

## Recent progress in *Helicobacter pylori* treatment

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### Abstract

The main challenge in the field of *Helicobacter pylori* (*H. pylori*) infection is antibiotic resistance, which influences the efficacy of eradication regimens. Bismuth-containing quadruple therapy has been confirmed as an effective regimen for eradicating *H. pylori*, especially in strains with antibiotic resistance. High-dose proton-pump inhibitor-amoxicillin dual therapy could decrease the use of unnecessary antibiotics, which is a promising alternative approach. Adjuvant therapy (specific probiotic or vitamin) also showed good results, although more evidence is needed. Novel anti-*H. pylori* drugs are needed, and the establishment of the *H. pylori* database is an effective way to acknowledge the real-time information of *H. pylori* management. This review provides the recent progress of *H. pylori* treatment, and further studies are needed to address the role of different regimens in improving *H. pylori* eradication rate, especially in strains with antibiotics resistance.

**Keywords:** *Helicobacter pylori*; Bismuth, dual therapy; Vonoprazan; Probiotics; Vitamin

### Introduction

*Helicobacter pylori* (*H. pylori*) is a gastric Gram-negative, spiral-shaped microaerophilic pathogen closely associated with gastric and extra-gastric diseases (chronic gastritis, peptic ulcers, gastric mucosa-associated lymphoid tissue lymphoma, gastric cancer, iron deficiency anemia, etc).<sup>[1,2]</sup> Appropriately half of the global population is infected with *H. pylori*, and the prevalence of *H. pylori* varied among regions, which appeared to be explained by the differences in economic and social conditions.<sup>[3,4]</sup> Additionally, *H. pylori* recurrence should not be neglected. The global annual *H. pylori* recurrence rate was higher in the 2010s (4.8%) than in the 1990s (3.9%) and 2000s (4.4%), which might increase the number of the infected person.<sup>[5]</sup> *H. pylori* infection persists for a lifetime if not eradicated. Several consensus reports have been published in the past 5 years, mainly focusing on the management of *H. pylori* infection.<sup>[6-10]</sup>

Currently, the main challenge in the field of *H. pylori* infection is antibiotic resistance, which influences the efficacy of eradication regimens. The latest systematic review and meta-analysis reported that the primary and secondary resistance rates to clarithromycin, metronidazole, and levofloxacin exceeded 15% (alarming levels) in all the World Health Organization (WHO) regions.<sup>[11]</sup> In 2017, clarithromycin-resistant *H. pylori* was defined as a

high-priority bacterium in the WHO priority list of antibiotic-resistant bacteria.<sup>[12]</sup> The traditional proton-pump inhibitor (PPI)-based triple therapy (PPI plus two antibiotics) has been used for eradicating *H. pylori* for more than 20 years. However, PPI-based triple therapy provides low treatment success (intention-to-treat [ITT] analysis below 80% in most studies),<sup>[13]</sup> which is defined as unacceptable according to the report card used to grade *H. pylori* therapy.<sup>[14]</sup> In 2012, the Maastricht IV/Florence Consensus Report<sup>[15]</sup> recommended that PPI-clarithromycin-containing triple therapy should be abandoned in areas with clarithromycin resistance rates above 15% to 20%. In addition, bismuth-containing quadruple therapy (BQT) is recommended as a first-line treatment for eradicating *H. pylori* in areas with high or low clarithromycin resistance because of its high efficiency, safety, and tolerance.<sup>[15]</sup> More recently, a number of studies were conducted to evaluate the efficiency of other regimens (eg, sequential, concomitant, hybrid therapy, high-dose PPI-amoxicillin dual therapy, vonoprazan [VPZ]-based triple therapy, probiotics supplemented triple therapy or combined with BQT) in *H. pylori* eradication. In this review, we summarize the recent progress in *H. pylori* eradication.

### BQT

Bismuth, a chemical element with the symbol Bi (atomic number 83), has been used for treating syphilis, colitis, and

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wound infection for over three centuries.<sup>[16]</sup> The treatment success of bismuth alone in eradicating *H. pylori* was 16% to 20%, although it belongs to the non-antibiotic.<sup>[17]</sup> Additionally, the bismuth add-on triple therapy can improve an additional 30% to 40% success in resistant strains. Recently, Ko *et al*<sup>[18]</sup> conducted a systemic review and meta-analysis to evaluate the efficacy of non-antibiotic (bismuth) supplements as a first-line regimen for *H. pylori* eradication. In total, twenty-five randomized trials (3990 patients) were included for analysis. According to per protocol (PP) analysis, the *H. pylori* eradication rate was higher in the BQT group (85.8%) than in the non-BQT regimen group (74.2%), which was significantly different. Of the three trials evaluating the efficiency of bismuth additions in standard triple therapy, BQT showed superior to triple therapy (odds ratio [OR]: 3.55, 95% confidence interval [CI]: 2.33–5.41). In five trials conducted in areas with a clarithromycin resistance rate greater than 15%, BQT also showed a higher eradication rate than that of the control group (OR: 3.55, 95% CI: 1.07–2.39). Moreover, an *in vitro* study<sup>[19]</sup> revealed that the bacterium-host cell adhesion, oxidative stress defense ability, and pH buffering ability of *H. pylori* were reduced by treatment with bismuth, which might explain the sustainable antimicrobial activity of bismuth against *H. pylori* and the relatively low *H. pylori* resistance to bismuth. These advantages of bismuth make BQT achieve acceptable or good or excellent outcomes in most studies, even in areas with high resistance rates.

There are still multiple researches conducted in this year to evaluate the efficiency and side effects of different antibiotics doses, frequency, combinations in BQT. Moreover, the efficiency and safety of BQT in real-world practice were evaluated in China and Europe. In 2013, the European Helicobacter and Microbiota Study Group promoted an international multicenter prospective non-interventional registry regarding *H. pylori* management, which will last for more than 10 years. The interim analysis of data from this registry was performed to evaluate the efficiency of BQT in treating 1141 infected patients with no history of *H. pylori* eradication.<sup>[20]</sup> According to the ITT and PP analyses, the eradication rates of these regimens were 88% and 94%, respectively. The 14-day regimens showed a higher eradication rate than the 10-day regimens (ITT: 92% *vs.* 79%). In addition, good compliance and no serious adverse reactions were observed in this study.<sup>[20]</sup> Considering the drugs used in *H. pylori* eradication regimens should be given 2 to 4 times daily, which might influence the compliance in a subset of patients, Auttajaron *et al*<sup>[21]</sup> conducted a prospective randomized pilot study to evaluate whether a once-daily dosing *H. pylori* eradication regimen (levofloxacin 750 mg, clarithromycin 1 g, rabeprazole 60 mg, and bismuth subsalicylate 1048 mg for 7 or 14 days) could provide a good compliance and eradication rate. It is noteworthy that a high dose of rabeprazole was used in this study, which would be expected to provide a median pH  $\geq 4$  for approximately 20 h/day and improve the efficiency of antibiotics. Fourteen-day regimens provided 94% treatment success in 50 subjects, and a high eradication rate was also achieved in cases with clarithromycin or levofloxacin resistance, which suggested that once-a-day tailored

14-day BQT could be the empiric therapy for eradicating *H. pylori* in Thailand.<sup>[21]</sup>

The prevalence of *H. pylori* primary resistance to clarithromycin, metronidazole, and levofloxacin was high and bismuth is available in China. In the *Fifth Chinese National Consensus*, seven BQT (different combinations of antibiotics) were recommended.<sup>[10]</sup> Our group conducted an observational study of furazolidone-containing BQT for eradicating 584 *H. pylori*-infected patients in real-world settings and found that 10- or 14-day regimens were efficient and safe.<sup>[22]</sup> A single-center, prospective, randomized, open-label study was conducted to compare the cost-efficacy of 14-day furazolidone-based and clarithromycin-based BQT as the first-line treatment for *H. pylori* infection in China, the results showed that no differences in the eradication rate and adverse reactions were observed in the two groups; however, furazolidone-based BQT was more cost-effective than clarithromycin-based BQT.<sup>[23]</sup> Considering that clarithromycin is expensive but available in most regions of China, Chen *et al*<sup>[24]</sup> investigated the efficiency and economy of half-dose or standard-dose clarithromycin-containing BQT in populations of China. The results indicated similar eradication frequencies in the two groups. However, the adverse reactions and cost were less in half-dose clarithromycin-containing BQT in comparison with standard-dose clarithromycin-containing BQT. In addition, the high efficiency and safety of different antibiotic combinations in BQT (eg, amoxicillin and doxycycline or cefuroxime and levofloxacin) were achieved in *H. pylori* clinical practice in China.<sup>[25,26]</sup> Interestingly, twice daily short-message-based re-education could improve compliance in the young population, leading to an increased eradication rate of BQT.<sup>[27]</sup> Improving the eradication rate of the first-line regimens is of great importance because it avoids the secondary resistance to antibiotics and reduces *H. pylori* prevalence. If the sensitive antibiotics are available, selecting two sensitive antibiotic combinations (amoxicillin + furazolidone or tetracycline + furazolidone or amoxicillin + tetracycline) in BQT is a good choice in clinical practice of China because the expected high eradication rate could be achieved. If not, the other antibiotic combinations (one sensitive and one resistant antibiotic) are also used.

A novel three-in-one single capsule (bismuth, metronidazole, and tetracycline; BMT) has been used in many countries. A meta-analysis of BMT plus PPI for *H. pylori* infection (studies were selected up to October 2018) showed that a 10-day treatment of this regimen provides approximately 90% success in the first-line and second-line treatment. In addition, this outcome was also achieved with clarithromycin- or metronidazole-resistant strains.<sup>[28]</sup> In the northwest of Spain, an area with a high clarithromycin resistance rate (22.4%), the eradication rates of BMT (four times a day) plus omeprazole (twice a day) for 10 days were 94.4% and 96.2% according to ITT and PP analysis.<sup>[29]</sup> In addition, this regimen was safe. This result was also confirmed by a recent pilot study.<sup>[30]</sup> Taken together, despite the different combinations of antibiotics and PPIs used in BQT [Table 1], this regimen is efficient, safe, and tolerated for eradicating *H. pylori* in an era of increasing antibiotic resistance.

**Table 1: Summary of bismuth-containing quadruple therapy studies conducted in 2019.**

Location	Bismuth	Antibiotics	PPIs	Days	n	Eradication rates (ITT, %)	Eradication rates (PP, %)	Adverse reaction rates (%)	References
Europe	BS (120 or 240 mg, bid)	Amo 1 g + Cla 500 mg, bid	E or O or P or R (20 or 40 mg, bid)	10 or 14	1141	88.0	94.0	36.0	[20]
Thailand	BS (1048 mg, qd)	Lev 750 mg + Cla 1 g, qd	R (20 mg, qd)	7	50	84.0	84.0	-	[21]
	BS (1048 mg, qd)	Lev 750 mg + Cla 1 g, qd	R (20 mg, qd)	14	50	94.0	94.0	-	[22]
China	BC (200 mg, bid)	Amo (1 g, bid)	I (5 mg, bid)	10	475	-	93.7	6.1	
		Fur (100 mg, bid)	R (10 mg, bid)	14	109	-	98.2	17.4	
		Tet (500 mg, bid)	E (20 mg, bid)						
		Lev (500 mg, qd)	L (30 mg, bid)						
China	BC (220 mg, bid)	Amo 1 g + Fur 100 mg, bid	P (40 mg, bid)	14	92	90.2	93.3	19.6	[23]
	BC (220 mg, bid)	Amo 1 g + Cla 500 mg, bid	E (20 mg, bid)	14	93	86.0	87.9	14.0	[24]
China	BC (600 mg, bid)	Amo 1 g + Cla 250 mg, bid	E (20 mg, bid)	14	105	86.7	91.0	34.3	
	BC (600 mg, bid)	Amo 1 g + Cla 500 mg, bid	E (20 mg, bid)	14	105	86.7	91.9	55.2	[25]
China	CBT (220 mg, bid)	Amo 1 g + Dox 100 mg, bid	R (10 mg, bid)	14	118	89.8	93.8	6.8	[26]
China	BC (220 mg, bid)	Lev 500 mg qd + Cef 500 mg bid	E (20 mg, bid)	14	152	85.5	90.1	21.3	[27]
China	CBP (200 mg + SMRE bid)	Amo 1 g + Cla 500 mg, bid	L (30 mg, bid)	14	155	74.2	82.1	30.7	
China	CBP (200 mg, bid)	Amo 1 g + Cla 500 mg, bid	L (30 mg, bid)	14	155	67.7	73.4	42.0	[29]
Spain	BC (420 mg, qid)*	Met 375 mg + Tet 375 mg, qid*	O (20 mg, bid)	10	54	94.4	96.2	46.3	[30]
Italy	BC (420 mg, qid)*	Met 375 mg + Tet 375 mg, qid*	E (40 mg, bid)	10	32	93.7	96.6	46.9	

\* As part of three-in-one capsules. PPI: Proton-pump inhibitor; ITT: Intention-to-treat; PP: Per protocol; BS: Bismuth salts or bismuth subsalicylate; qd: Once per day; BC: Bismuth citrate or bismuth potassium citrate; CBT: Colloidal bismuth tartrate; CBP: Colloidal bismuth pectin; SMRE: Short-message-based re-education Amo: Amoxicillin; Cla: Clarithromycin; Cer: Cefuroxime; bid: Twice per day; Lev: Levofloxacin; qid: Four times per day; Fur: Furazolidone; Tet: Tetracycline; Dox: Doxycycline; Met: Metronidazole; E: Esomeprazole; O: Omeprazole; P: Pantoprazole; R: Rabeprazole; I: Ilaprazole; L: Lansoprazole; -: Unavailable information.

### Sequential, hybrid, and concomitant therapy

Compared to the conventional regimens, drug administration sequences were modified in sequential, hybrid, and concomitant therapy. The sequential therapy was initially reported to achieve a high eradication rate and is widely used in Italy.<sup>[31]</sup> However, the efficiency of this regimen has decreased over time because it was influenced by clarithromycin and metronidazole resistance.<sup>[7,32]</sup> Therefore, sequential therapy was not recommended by the recent consensus reports.<sup>[7,8,33]</sup> Few sequential therapy articles were reported this year. Zullo *et al*<sup>[34]</sup> reported that 10- and 14-day sequential therapies (esomeprazole 40 mg and amoxicillin 1 g twice for 5 or 7 days followed by esomeprazole 40 mg, clarithromycin 500 mg, and tinidazole 500 mg twice for 5 or 7 days) achieved high treatment success (above 90% according to PP analysis) for first-line *H. pylori* eradication in clinical practice in Italy. However, the antibiotic resistance information was lacking in this study, and the efficiency of these regimens in the sub-groups of antibiotic resistance was unclear. In Korea, where the antibiotic resistance rates are relatively high, the efficiency of 10-day sequential therapy was reported as 76.3% and 85.0% according to ITT and PP analysis, which was defined as an unsatisfied outcome, although it showed superior to 7-day clarithromycin-containing triple therapy.<sup>[35]</sup>

Concomitant and hybrid therapy contain three antibiotics and PPI; the eradication rate of these regimens were not undermined by clarithromycin or metronidazole resistance, except for dual resistance. A prospective, open-label study conducted in Greece showed that the eradication rates of 10- and 14-day concomitant therapy were above 90% according to PP analysis, in addition, the regimens were tolerated, and 31.3% of treated patients presented side effects.<sup>[36]</sup> Consistent with this study, 10-day concomitant therapy also showed a markedly higher eradication rate than 7-day triple therapy (PP: 90.6% *vs.* 71.4%).<sup>[35]</sup> Moreover, the efficiency of 14-day concomitant therapy was similar with 10-day BQT.<sup>[29]</sup> Hybrid therapy has attracted widespread attention in recent years. A systemic review and meta-analysis (eight studies with 2516 subjects included)<sup>[37]</sup> showed that the mean cure rates of hybrid therapy were 88.5% (1207 patients) and 93.3% (1109 patients) according to ITT and PP analysis. No difference in eradication rate was observed between hybrid and concomitant therapy. Recently, Francesco *et al*<sup>[38]</sup> conducted a prospective, open-label pilot study showing that a novel hybrid therapy with a 5-day dual therapy followed by a 5-day BMT therapy achieved excellent outcome (ITT: 97.5%, PP: 100%) as the first-line therapy for *H. pylori* infection. Moreover, reverse hybrid therapy (PPI plus amoxicillin for 14 days and clarithromycin plus metronidazole for the initial 7 days) achieved a similar eradication rate in comparison with 14-day BQT in the total infected population and in cases with clarithromycin-resistant strains or metronidazole-resistant strains. Fewer adverse events were observed in reverse hybrid therapy (18.7%) than in BQT (47.7%).<sup>[39]</sup> Although comparable outcomes were achieved between concomitant, hybrid therapy, and BQT in some studies,<sup>[29,39]</sup> the drug administrations of concomitant and hybrid therapy were complex, which might influence the patient

compliance. Moreover, the effect of concomitant and hybrid therapy on the short- or long-term gut microbiota remained uncertain and need to be further investigated.

### High-dose PPI-amoxicillin dual therapy

High-dose dual therapy (HDDT) was defined as the combination of amoxicillin (eg, 1 g tid or 750 mg qid) and PPI (standard-dose tid or qid or double standard-dose bid) for 14 days. Previous studies<sup>[40,41]</sup> showed that HDDT achieved high treatment success as empirical first-line or rescue therapy for *H. pylori* infection. A recent systematic review and meta-analysis included four randomized clinical trials with 829 patients to compare the efficiency and side effects in the HDDT and BQT groups. Similar eradication rates and compliances were observed in both groups. However, the number of side effects was less in HDDT than BQT.<sup>[42]</sup> Three randomized trials were conducted this year to evaluate the efficiency of HDDT for first-line *H. pylori* therapy. Yang *et al*<sup>[43]</sup> randomly allocated *H. pylori*-infected, treatment-naïve patients into two groups: modified HDDT (amoxicillin 750 mg and esomeprazole 20 mg, qid) and BQT (bismuth potassium citrate 1 g, amoxicillin 1 g, clarithromycin 500 mg, and esomeprazole 20 mg; bid), the results showed that modified HDDT showed a similar eradication rate as BQT, although the antibiotic resistance was higher in the HDDT group than in the BQT group, and the side effects and cost of medications were lower in the HDDT group than those in the BQT group. Moreover, variations in the *CYP2C19*, *IL-1B-511*, and *H. pylori VacA* genotypes were ameliorated by HDDT.<sup>[43]</sup> HDDT (esomeprazole 40 mg tid and amoxicillin 750 mg qid) was also confirmed to achieve a high eradication rate (ITT: 91.7%, PP: 95.7) as first-line *H. pylori* therapy in comparison with 7-day non-bismuth quadruple but with fewer side effects.<sup>[44]</sup> Considering the role of bismuth in improving the additional eradication rate in resistance strains,<sup>[43]</sup> Yu *et al*<sup>[46]</sup> conducted an open-label, randomized single-center study to address whether the addition of bismuth to HDDT could improve the eradication rate. The study indicated that the eradication rate was higher in the HDDT group than in the HDDT with bismuth group (ITT: 92.5% *vs.* 88.8%, PP: 96.1% *vs.* 93.3%), although there was no significant difference. The additional effect of bismuth on HDDT was only observed among infected smokers. High-dose PPI-amoxicillin dual therapy could achieve acceptable outcomes and decrease the use of unnecessary antibiotics, which is a promising alternative approach. Considering the concomitant medication and the side effects were common in elderly populations, it is of great interests to investigate the efficiency and safety of HDDT in elderly populations.

### VPZ-based therapy

VPZ is a new, potent acid-inhibitory drug, which became clinically available in Japan in 2015. Compared to conventional PPI, gastric acid was inhibited by VPZ more rapidly, more strongly and for a longer duration. Moreover, it does not require pharmacological activation and has a longer half-life.<sup>[47]</sup> A study<sup>[48]</sup> reported that VPZ (20 mg bid) potently suppressed acid for 24 h irrespective of

**Table 2: Summary of vonoprazan-based studies conducted in 2019.**

Location	Competitive acid blocker	Antibiotics	Days	n	F or S or T-line	Eradication rates (ITT, %)	Eradication rates (PP, %)	References
Japan	VPZ (20 mg, bid)	Amo 750 mg, bid + Cla 200 or 400 mg, bid	7	-	F-line	81.4	89.1	[51]
Japan	VPZ (20 mg, bid)	Amo 750 mg + Met 250 mg, bid	7	-	S-line	80.0	90.1	[52]
	VPZ (20 mg, bid)*	Amo 750 mg + Cla 400 mg, bid*	7	293	F-line	-	92.2	
Japan	VPZ (20 mg, bid)	Amo 750 mg + Cla 200 mg, bid	7	189	F-line	91.0	91.0	[53]
Japan	VPZ (20 mg, bid)	Amo 750 mg + Stf 100 mg, bid	7	31	T-line	75.8	83.3	[54]
Japan	VPZ (20 mg, bid)	Amo 750 mg + Cla 400 mg, bid	7	290	F-line	79.0	88.4	[55]
	VPZ (20 mg, bid)	Amo 750 mg + Met 250 mg, bid	7	60	S-line	81.7	90.7	[56]
	VPZ (20 mg, bid)	Amo 750 mg + Stf 100 mg, bid	7	57	T-line	93.0	93.0	
Japan	VPZ (20 mg, bid)	Amo 500 mg, tid	7	56	F-line	92.9	94.4	
	VPZ (20 mg, bid)	Amo 750 mg + Cla 200 mg, bid	7	56	F-line	91.9	92.7	

\* As part of VPZ blister-packaged drug. ITT: Intention-to-treat; PP: Per protocol; VPZ: Vonoprazan; Amo: Amoxicillin; bid: Twice per day; Cla: Clarithromycin; Met: Metronidazole; Stf: Sifloxacin; tid: Three times per day; F: First; S: Second; T: Third; -: Unavailable information.

*CYP2C19* genotype, with intra-gastric pH 4 and 5 holding time rates as high as 100% and 99%, respectively. In this regard, the advantages of VPZ were considered to improve the efficiency of *H. pylori* eradication regimens. A recent systematic review with meta-analysis reported that VPZ-based triple therapy showed superior efficacy for *H. pylori* eradication in comparison with PPI-based triple therapy, which was attributed to the increased eradication rate among the clarithromycin-resistant *H. pylori* strains.<sup>[49,50]</sup>

The Tokyo *H. pylori* Study Group conducted a retrospective analysis to examine the trend of the eradication rate of *H. pylori* from 2013 to 2018 and examined factors concerning successful eradication,<sup>[51]</sup> in total, 4097 and 3572 patients (from the metropolitan area) in the first- and second-line eradication therapies were included in the study, the percentages of lansoprazole in the first-line and second-line regimens dramatically decreased from 81.8% in 2013 to only 3.4% in 2018 and 65.7% in 2013 to only 1.6% in 2018. A similar trend was also observed in rabeprazole. In contrast, the percentage of VPZ in the first- and second-line eradication therapies rapidly increased to 95.5% and 90.2% in 2018, respectively. The eradication rate of the first-line therapy was relatively low (<80%) in 2013 and 2014. However, the eradication rate of the first-line therapy increased from 2015 to 2018 because of the increased use of VPZ in the regimens. Univariate logistic regression analysis revealed that VPZ and age over 75 years were independent factors for successful eradication. Compliance is an important factor influencing successful *H. pylori* eradication.<sup>[51]</sup> The VONOSAP pack (available in Japan since 2016) is a triple-drug blister pack containing VPZ as packaged medicine, which may be able to increase drug adherence of *H. pylori* eradication. Nishida *et al*<sup>[52]</sup> found that the overall successful eradication rates were above 90% in the VPZ-based therapy group and the VONOSAP group. In the sub-group analysis of patients older than 75 years, the VONOSAP group showed a better treatment benefit than the VPZ group. In addition, smoking, drinking, and lifestyle-related factors had no effects on the failure of *H. pylori* eradication using VPZ-based therapy.<sup>[53]</sup>

Sifloxacin is the major antibiotic used in the third-line treatment of *H. pylori* in Japan. The VPZ group (VPZ 20 mg, amoxicillin 750 mg, and sifloxacin 100 mg, bid) showed a significant difference compared to the PPI group in the third-line treatment of *H. pylori*.<sup>[54]</sup> Moreover, the *H. pylori* eradication rate in the third-line treatment was higher in VPZ-based therapy than in PPI-based therapy, even in the sifloxacin-resistant *H. pylori* strains.<sup>[55]</sup> Considering the high eradication rate of VPZ-based triple therapy in the resistant *H. pylori* strains, VPZ with amoxicillin dosed in tid or qid manners is theoretically expected to achieve a sufficient eradication outcome. Recently, Furuta *et al*<sup>[56]</sup> confirmed that dual therapy with VPZ and amoxicillin was not inferior to VPZ-based therapy as the first-line therapy for *H. pylori*. Overall, VPZ-based triple therapy showed a high efficiency in the first or second or third-line treatment of *H. pylori* in Japan. Moreover, VPZ-based dual therapy showed a similar result with VPZ-triple therapy in the first-line *H. pylori* treatment [Table 2]. The emergence of VPZ shed a new light in eradicating *H. pylori* especially in an era of increasing antibiotic resistance.

### Susceptibility-guided therapy or tailored therapy

Theoretically, susceptibility-guided therapy is considered to achieve a high success rate because it is based on the results of antibiotic resistance and avoids misused antibiotics. Studies also indicated that susceptibility-guided therapy was as effective as the first-line or second-line treatment for *H. pylori* eradication, especially in regions with high antibiotic resistance.<sup>[57,58]</sup> However, Chen *et al*<sup>[59]</sup> found that susceptibility-guided therapy was not superior to local empiric therapy (esomeprazole 20 mg, bismuth 220 mg bid, amoxicillin 1 g, and metronidazole 400 mg tid) in Shanghai, China. Considering that susceptibility-guided therapy is time consuming and expensive, the clinical choice should depend on the availability of susceptibility testing and the efficiency of local empiric therapy. Recently, dual priming oligonucleotide-based multiplex polymerase chain reaction (DPO-PCR) has been introduced, which can detect *H. pylori*

infection and clarithromycin resistance based on the A2142G and A2143G mutations of 23S rRNA. A tailored therapy based on DPO-PCR showed a high efficiency and cost-effectiveness as the first-line treatment of *H. pylori* infection in Korea.<sup>[60-62]</sup> Moreover, the DPO-PCR method is well correlated with the culture-based susceptibility test.<sup>[60]</sup> GenoType HelicoDR is a molecular test that detects *H. pylori* infection and clarithromycin and levofloxacin resistance. A multi-center prospective open-label randomized study (526 patients included) conducted in France demonstrated that the eradication rate of tailored therapy based on the GenoType HelicoDR test was higher than empirical triple therapy and that tailored therapy in routine practice might be a means to limit the emergence of antibiotic resistance.<sup>[63]</sup> The emergence of PCR method provides a quick, convenient way to guide tailored therapy in clinical practice of *H. pylori*. However, the clinical application of this method should be elucidated using a large-scale prospective study.

### Probiotics

The effect of probiotic supplementation on the increased *H. pylori* eradication rate and reduced adverse reactions might be strain-specific. Several potential mechanisms included inhibiting colonization and adhesion of *H. pylori*, alleviating inflammation induced by *H. pylori*, regulating immune responses of *H. pylori*, reducing the incidence of adverse effects and subsequently improving compliance.<sup>[64,65]</sup> Zhou *et al*<sup>[66]</sup> conducted an updated systematic review and meta-analysis with trial sequential analysis to explore the effects of *Saccharomyces boulardii* as an adjuvant therapy on *H. pylori* eradication rates and adverse effects. The results showed that a significantly increased eradication rate and reduced side effects were observed in triple therapy with the *S. boulardii* group compared with the triple therapy group. *Lactobacillus*, as an adjunct to triple therapy, can also increase the efficiency of triple therapy and reduce the incidence of therapy-related diarrhea in adults and children.<sup>[67,68]</sup> Multiple shifts and alterations in the intestinal microbiota can be caused by *H. pylori* eradication.<sup>[69]</sup> However, supplementation with *Bacillus subtilis* and *Enterococcus faecium* with triple therapy could protect and restore the intestinal microbiota.<sup>[70]</sup>

### Vitamins

Vitamins (eg, vitamin C and E) could decrease oxidation reactions, eliminate reactive oxygen species and decrease N-nitrosamine in gastric fluid and exert an anti-oxidant effect, which may act as a protected role in gastric carcinogenesis. Li *et al*<sup>[71]</sup> conducted a blinded randomized placebo-controlled trial (3365 residents of high-risk region for gastric cancer included) to evaluate the effect of *H. pylori* treatment and vitamin supplementation on the incidence and mortality of gastric cancer. A total of 1130 *H. pylori*-infected participants received *H. pylori* eradication, and 1677 participants received one capsule of 250 mg of vitamin C, 100 U of vitamin E, 37.5 µg of selenium for 7.3 years and 7.5 mg of β-carotene for 6 months. After 22 years post-intervention, the results indicated that *H. pylori* treatment for 2 weeks and vitamin supplementation for 7.3 years

could reduce the incidence and mortality of gastric cancer. In addition, vitamin C and E are reported to have an inhibitory effect on *H. pylori* intensity and neutrophilic activity. The levels of vitamin C and E were decreased in *H. pylori*-positive patients and increased after *H. pylori* eradication. Our previous systematic review with meta-analysis showed that the addition of vitamin C and E at a high dose to eradication regimens could improve the efficiency.<sup>[72]</sup>

A multi-center observational prospective cohort study was conducted in China to explore whether serum vitamin D levels affected *H. pylori* infection and eradication rates. The level of vitamin D was significantly lower in 496 *H. pylori*-positive patients (17.0 ± 6.9 ng/mL) than in 257 *H. pylori*-negative patients (19.2 ± 8.0 ng/mL). Moreover, the *H. pylori* eradication rate was higher in patients with high serum vitamin D levels (≥10 ng/mL) than in patients with low serum vitamin D levels (<10 ng/mL).<sup>[73]</sup> Another study also reported the associations between vitamin D deficiency and increased risk of *H. pylori* infection.<sup>[74]</sup> A recent meta-analysis regarding the effect of vitamin D on *H. pylori* infection and eradication demonstrated that the average vitamin D level was lower in *H. pylori*-positive patients than in *H. pylori*-negative patients, and a lower *H. pylori* eradicate rate was observed in individuals with vitamin D deficiency.<sup>[75]</sup> Although the recent studies showed a correlation between vitamin D levels and eradication rates, a large-scale prospective study need to be conducted to address whether the addition of vitamin D could improve the eradication rate.

### Anti-*H. pylori* compounds

The search for new anti-*H. pylori* compounds can be a valuable route for drug discovery, which is an effective way to mitigate the challenges of anti-microbial resistance. A total of 1120 US Food and Drug Administration-approved drugs for molecules that bind to HP1043 (also named HsrA, involved in cell viability, transcriptional activator, and crucial cellular functions of *H. pylori*) were screened and identified to explore the bactericidal activities against *H. pylori*, and only four of them (apigenin, chrysin, kaempferol, and hesperetin) showed high bactericidal activities against *H. pylori*. Notably, chrysin exhibited synergy function with clarithromycin or metronidazole, and hesperetin had an additive or synergetic function with clarithromycin or metronidazole, supporting their potential role as adjuvant in regimens, especially in the treatment of *H. pylori* strains with multidrug-resistance.<sup>[76]</sup> *H. pylori* flavodoxins, a small acidic redox protein, is essential for *H. pylori* survival and maybe a suitable drug target for *H. pylori*. An *in vivo* and *in vitro* study showed that a family of nitrobenzoxadiazole-based flavodoxin inhibitors had low toxicity and were effective against metronidazole-, clarithromycin-, and rifampicin-resistant *H. pylori* strains. In addition, these inhibitors could reduce the gastric colonization rate of *H. pylori* and were able to eradicate *H. pylori* in 60% of infected mice.<sup>[77]</sup>

### *H. pylori* databases

The European *Helicobacter* and Microbiota Study Group promoted an international multicenter prospective

non-interventional registry to include clinical, diagnostic, treatment, eradication confirmation, and outcome data of *H. pylori* in routine clinical practice of Europe. This project will last more than 10 years.<sup>[78]</sup> All study data are collected and managed using REDCap Electronic Data Capture tools. The database will allow researchers to acknowledge the real-time information regarding the management of *H. pylori* infection and perform specific sub-analyses after approval by the scientific committee of the study. To date, an interim analysis of the effectiveness and safety of BQT in eradication of *H. pylori* infection has been conducted using this database.<sup>[20]</sup>

## Conclusions

In 2019, multiple clinical trials or meta-analyses have been published to evaluate the efficiency and safety of different regimens for eradicating *H. pylori*, especially for strains with antibiotic resistance. In conclusion, BQT could still achieve high efficiency, although the resistance rate of *H. pylori* has increased. Hybrid and concomitant therapy could be an option if the dual resistance rate of *H. pylori* was not high. HDDT and VPZ-based therapy showed good outcomes and need to be further evaluated in more populations. The clinical choice should depend on the availability of susceptibility testing and the efficiency of local empiric therapy, although susceptibility-guided therapy is considered to achieve a high success rate. The effect of probiotics might be strain-specific, and the dose and frequency of vitamins in the eradication regimens should be explored in more studies. The discovery of novel anti-*H. pylori* drugs and the establishment of *H. pylori* databases in different regions are warranted in the future.

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## Conflicts of interest

None.

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