

# REVIEW – TREATMENT OF *HELICOBACTER PYLORI* INFECTION

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**Abstract:** *Helicobacter pylori* continues to present therapeutic challenges for clinicians across the world. This review article aims to consolidate current knowledge of *H. pylori* infection with a particular emphasis on treatment strategy and summarizes important studies regarding *H. pylori* therapy published from April 2020 to March 2021. Proton pump inhibitor (PPI)-amoxicillin dual therapy can be considered when antimicrobial susceptibility testing cannot be performed. Triple therapy for 14 days may be sufficient in some regions with low clarithromycin resistance. Less expensive sequential and hybrid therapy were more successful and as well tolerated as the currently recommended concomitant therapy and should be favored as non-bismuth quadruple regimens. Bismuth quadruple therapy with tetracycline and modified bismuth quadruple therapy with amoxicillin were highly effective and safe in *H. pylori* eradication and should be kept in mind as *H. pylori* first-line therapy in regions with high resistance to clarithromycin. These therapies also have a good performance as second-line and third-line regimens and revealed a satisfactory eradication rate as rescue therapy. In patients allergic to penicillin, quadruple regimen with PPI + bismuth + tetracycline and metronidazole seems to be a good option. Rifabutin and nitazoxanide-based regimens are safe and effective as a salvage therapy in patients who have failed prior treatments. Superiority of vonoprazan in eradicating *H. pylori* was observed, notably on the resistant strains. The drug-resistance phenomenon in *H. pylori* underlines the need for novel strategies to improve the eradication rate, especially susceptibility-guided therapy.

**Keywords:** Resistance, Susceptibility-guided therapy, Bismuth quadruple therapy, Dual therapy, Vonoprazan.

## INTRODUCTION

*Helicobacter pylori* continues to present therapeutic challenges for clinicians across the world. A rapid increase in antibiotic resistance leads to the need for new treatment strategies. These strategies should be selected based on regional resistance patterns, previous antibiotic exposure, susceptibility guidance and the need to be more effective and safer. Clarithromycin triple therapy can no longer be a first-line empiric therapy without antibiotic susceptibility testing. Other therapeutic modalities, such as bismuth quadruple therapy (BQT), could be recommended. Levofloxacin-based or alternative macrolide-containing therapies are other options. The efficacy of BQT as a second-line therapy has been proven, there is clear evi-



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dence that it is the most effective first-line therapy. The management of *H. pylori* infection by European gastroenterologists is heterogeneous and only quadruple therapies lasting at least 10 days are able to achieve a >90% eradication rate<sup>1</sup>. It is essential to test and treat the infection, as untreated *H. pylori* is associated with serious complications including peptic ulcer disease, MALT lymphoma and gastric cancer. Successful treatment of *H. pylori* may lead to the recovery of vitamin C secretion by gastric mucosa and potentiate regression of premalignant gastric lesions<sup>2</sup>. Also, numerous studies last year assessed the long-term alterations of gut microbiota after *H. pylori* treatment. This review article aims to consolidate current knowledge of *H. pylori* infection with a particular emphasis on treatment strategy and summarizes important studies published from April 2020 to March 2021.

## DUAL THERAPY

Dual therapy may improve compliance and eradication rate. A published meta-analysis including 2,249 patients suggested that proton pump inhibitor (PPI)-amoxicillin dual therapy had a similar efficacy to the current guidelines-recommended therapies (83.2% vs. 85.3%, respectively). PPI-amoxicillin dual therapy is an effective and safe regimen for *H. pylori* eradication for patients' first line or rescue therapies<sup>3</sup>. A Chinese study was conducted on elderly patients with comorbidities who were given both rabeprazole (10 mg) and amoxicillin (1,000 mg) thrice a day for 14 days as first-line treatment. Successful eradication was achieved in 90.9% patients. Adverse effects were noted in 11.1% of the treated patients. This therapy used as a first-line treatment appears to be effective and safe for *H. pylori* infection in elderly patients or those with multiple comorbidities<sup>4</sup>.

## TRIPLE THERAPIES

Triple therapies remain the proposed first-line treatment in many countries with low clarithromycin resistance rates. A number of interesting studies looked this year at the role of triple therapy in peer *H. pylori* eradication treatment (Table 1). Standard triple therapy (STT) remains the standard of care in the published international guidelines of the European gastroenterologists in areas of low clarithromycin resistance. Lee et al<sup>5</sup> demonstrated that a 10-day STT with ilaprazole was more effective than a 7-day STT for *H. pylori* eradication. Indonesian data from Heradi et al<sup>7</sup> with patients randomized to be given a triple therapy, such as rabeprazole (20 mg), amoxicillin (1,000 mg), and clarithromycin (500 mg) twice daily for 14 days, or 10 days plus 4 days placebo revealed in the intention-to-treat (ITT) analysis an eradication rate of 67.6% for the 10-day group vs. 86.8% for the 14-day group. In a Pakistani cohort, quadruple therapy showed a better performance than triple therapy with a 93.8% vs. 84.6% success rate, respectively<sup>8</sup>. Rabeprazole (20 mg) had similar *H. pylori* eradication rates compared with omeprazole (40 mg) in Nepal, when co-administered with amoxicillin and clarithromycin for two weeks<sup>9</sup>, while in Buthan, overall eradication rates of 7-day and 14-day STT regimens were 51.9% and 80.0%, respectively, which support a 14-day treatment period<sup>10</sup>.

## NON-BISMUTH QUADRUPLE THERAPY (CONCOMITANT, SEQUENTIAL AND HYBRID THERAPIES)

Original articles on concomitant (CT), sequential, and hybrid non bismuth quadruple therapies (NBQT) were published during the past year. A study<sup>11</sup> in Taiwan compared the effects of reverse hybrid therapy (dexlansoprazole 60 mg o.d. plus amoxicillin 1 g b.d. for 14 days, and clarithromycin 500 mg plus metronidazole 500 mg b.d. for the initial 7 days) and concomitant therapy (dexlansoprazole 60 mg once o.d. plus amoxicillin 1 g, clarithromycin 500 mg, and metronidazole 500 mg b.d. for 14 days). Fourteen-day reverse hybrid therapy and 14-day concomitant therapy were equivalent in efficacy as first-line treatment of *H. pylori* infection, however, reverse hybrid therapy was considered safer. A study<sup>12</sup> in Myanmar analyzed a first-line CT 14-day regimen of rabeprazole, clarithromycin, amoxicillin and tinidazole

**TABLE 1. STUDIES CONCERNING TRIPLE THERAPIES TO ERADICATE *HELICOBACTER PYLORI* PUBLISHED IN 2020 AND 2021.**

Author	Country	N	Therapy regimen	Eradication rate	Study design
Lee et al <sup>5</sup>	Korea	254	STT (ilaprazole, clarithromycin, amoxicillin) 7 days	65.4%	Prospective randomized controlled trial
			STT (ilaprazole, clarithromycin, amoxicillin) 10 days	74.8%	
Kim et al <sup>6</sup>	Korea	369	STT (PPI-clarithromycin-amoxicillin) 7 days	78.5%	Randomized Clinical Trial
			STT (PPI-clarithromycin-amoxicillin) 14 days	78.6%	
Heradi et al <sup>7</sup>	Indonesia	75	STT (rabeprazole, amoxicillin, clarithromycin) 10 days	73.5%	Double-Blinded Randomized Clinical Trial
			STT (rabeprazole, amoxicillin, clarithromycin) 14 days	86.8%	
Asim et al <sup>8</sup>	Pakistan	196	STT (omeprazole, clarithromycin, amoxicillin) 14 days	84.6%	Randomised controlled trial
			STT + bismuth subcitrate 14 days	93.8%	
Gurung et al <sup>9</sup>	Nepal	100	STT with omeprazole	92%	Cross-sectional study
			STT with rabeprazole	94%	
Vilaichone et al <sup>10</sup>	Bhutan	77	Omeprazole, tetracycline, amoxicillin 7 days	51.9%	Prospective Randomized Trial
			Omeprazole, tetracycline, amoxicillin -14 days	80.0%	

STT: standard triple therapy.

and a 10-day sequential therapy of rabeprazole, clarithromycin, amoxicillin and tinidazole, with no significant statistical difference in the cure rates (82% vs. 87%, respectively). In an open-label, randomized clinical trial, including 140 patients in Croatia, a CT (esomeprazole 40 mg, amoxicillin 1 g, metronidazole 500 mg, clarithromycin 500 mg, twice daily for 14 days) was compared to a hybrid therapy (esomeprazole 40 mg and amoxicillin 1 g twice daily for 14 days with addition of metronidazole 500 mg and clarithromycin 500 mg, twice daily, in the last 7 days) with eradication rates of 84.1% and 83.1% respectively. Hybrid therapy has lower adverse event rates<sup>13</sup>. Another Taiwanese study<sup>14</sup> included 206 *H. pylori*-infected naïve patients who were prescribed one of two 7-day non-bismuth containing quadruple therapies: esomeprazole 40 mg, amoxicillin 1 g, metronidazole 500 mg; clarithromycin 500 mg, all given twice daily, or lansoprazole 30 mg, amoxicillin 1 g, metronidazole 500 mg, clarithromycin 500 mg, also given twice daily. The eradication rates in the esomeprazole and lansoprazole group were 86.1% and 90.1% respectively.

### BISMUTH-CONTAINING QUADRUPLE THERAPIES

BQTs were examined in great detail this year both as primary- and second-line therapies. A systematic review on recent studies was carried out in European countries. A total of 24 studies, with 3,804 patients, were identified. As second-line therapy, Pylera<sup>®</sup> and sequential therapy achieved significantly higher cure rates (89.2% and 92.5%, respectively) compared to

all the other regimens. As third-line therapy, levofloxacin-based therapy and Pylera<sup>®</sup> achieved similarly high cure rates 84.1% and 83.6%, respectively), whereas standard BQT achieved the lowest (61.4%). Rifabutin-based rescue therapy had an eradication rate close to 75% with data from a small sample size<sup>15</sup>. Some other meta-analyses were performed to evaluate the cure rates and compare efficacy and safety of BQT and CT for *H. pylori* eradication as first-line treatments. Ten studies were collected. BQT and CT in ITT analysis revealed eradication rates of 84.6% vs. 82.9%, respectively. BQT and CT may be acceptable in a sub-group analysis for *H. pylori* infection treatment. However, BQT was superior to the current scheme of CT (amoxicillin + clarithromycin + metronidazole + PPI) in a subgroup analysis<sup>16</sup>. In a Korean study<sup>17</sup>, participants with *H. pylori* infection were randomly assigned to either a 10-day BQT (bismuth 300 mg q.i.d., lansoprazole 30 mg t.i.d., metronidazole 500 mg t.i.d., tetracycline 500 mg q.i.d.) or a 7-day STT (lansoprazole 30 mg, amoxicillin 1,000 mg, clarithromycin 500 mg, b.i.d.). Similar to previous results, the BQT-group achieved a significantly higher eradication rate than the STT-group in the ITT analysis (74.3% vs. 57.1%, respectively) in first-line treatment<sup>17</sup>. Chinese and Korean studies analyzed a 14-day therapy with a PPI plus high-dose amoxicillin and metronidazole and concluded (in the Chinese study) that regimens with or without bismuth achieved excellent eradication rates and were well tolerated despite most patients harboring metronidazole-resistant bacteria<sup>18</sup>. In the Korean study, modified BQT comprising rabeprazole, amoxicillin, metronidazole, and bismuth was an effective first-line treatment for *H. pylori* infection in regions with high clarithromycin and metronidazole resistance. BQT with tetracycline yielded a similar performance in this study (82.8% vs. 87.2% with amoxicillin). The amoxicillin, metronidazole, tetracycline, clarithromycin, and levofloxacin resistance rates were 8.3, 40, 9.4, 23.5, and 42.2%, respectively<sup>19</sup>. Also, both bismuth-containing treatment regimens, BQT with tetracycline, and modified BQT with amoxicillin were highly effective and safe in *H. pylori* eradication in Turkey<sup>20</sup>. A Chinese study<sup>21</sup> found that treatment with 20 mg of rabeprazole, 1,000 mg of amoxicillin, 500 mg of clarithromycin, and 220 mg of bismuth potassium citrate (BACPPi), administered twice a day for 10 days, was as effective as a 14-day regimen. A 10-day amoxicillin-clarithromycin-containing BQT with a >85% eradication rate may be recommended for the primary empirical treatment of *H. pylori* infection in Beijing, China.

## RESCUE THERAPIES

Given the falling eradication rates noted for all conventional therapies, there is a clear need for antibiotics, or combinations of antibiotics to be used in refractory and resistant cases of *H. pylori* infection according to local antibiotic resistance rate and inconsistent adherence to use of guidelines. There has been an increased interest in the rescue therapies in last year. Failure of first-line therapy exacerbates the difficulty for rescue treatment, mainly due to increased clarithromycin and metronidazole resistance. Therefore, it is imperative to introduce new antibiotics with low drug resistance for the current treatment options. Spanish data of the "European Registry on *H. pylori* Management" (Hp-EuReg) showed 3 protocols after previous failure with clarithromycin- and levofloxacin-containing therapies; patients receiving a third-line regimen with 10/14-day bismuth salts, metronidazole, and tetracycline (BQT-Tet), or single capsule (BQT-three-in-one Pylera). Overall modified ITT eradication rates were 81% (BQT-Tet: 76%, BQT-three-in-one: 88%)<sup>22</sup>. As resistance of *H. pylori* to furazolidone remains below 5% in Asia and South America, a systematic review and meta-analysis of 14 studies compared furazolidone- with non-furazolidone-containing regimens. Twelve studies evaluated the safety of furazolidone with different treatment durations, and four studies assessed variable doses; finally, four studies analyzed high versus low dose of furazolidone. Compared with other antibiotic regimens, furazolidone-containing regimens had superior efficacy with a similar risk of total adverse events. A low daily dose of 200 mg is safe and well-tolerated for a 14-day regimen, which should be recommended for *H. pylori* infection<sup>23</sup>. The effectiveness of a novel rifabutin-based therapy (rifabutin, amoxicillin, omeprazole) for *H. pylori* eradication was higher than dual therapy with a high dose of amoxicillin (3 g) and lansoprazole and these findings suggest the potential use of a rifabutin-based therapy as first-line empirical *H. pylori* treatment. No rifabutin resistance was detected with a satisfactory safety profile<sup>24-26</sup>. Some other systematic reviews and me-

ta-analyses evaluated the efficacy of nitazoxanide-based regimen for the eradication of *H. pylori*. Thirteen studies including 1,028 patients were analyzed in a meta-analysis<sup>27</sup>. *H. pylori* eradication was successful in 867 patients with a pooled eradication rate of 86%. The nitazoxanide-based regimen is safe and successful as a salvage therapy in patients who have failed prior treatments<sup>27</sup>. A systematic review<sup>28</sup> from the Hp-EuReg was performed to evaluate the efficacy and safety of first-line and rescue treatments in patients allergic to penicillin. In these patients, a triple combination with PPI + clarithromycin + metronidazole should not be generally recommended as a first-line treatment, while a quadruple regimen with PPI + bismuth + tetracycline + metronidazole seems to be a better option. As a rescue treatment, this quadruple regimen (if not previously prescribed) or a triple regimen with PPI + clarithromycin + levofloxacin could be used but they achieved suboptimal (<80%) results<sup>28</sup>. In a randomized, open-label, multicenter study from China, esomeprazole and bismuth plus either berberine and amoxicillin or tetracycline and furazolidone for 14 days were analyzed. The efficacy of both regimens as rescue treatments was satisfactory and reached similar results (81.5% and 85.0%, respectively)<sup>29</sup>.

### SUSCEPTIBILITY-GUIDED THERAPY

Because of the decline of eradication rates and increase in antibiotic resistance, susceptibility-guided treatments have been proposed as a means of improving falling eradication rates. In the last year three Chinese studies were conducted with susceptibility-guided therapies.

Luo et al<sup>30</sup> revealed that, overall, susceptibility-guided therapy achieved eradication rates of 92.9%. The eradication rates in a study by Pan et al<sup>31</sup> for tailored triple therapy (TATT), tailored bismuth containing quadruple therapy (TABQT), and traditional bismuth containing quadruple therapy (TRBQT) were 67.32%, 63.69%, and 85.99%, respectively, in the ITT analysis. Kong et al<sup>32</sup> showed significantly higher eradication rates in the TABQT group than in the levofloxacin-bismuth quadruple therapy (LBQT) group (89.6% and 64.8%, respectively). Among patients in the TABQT group with levofloxacin susceptibility, eradication rates were similar in the amoxicillin, levofloxacin, esomeprazole and colloidal bismuth pectin (ALEB) and amoxicillin, furazolidone, esomeprazole and colloidal bismuth pectin (AFEB) subgroups (86.3% vs. 90.0%).

### ANTIBIOTIC RESISTANCE

A number of studies in the last few years reported on the important topic of antimicrobial resistance of *H. pylori* strains. A Taiwanese study<sup>33</sup> yielded progressively higher primary resistance rates for clarithromycin, levofloxacin and metronidazole among naïve patients who received first-line eradication therapy. In the Russian Federation, 11 studies, (on 808 isolates) revealed the following *H. pylori* resistance rates: clarithromycin: 10.39%, metronidazole: 33.95%, amoxicillin: 1.35%, and levofloxacin: 20.0%<sup>34</sup>. A Korean study showed similar resistance rates<sup>19</sup> (Table 2). Brazilian researchers showed that *H. pylori* J99 and *Candida albicans* ATCC 10231 were cocultured in the presence of subinhibitory concentrations of amoxicillin and clarithromycin as stressors. The viability of bacteria within yeasts was evaluated, confirming the entry of bacteria into *Candida*, amplifying, by PCR, the *H. pylori* 16S rRNA gene in total yeast DNA. The internalization of *H. pylori* into *C. albicans* in the presence of antibiotics is dependent on the type of antibiotic used, and the researchers propose that a therapy including amoxicillin may induce the entry of the bacterium into *Candida*, thus negatively affecting the success of the treatment<sup>35</sup>.

### CHANGES IN GUT MICROBIOTA

Recent data suggest that the perturbation of gut microbiota is transient, being restored to pre-treatment states 2 months after triple therapy, but the recovery was slower in patients treated with CT. *Acinetobacter lwoffii*, *Streptococcus anginosus* and *Ralstonia* were

**TABLE 2. ANTIBIOTIC RESISTANCE RATES TO *HELICOBACTER PYLORI* ISOLATES, PUBLISHED IN 2020 AND 2021.**

Author	Country	Sample size	Antibiotic	Resistance	
Liang et al <sup>33</sup>	Taiwan	Primary resistance N=1,369	Clarithromycin	11.8-20.4%	
			Levofloxacin	17.3-38.8%	
		Secondary resistance N=196		Primary	30.5-64.7%
				Secondary	65.9-100%
Tertiary resistance N=184	Metronidazole	Primary	25.6-42.3%		
		Secondary	40.5-77.4%		
		Tertiary	44.4-88.2%		
		Dual CLA+MET resistance	2.4-10.4%		
Andreev et al <sup>34</sup>	Russia	N=808	Clarithromycin	10.39%	
			Levofloxacin	20.0%	
			Metronidazole	33.95%	
			Dual CLA+MET resistance	2.7%	
Bang et al <sup>19</sup>	Korea	N=233	Clarithromycin	23.5%	
			Levofloxacin	42.2%	
			Metronidazole	40.0%	
			Dual CLA+MET resistance	6.7%	

CLA: clarithromycin, MET: metronidazole.

enriched, while *Roseburia* and *Sphingomonas* were depleted in patients with persistent inflammation a year after *H. pylori* eradication. A distinct cluster of oral bacteria comprising *Peptostreptococcus*, *Streptococcus*, *Parvimonas*, *Prevotella*, *Rothia* and *Granuli-catella* genera were associated with emergence and persistence of gastric atrophy (GA) and intestinal metaplasia (IM). The probiotic *Faecalibacterium prausnitzii* was depleted in subjects who developed GA following *H. pylori* eradication<sup>36</sup>. A Chinese population-based study<sup>37</sup> yielded that *H. pylori* infection contributes significantly to gastric microbial dysbiosis that may be involved in carcinogenesis. A prospective study<sup>38</sup> which analyzed the effects of vonoprazan (VPZ) on gut microbiota, showing interesting results, compared stool samples collected at the following three time points: before treatment, 1-2 days after completion of treatment, and at a later time when treatment was successful. The number of Actinobacteria decreased immediately after eradication therapy and returned to pre-treatment conditions three months later. The alpha-diversity was lost immediately after eradication therapy; however, it was restored to pretreatment conditions 3 months later<sup>38</sup>. In the *H. pylori*-uninfected stomach, relative abundance of Proteobacteria increases, relative abundance of Firmicutes and Fusobacteria decreases, and microbial diversity decreases with aging. *H. pylori* eradication does not always restore gastric microbiota; in some individuals, gastric colonization by *Acinetobacter* sp. occurs after anti-Helicobacter treatment<sup>39</sup>. Fecal samples from Chinese children were collected at weeks 0, 2, 6, and 52, and alterations in the gut microbiota were analyzed by 16S rRNA gene. Eradication of *H. pylori* infection led to a transient dysbiosis of gut microbiota, and these changes almost recovered a year post-eradication, which indicates the long-term safety of *H. pylori* therapy<sup>40</sup>. In patients who received 14-day BQT consisting of omeprazole, clarithromycin, metronidazole, and bismuth, some beneficial bacteria were decreased including *Bacteroides*, *Faecalibacterium*, *Phascolarctobacterium*, *Roseburia*, *Bifidobacterium*, and *Blautia* genera. Some detrimental bacteria were increased including genera *Escherichia*, *Shigella*, *Klebsiella*, *Enterococcus* and *Streptococcus*. The changes almost returned to the pre-eradication level one year after therapy<sup>41</sup>. A pilot study<sup>42</sup> on washed microbiota transplantation in 32 eligible patients revealed an overall *H. pylori* eradication rate of 40.6%. Compared with lower gastrointestinal tract delivery route, middle gastrointestinal tract delivery route seems to be a more suitable way to treat *H. pylori* infection (58.33% and 16.67%, respectively).

## OTHER THERAPIES

Probiotics decrease side-effects, and improve compliance, thereby leading to increased eradication rates. Probiotics are beneficial to patients with *H. pylori* infection by modulating the gut microbiota. Biofermin-R (BFR) is a multiple antibiotic-resistant lactic acid bacteria preparation of *Enterococcus faecium*. Patients in group 1 (BFR<sup>-</sup>) received VPZ (20 mg twice daily), amoxicillin (750 mg twice daily), and clarithromycin (400 mg twice daily) for 7 days. Patients in group 2 (BFR<sup>+</sup>) received BFR (3 tablets/day) for 7 days. Supplementation with BFR prevented the decrease in alpha-diversity after eradication therapy (day 7). The incidence rate of diarrhea was not significantly higher in the BFR<sup>-</sup> than in the BFR<sup>+</sup> group (73.1% and 56.5%, respectively). Stool consistency was comparable and with suppressed stool softening in the BFR<sup>-</sup> group<sup>43</sup>. In a Japanese study<sup>44</sup> which included naïve patients to either VA-dual therapy (vonoprazan 20 mg + amoxicillin 750 mg twice daily) or VAC-triple therapy (vonoprazan 20 mg + amoxicillin 750 mg + clarithromycin 200 mg twice daily) for 7 days. The eradication rates of VA-dual and VAC-triple therapies were 84.5% and 89.2%, respectively. The 7-day VPZ and low-dose amoxicillin dual therapy provided acceptable *H. pylori* eradication rates. The effectiveness and safety of second-line *H. pylori* eradication therapy were compared for VPZ- and PPI-based regimens. The VPZ-based regimen shows a significant superiority over the PPI-based regimen for second-line *H. pylori* eradication therapy<sup>45</sup>. A non-inferiority trial of the *H. pylori* eradication rate using the dual therapy with VPZ (20 mg b.i.d.) and amoxicillin (500 mg t.i.d.) for 1 week to that of the triple therapy with VPZ (20 mg b.i.d), amoxicillin (750 mg b.i.d) and clarithromycin (200 mg b.i.d) for 1 week was retrospectively studied. The results showed that the dual therapy (92.9%) was not inferior to triple therapy (91.9%). VPZ-based dual therapy (VPZ 20 mg b.i.d and amoxicillin 500 mg t.i.d for 1 week) provides an acceptable eradication rate of *H. pylori* infection without the need for a second antimicrobial agent, such as clarithromycin<sup>46</sup>. Several comparative randomized controlled trials and meta-analyses revealed the superiority of VPZ in eradicating *H. pylori*, notably the resistant strains. The adverse effect caused by VPZ is the long-term acid suppression that may induce elevated gastrin serum, hypochlorhydria, and malabsorption. The main limitation to these conclusions is that all VPZ studies have been conducted in Japan<sup>47</sup>. A randomized control trial which analyzed adding atorvastatin as a potential anti-inflammatory and antibacterial drug to the four-drug regimen of omeprazole, clarithromycin, bismuth, and amoxicillin is effective in the eradication of *H. pylori* with eradication rates in the intervention and control groups of 78.18% and 65.45%, respectively<sup>48</sup>. The drug-resistance phenomenon in *H. pylori* underlines the need for novel strategies to improve the eradication rate including alternative treatments combining antibiotic and non-antibiotic compounds with synergistic action. In an Italian study<sup>49</sup>, the antibacterial (minimum inhibitory and minimum bacterial concentrations) and anti-virulence effects (biofilm reduction and swarming motility inhibition) of resveratrol and new synthesized resveratrol-phenol derivatives, with a higher bioavailability, given alone and combined with levofloxacin were evaluated against resistant clinical *H. pylori* isolates. Resveratrol-phenol derivatives should be considered as candidates for innovative therapeutic schemes to tackle the *H. pylori* antibiotic resistance<sup>49</sup>. Furthermore, an interesting study aimed to assess the *in vitro* and *in vivo* effects of a natural herbal compound, dihydrotanshinone 28 I (DHT), against standard and clinical *H. pylori* strains. DHT demonstrated effective antibacterial activity against *H. pylori in vitro* with no development of resistance during continuous serial passaging. DHT eliminated preformed biofilms and killed biofilm-encased *H. pylori* cells more efficiently than the conventional antibiotic, metronidazole. In mouse models of multi-drug resistant *H. pylori* infection, dual therapy with DHT and omeprazole had a superior *in vivo* killing efficacy than standard triple therapy. Moreover, DHT treatment shows neglectable toxicity against normal tissues. These results suggest that DHT could be suitable for use as an anti-*H. pylori* agent in combination with PPIs to eradicate multidrug-resistant *H. pylori*<sup>50</sup>. Armeniaspirols, natural products isolated from *Streptomyces armeniacus*, have been previously identified as antibacterial agents against Gram-positive pathogens. In this study, armeniaspirol A (ARM1) exhibited potent antibacterial activity against *H. pylori*, including multidrug-resistant strains. In a mouse model of multidrug-resistant *H. pylori* infection, dual therapy with ARM1 and omeprazole showed efficient *in vivo* killing efficacy comparable to the STT and induced minimal toxicity against normal tissues<sup>51</sup>. *Clostridium butyricum* and *Bacillus coagu-*

lans eradicate *H. pylori* to some extent, and one study recommends them as an alternative option for patients who are unwilling to receive standard therapies or who are intolerant to antibiotics<sup>52</sup>.

## CONCLUSIONS

High-dose PPI-amoxicillin dual therapy is an effective and safe regimen for *H. pylori* eradication as recommended by the current guidelines for patients undergoing initial or rescue therapies and can be considered when drug susceptibility tests are not available. Triple therapy for 14 days may be sufficient in regions with low clarithromycin resistance. Less expensive sequential and hybrid therapies were more successful and as well tolerated as CT. BQT with tetracycline and modified BQT with amoxicillin were highly effective and safe for *H. pylori* eradication and should be kept in mind in *H. pylori* first-line therapies in regions with high metronidazole and clarithromycin resistance. Also, these therapies showed good performance in second- and third-line regimens and revealed satisfactory eradication rates as a rescue therapy. In patients allergic to penicillin, quadruple regimens with BQT seem to be a good option. Rifabutin- and nitazoxanide-based regimens are safe and effective as salvage therapies in patients who have failed prior treatments. An important note is the progressively higher primary resistance rates for clarithromycin, levofloxacin and metronidazole in patients who received first-line eradication therapy, which imposes susceptibility-guided therapy for acceptable eradication rates. VPZ is promising in eradicating *H. pylori* infection, notably the resistant strains. The drug-resistance phenomenon in *H. pylori* underlines the need for novel strategies to improve eradication rates, including alternative treatments which require further research. Eradication of *H. pylori* infection can lead to transient dysbiosis of gut microbiota, and these changes were recovered one-year post-eradication, which indicates the long-term safety of *H. pylori* therapy.

## Conflict of interest

The authors declare to have no conflict of interests.

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