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Archives of Gastroenterology Research Editorial

Treatment and Drug Resistance to *Helicobacter Pylori*: A Brief Review

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Introduction

Helicobacter pylori is a gram-negative, spiral-shaped bacterium that inhabits the gastric environment of 60.3% of the global population [1]. Though most individuals infected with the bacterium remain asymptomatic, it is known that this infection plays a pivotal role in the development of diseases such as chronic gastritis, peptic ulcer, gastric cancer and gastric MALT lymphoma [2,3]. Hence, eradication of *H. pylori* is associated with the potential prevention of many gastric and extra gastric diseases, such as gastric cancer [4].

In the late 1990s, triple therapy with clarithromycin (500 mg), metronidazole (500 mg) or amoxicillin (1000 mg), and proton pump inhibitors (PPIs) in standard doses twice a day for 7 to 10 days became the first-line regimen for eradication of *H. pylori* in many countries. At the time, different clinical trials showed that this therapy achieved eradication rates of 90%, which were considered acceptable [5,6]. Nevertheless, the effectiveness of this regimen has been largely affected by clarithromycin resistance, which has reduced the eradication rate to 80% or even lower in some regions [7]. In view of this, the main guidelines for the treatment of *H. pylori* infection, currently recommend quadruple bismuth therapy (QBT) for first-line treatment, in preference to triple therapy, restricted to areas with low rates of resistance to clarithromycin (<15%) [8]. The QBT consists of PPI (standard dose, BID), bismuth (QID), metronidazole (400 mg, QID or 500 mg, TID-QID) and tetracycline (500 mg, QID) for 10 to 14 days. Furthermore, concomitant non-bismuth quadruple therapy with PPI (standard dose, BID), amoxicillin (1000 mg, BID), metronidazole (500 mg, BID) and clarithromycin (500 mg, BID) for 10-14 days is also recommended in regions where bismuth is not available [9-11].

Drug Resistance

In view of the pharmacological therapy currently used, it should be noted that the main medications in use may not have an effect, mainly due to drug resistance. Therefore, it is known that *H. pylori* is a high priority group in urgent need of new antimicrobials, considering that the efficacy of empirical treatment has decreased and that *H. pylori* eradication rates are directly dependent on the susceptibility of the strain to the currently used antibiotics [12,13]. Metronidazole resistance mechanism occurs due to changes in the enzymatic systems that interfere with microbial growth and development [14]. This antimicrobial demonstrates the most common antibiotic resistance in *H. pylori* (20-95%): 99.5% in Asia, 79.4% in America, 83.0% in Europe, and 57.0% in Oceania. Clarithromycin is the antimicrobial of first choice for *H. pylori* eradication and, at the moment, is of great concern due to its high resistance rates (0-50%). Its resistance mechanism occurs due to changes in genes that encode a domain of one of the subunits of the prokaryotic ribosome, in addition to other enzymes related to the process of protein synthesis [14]. Amoxicillin resistance rates are also highly variable (0-30%), mainly in regions where it can be obtained without a prescription [13]. Amoxicillin resistance is related to structural modification, such as changes in penicillin-binding proteins [14]. Levofloxacin, Rifampicin, and Furazolidone resistance in *H. pylori* are low and considered insignificant, but all of these antimicrobial resistance levels are increasing over time [12,13]. Thus, understanding the

resistance mechanism and prevalence of the antibiotics used in *H. pylori* eradication is crucial to search for new drugs and improved treatment.

Novel Therapy Options

Faced with drug resistance, novel therapies can assist in the management of positive *H. pylori* patients. New options of PPIs as Vonoprazan (VPZ), administration of medications with different combinations and dosages, as well as other antimicrobials, probiotics and *in vitro* tested therapies are also able to assist in the management of positive *H. pylori* patients.

VPZ is a Potassium Competitive Acid Blocker that inhibits gastric acid stronger and longer since the first day of therapy [15,16]. However, it is not indicated to penicillin allergic patients, besides non-availability in some countries [17]. High Dose Double Therapy (HDDT), a combination of amoxicillin (1g tid or 750 mg qid) and PPI (standard dosage TID or QID or standard double dosage BID) for 14 days [18], showed similar effectiveness with the bismuth therapy, in addition to fewer side effects [19]. Thus, as the successful achievement of HDDT depends on an appropriate pH, double therapy with VPZ appears as a satisfactory possibility of eradicating the bacterium with few antibiotics and shorter treatment [17]. On the other hand, a new capsule containing Bismuth, Metronidazole and Tetracycline has been related to a success rate of approximately 90% in first-line and second-line treatments [20]. Furthermore, the Bismuth Quadruple Therapies (BQTs) are still effective and safe in most countries, and addition of bismuth on triple therapies improved cure rates in 30% to 40% of subpopulations with resistant strains [21]. Moreover, Rifabutin is an antimicrobial non-degradable by the gastric acid and with rare resistance to *H. pylori* strains that, along with PPI and amoxicillin or in BQT, achieved elimination rates of approximately 70%. Nevertheless, the high cost turns difficult the establishment of this therapy [22,23].

New pathways, such as the addition of probiotics to therapy, can inhibit colonization and adhesion of *H. pylori* and decrease the side effects, which improves the treatment adherence [24]. However, the use of single or multiple strains remains uncertain due to the low quality of studies currently available, which makes further research necessary [8]. Furthermore, the use of C and E vitamins can reduce oxidative stress and free radical production during the therapy, contributing to preventing tissue damage and gastric cancer development [25]. Lastly, drugs like Apigenin, Chrysin, Kaempferol and Hesperetin demonstrated *in vitro* antimicrobial activity to some strains resistant either by metronidazole and clarithromycin [18].

Future Perspectives

Dealing with *H. pylori* is an arduous task, and the main challenge against this disease is antibiotic resistance and consequent decrease of eradication rates [18,21]. The low availability of treatments capable of promoting effective bacterial eradication, especially with a single therapeutic attempt, is an issue that, along with insufficient bacterial culture with antibiotics susceptibility, makes it difficult to manage the course of the disease [26]. Of note, the World Health Organization listed, in 2017, clarithromycin-resistant *H. pylori* as a high-priority bacterium, which emphasizes the need to search for effective treatment regimens against this infection and for surveillance in this regard, given that high resistance rates also mean decline of possible options of treatment [14,26]. In this sense, studies assessing alternative treatments for bacterial eradication should be encouraged, in order not only to improve the effectiveness of antimicrobial drugs, but also to reduce their doses, side effects, and therapy length, enhancing the therapeutic adherence. An example is the use of VPZ combined with amoxicillin, since the association of this new acid secretion inhibitor increases the therapy success rate as well as reduces the frequency of side effects [8]. Although resistance rates remain low, the development of monitoring methods to Rifabutin effectiveness are needed in the future [27]. In addition, physicians should be instructed to choose more suitable empirical regimens for their patients, taking into consideration the local resistance profile and previous use of antimicrobial drugs by the patient. Thus, the verification of bacterial eradication or therapeutic failure should be performed in order to gather information on the effectiveness of therapeutic regimens and to characterize the local susceptibility profile [28].

Another option that has been studied is the use of antimicrobial peptides, which are compounds produced by cells as a result of innate immunity to generate protection against several pathogens. They can act on cell membranes or intracellular processes [29]. The 3 peptides with the highest anti-*H. pylori* activity were pexiganan, tilapia piscidin 4 and PGLa-AM1 [30]. Another approach that still lacks evidence is the use of natural compounds, such as medicinal plants, against *H. pylori* infection, mainly as an auxiliary agent in the treatment, but not as a monotherapy [31]. Ally to this, the use of anti-biofilm agents can also assist in the management of positive *H. pylori* patients. Despite being a new method, two peptides anti-biofilm (IDR-1018 e DJK-5) were identified to act against strains of the bacteria, by affecting different stages from *H. pylori* biofilm, which helps to circumvent drug resistance [32].

Finally, anti-*H. pylori* vaccines can be a potential strategy to reduce the infection prevalence and the number of unsuccessfully eradicated patients. However, the escape mechanisms of the bacteria make this process more difficult. Therefore, more studies are necessary to develop an adequate vaccine against *H. pylori*. [33,34]. (Figure 1) summarizes the main aspects the aspects addressed in this work related to the treatment against the *H. pylori*.

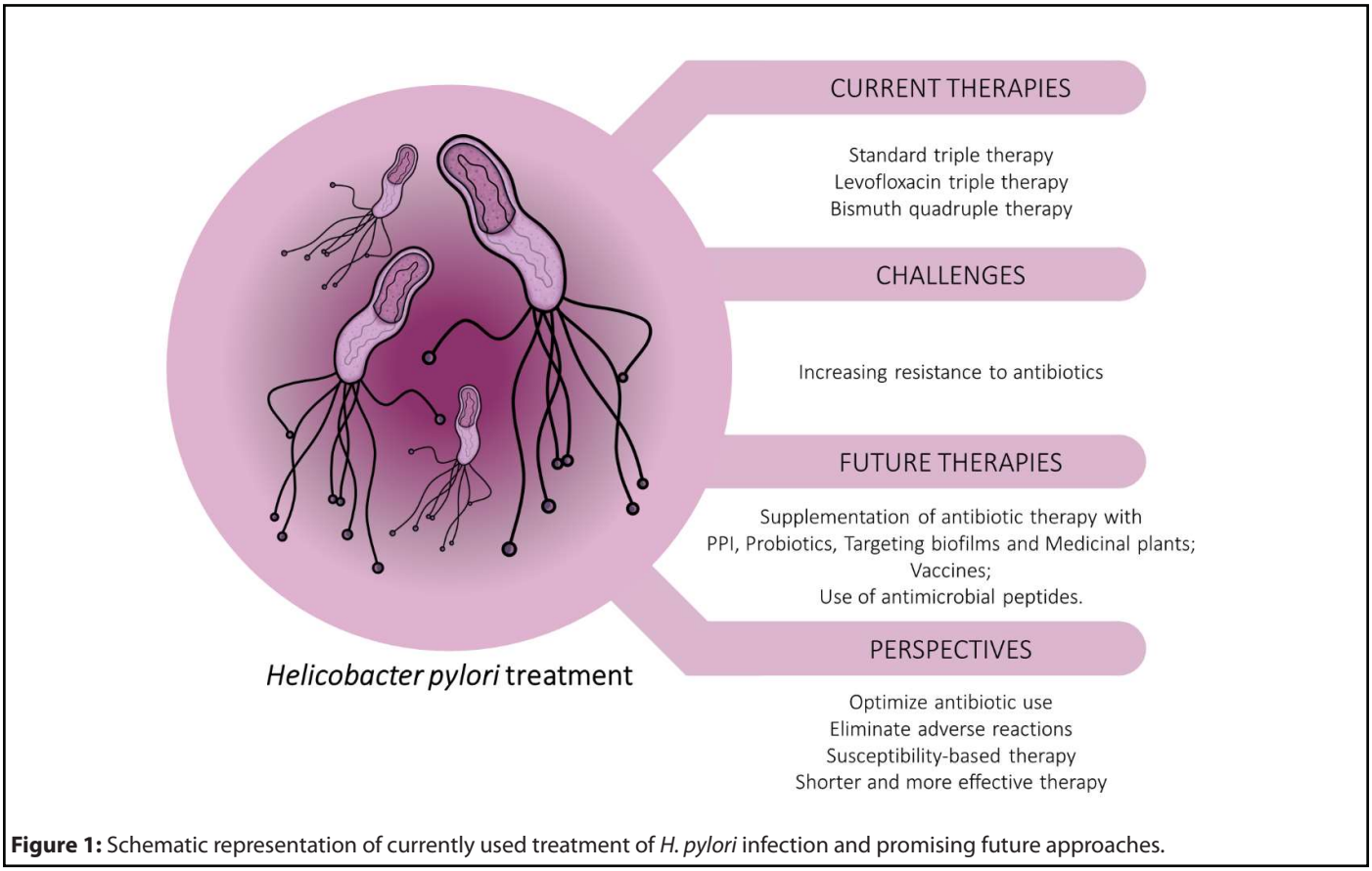

Figure 1: Schematic representation of currently used treatment of *H. pylori* infection and promising future approaches.

Conclusion

In this editorial, we outline the urgent global issue of treatment for *H. pylori* infection and antimicrobial resistance. It is evident that the treatment for *H. pylori* has become challenging, as the aforementioned standard therapies are losing effectiveness and there is an increase in antimicrobial resistance, which demands new effective eradication therapies, with medications that provide good safety profiles, minimum adverse effects and good patient compliance. The use of vonoprazan in dual therapy with amoxicillin seems to be a viable option. In addition, acid blockers, antibiotic adjuvants, anti-biofilm agents and vaccines appear to be important agents to control multidrug resistance. New controlled and randomized trials are essential to determine the future of the treatment against this bacterial infection.

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