failures. The authors reported 92% *H. pylori* eradication in the ITT analysis and 91.8% in the PP analysis. Ten patients reported minor side effects with 1 patient changing drugs for skin rash.[9] Thus, this study reported a very high eradication rate with a bismuth-based treatment. The authors speculated that these interesting results could be due to the addition of probiotics to the antibiotic-based regimen. It is well-known that adding probiotics to *H. pylori* eradication therapies may reduce the adverse effects of antimicrobials and also improve eradication rates through better compliance. Since probiotics are living bacteria capable of conferring benefits to the host, the rationale behind their administration is to induce competition with *H. pylori* for colonization and survival. Systematic reviews and meta-analyses have generally shown beneficial effects of probiotics in improving *H. pylori* eradication, with positive results reported for *Saccharomyces boulardii* (*S. boulardii*) and *Lactobacillus* supplementation. Adding *S. boulardii*, a yeast probiotic, as supplementation to a standard eradication regimen, increased the *H. pylori* eradication rate from 71% to 80% (relative risk [RR] = 1.11, 95% confidence interval [CI]: 1.06-1.17), based on the moderate quality of evidence (assessed by the Grading of Recommendations, Assessment, Development and Evaluation guidelines). Moreover, *S. boulardii* reduced the risk of overall *H. pylori* therapy-related adverse effects, particularly diarrhea and nausea, with high and moderate quality of evidence, respectively.[15] Focusing on *Lactobacillus* supplementation, a recent meta-analysis included 11 randomized controlled trials involving a total of 724 patients. *H. pylori* eradication rate was significantly higher in patients treated with *Lactobacillus* supplementation than that in the control group (RR = 1.16, 95% CI: 1.08–1.25, $P < 0.0001$). Subgroup analysis showed that the eradication rates were significantly enhanced in both adults and children, and no significant difference was detected between Asian and European patients.[16] However, since there are several sources of heterogeneities among studies, including species and strains, additional work needs to be performed to determine optimal strain, dose, and duration to be used.

In conclusion, the introduction of the new formulation of bismuth-based quadruple therapy and the probiotic supplementation of *H. pylori* regimens in Saudi Arabia represent encouraging perspectives to face the challenge imposed by the increase in antibiotic resistance.

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