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Review Article

High-dose dual therapy versus bismuth-containing quadruple therapy for the treatment of *Helicobacter pylori* infection – A review of the strengths, weaknesses, and proposed solutions

*Chi-Tan Hu**

Division of Gastroenterology, Department of Internal Medicine, Hualien Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation and Tzu Chi University, Hualien, Taiwan

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Abstract

Helicobacter pylori is the principal cause of peptic ulcers, gastric cancer, and mucosa-associated lymphoid tissue lymphoma. The first treatment to *H. pylori* infection is dual therapy (a bismuth compound plus metronidazole). On the launch of omeprazole in 1988, dual therapy became omeprazole and amoxicillin (low dose). The poor *H. pylori* eradication rates by either bismuth-based or low-dose dual therapy drove more combinations of antibiotics were needed. Antibiotic resistance, especially clarithromycin and metronidazole, has made bismuth-containing quadruple therapy (BCQT) a savior for first-line and second-line treatments. However, its complicated dosing regimen commonly causes more adverse events and poor drug compliance. Thus, high-dose dual therapy (HDDT) has been re-arising. This article reviews the strengths and weaknesses of HDDT versus BCQT with proposed solutions.

Keywords: *Bismuth-containing quadruple therapy, Helicobacter pylori, High dose dual therapy*

Introduction

Helicobacter pylori, a Gram-negative bacterium, is the main cause of peptic ulcers, gastric cancer, and mucosa-associated lymphoid tissue lymphoma. *H. pylori* eradication prevents and can cure these diseases [1]. However, *H. pylori* has been getting resistant to many antibiotics. Initially, clarithromycin containing triple therapy was recommended as first-line therapy [2]. However, clarithromycin resistance has been increasing worldwide and the eradication rate by triple therapy has decreased to near 80% or below in Asia and Europe [2]. *H. pylori* resistance to both clarithromycin and metronidazole is also of great concern [3].

To overcome clarithromycin resistance, other first-line regimens have been studied to replace triple therapy including bismuth-containing quadruple therapy (BCQT) [4], non-bismuth quadruple (concomitant therapy [CT]) [5], sequential therapy [6], hybrid therapy [7], and high-dose dual therapy (HDDT) [8-10], all of which feature in the current guidelines [2,11-13]. The Maastricht V/Florence guideline recommended that, in areas exhibiting high-level (>15%) clarithromycin resistance but low-level dual clarithromycin and metronidazole resistance (<15%), BCQT or CT should be recommended. In areas exhibiting high-level dual clarithromycin/metronidazole resistance (>15%), BCQT is the recommended first-line treatment [2]. However, the complexity and side effects by BCQT have made HDDT re-surfaced to be an alternative solution. However, direct comparisons on the efficacy of HDDT and BCQT are rare. Therefore, in this article, we reviewed the strengths, weaknesses, and proposed solutions for HDDT as an alternative to BCQT for the treatment of *H. pylori* infection.

Historical progress of anti-*Helicobacter pylori* regimens

Given more and more unsatisfactory eradication rates by triple therapy for the eradication of *H. pylori*, earlier guidelines have suggested sequential therapy to be an alternative to triple therapy [14]. Nevertheless, meta-analyses revealed that the *H. pylori* eradication rates by sequential therapy were heterogeneous, and several published studies were unable

Address for correspondence: Dr. Chi-Tan Hu, Division of Gastroenterology, Department of Internal Medicine, Hualien Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, 707, Section 3, Chung-Yang Road, Hualien, Taiwan.
E-mail: chitan.hu@msa.hinet.net

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to show significant differences between sequential and triple therapies. Therefore, CT was resurfaced [15].

However, like BCQT, CT has been known to induce more severe adverse events than standard triple therapies [16]. One study showed the side effects by the CT was 38.2%, significantly higher (P = 0.001) than the 14-day high-dose esomeprazole and amoxicillin (13.8%) and the 10-day sequential therapy group (22%) [17]. Nowadays, more dosing schedules are used in currently proposed treatment regimens [Figure 1].

High-dose dual therapy

Dual therapy is the first in the historical progress of anti-*Helicobacter pylori* treatment

The first dual therapy**,** if not the first, was used by Doctor Barry Marshall, who treated his patient with gastritis in 1984. Barry got the bacteria and cultured them and found bismuth plus metronidazole could kill the bacteria by *in vitro* experiment. He performed an endoscopy to make sure his patient's infection was gone. Later on, he treated his own gastritis, which developed following intentional ingestion of *H. pylori* culture broth. He used the same regimen to cure his gastritis and eliminate the *H. pylori* infection [18].

How high-dose dual therapy raised, declined, and re-arising

Although many regimens such as quadruple, sequential, and concomitant therapies, are suggested as first-line or rescue therapies, eradication rates are still below 90% in intention-to-treat (ITT) analysis [19]. Primary eradication failure increases the chance of secondary antibiotic resistance. Thus, antibiotic susceptibility testing has been recommended in areas of high antibiotic resistance after first-line treatment failure. However, *H. pylori* culture is not available in most countries. Thus, treatment regimens with high eradication rates and low antibiotic resistance are necessary. Although regimens comprising clarithromycin, metronidazole, and levofloxacin are initially satisfactory, the eradication rates of these antibiotics decrease gradually due to acquired resistance [20]. Dual PPI-amoxicillin therapy or low-dose dual therapy was introduced in 1989 [21]. However, dual proton pump inhibitor (PPI)-amoxicillin therapy had been abandoned because of the poor results obtained with the administration of standard amoxicillin and PPI twice a day [22]. HDDT has been re-arising when we optimized the dosage and dosing frequency of PPI and amoxicillin [8-10].

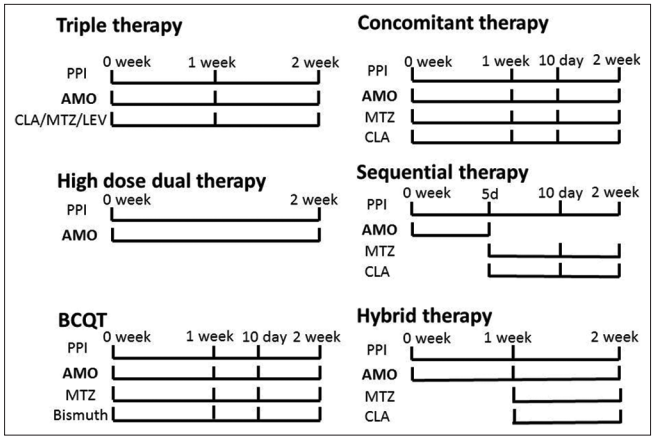

Figure 1: Dosing schedules in currently proposed regimens for anti-*Helicobacter pylori* treatment. AMO is always used as a part of these regimens except in some BCQT. PPI: Proton pump inhibitor, CLA: Clarythromycin, MTZ: Metronidazole, LEV: Levofloxacin, AMO: Amoxicillin, BCQT: Bismuth containing quadruple therapy

Rationale of using high dose dual therapy

HDDT is appealing because it is a simple and widely available regimen with low antibiotic resistance. Amoxicillin, which is a β-lactam antibiotic, is used in almost all current therapeutic eradication regimens for *H. pylori* infection. *H. pylori* resistance to amoxicillin, no matter primary or acquired, is rare [23]. Only about 1% of *H. pylori* infections are resistant to amoxicillin worldwide [24]. Dual therapy using a proton PPI and amoxicillin was popular in the mid-1990s, especially in Europe; however, dosage and dosing frequency of them were suboptimal [25]. *H. pylori* only replicate when the pH is high so that increasing the pH to approximately 5.5 will turn *H. pylori* into a replicative state and become susceptible to antibiotic effect. The key words "high dose" refer to the use of high-dose PPI but not amoxicillin [26]. In fact, many basic parameters can influence the efficacy of *H. pylori* eradication [Figure 2]. More studies are needed to evaluate the effects of high frequency compared with high dosage in both PPIs and amoxicillin.

Importance of high frequency using amoxicillin in high dose dual therapy

However, controversial results in earlier studies made suboptimal dual therapy not to be considered. In recent years, optimal dual therapy has been tailored and reconsidered for the treatment of *H. pylori* infection worldwide [8-10,27]. HDDT appears to be promising as a potential therapy for *H. pylori.* The discrepancy in results can be explained by the optimal or suboptimal application of dosage and dosing frequency, PPI selection, and the compliance of diet restriction [8-10,28]. Arancibia et investigated the pharmacokinetic profile of amoxicillin in healthy volunteers [29]. When being used

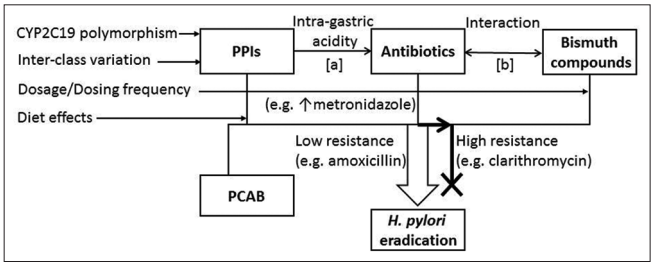

Figure 2: Parameters influencing the efficacy of *Helicobacter pylori* eradication. The footnote (a) represents the PPI-antibiotic axis in which intra-gastric acidity achieved by PPIs can influence the effect of an antibiotic [31]. The footnote (b) represents the interaction between a bismuth compound and an antibiotic [47]. CYP2C19 polymorphism, inter-class variation and diet effects mostly influence PPIs but not PCAB. Dosage and dosing frequency influence PPIs, antibiotics and bismuth compounds. Avoiding those antibiotics with high resistance (e.g., clarithromycin), using those with low resistance (e.g., amoxicillin) and applying adequate dosage and/or dosing frequency (e.g. metronidazole) are also important to achieve *Helicobacter pylori* eradication. PCAB: Potassium competitive acid blockers, PPIs: Proton pump inhibitors, CYP2C19: Cytochrome P450 2C19

500 mg every 6 h per os, at this dosage interval, the total time (T) that amoxicillin serum level exceeds the minimal inhibitory concentration (T > MIC) is 20 h (83%) per 24 h. In contrast, when being consumed 500 mg every 12 h, the T > MIC is only 11 h (46%) of the whole day [Figure 3].

Median 24-h intragastric pH profile

As shown in Figure 2, the success of *H. pylori* eradication is influenced by various factors including antibiotic resistance, therapy duration, drug compliance, intragastric acidity, and cytochrome P450 2C19 (CYP2C19) genetic polymorphism [30]. Based on the pharmacokinetic and pharmacodynamic characters of amoxicillin, it is more effective under high intragastric pH >5.5 [31] and high dosing frequency [four times daily, Figure 3] [29]. Since most PPIs are mainly metabolized by CYP2C19, the efficacies for *H. pylori* eradication would be affected by different CYP2C19 genotypes. The influence of the CYP2C19 genotype becomes less significant when PPI dosage and dosing frequency are increased [8,31,32]. Thus, it should be beneficial to use four-times daily dosing of PPI for the patient who are CYP2C19 extensive metabolizers [33].

Regarding the intragastric pH, a study from Japan showed that when a total of 40 mg rabeprazole was used per day, 10 mg four times daily is the best to achieve a median 24-h intra-gastric pH always higher than 5.5 when compared with 20 mg twice daily and 40 mg once daily [34]. This study exactly shows that in HDDT, rabeprazole four times daily can achieve the best to maintain a high intragastric pH for the whole day. Another study also from Japan found the median pH values in the high-frequency group (esomeprazole 20 mg four times a day) were significantly higher than those in the low-frequency group (esomeprazole 20 mg two times a day). In extensive metabolizers (6.6 vs. 5.3, P = 0.022), intermediate metabolizer (6.8 vs. 5.5, P = 0.005) and poor metabolizer (7.0 vs. 6.2, P = 0.047), respectively [35]. From the beginning, we chose rabeprazole-based regimens in our studies to minimize the effect of CYP2C19 polymorphism on PPI clearance and intra-gastric acidity [8-10]. Thus, according to these studies [29,34,35], when HDDT is applied, amoxicillin and PPIs, at least for rabeprazole and esomeprazole, should be optimally used four times a day [Figure 4].

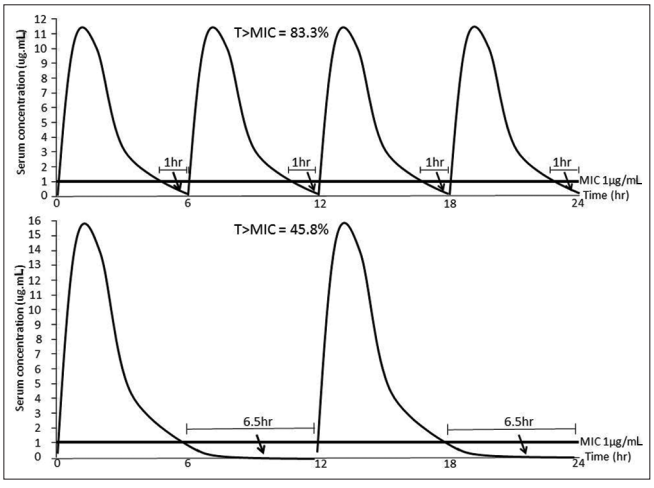

Figure 3: The pharmacokinetic profile of amoxicillin. When being used 500 mg every 6 h per os, at this dosage interval, the total time (T) that amoxicillin serum level exceeds the minimal inhibitory concentration (T > MIC) is 20 h (83%) per 24 h. In contrast, when being consumed 500 mg every 12 h, the T > MIC is only 11 h (46%). MIC: Minimal inhibitory concentration

Importance of diet control in how high dose dual therapy

The eradication rates by HDDT in the United States were not satisfactory even when given as high dose PPI and amoxicillin every 6 h [36]. Similar unsatisfactory eradication rates in China based on ITT analysis (<82%) and per-protocol analysis (PP <90%) [37]. The major difference between the success by our group's studies is that diet restriction is mandatory [8-10]. During the treatment period, patients were instructed to avoid acidic foods (e.g., citrus fruits or juices) to minimize the impact of ingested foods on increasing intragastric acidity which can alter drug activity [8-10]. We proposed a diet control mnemonic during anti-*Hp* therapy using HDDT [Table 1].

How high dose dual therapy versus other regimens

Recently, we have for the first time conducted a large-scale prospective randomized study using HDDT. The results showed that HDDT using rabeprazole 20 mg and amoxicillin 750 mg both four times daily for 2 weeks cured about 95% of treatment-naïve patients and 90% treatment-experienced patients, and was superior to sequential therapy, clarithromycin-containing, or levofloxacin-containing triple therapy [8]. Obviously, the next head-to-head target to which HDDT should compare is bismuth-containing quadruple therapy (BCQT).

Bismuth-containing quadruple therapy

Rationale of using bismuth-containing quadruple therapy

Bismuth-based quadruple therapy is suggested as first-line treatment in geographical areas of high clarithromycin resistance (≥20%), in patients who have been treated with a macrolide antibiotic, or as second-line therapy for patients whose infection persists after primary treatment with triple therapy [2]. Bismuth is widely used because it does not develop resistance. It is a reasonable agent in regions where resistance to other antibiotics is common and retreatment

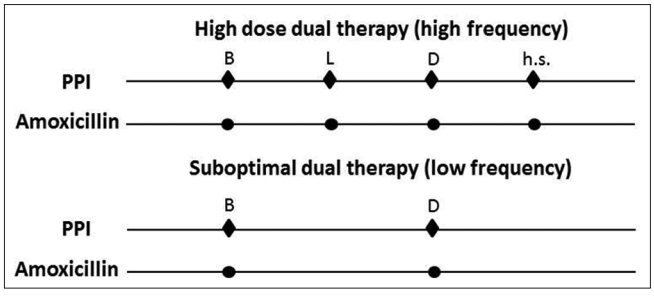

Figure 4: The importance of high frequency in HDDT dosing schedule. High frequency seems to be more important than high dose when using amoxicillin, the same applies to the use of rabeprazole and esomeprazole [29,34,35]. PPI: Proton pump inhibitor, B: Breakfast, L: Lunch, D: Dinner; h.s.: At bedtime, HDDT: High dose dual therapy

Table 1: Diet control mnemonic during anti-*Helicobacter pylori* therapy using high dose dual therapy

Mnemonics	Diet items	Examples
3s	Sour food	E.g., Vinegar, sour bamboo shoot, plum essence, preserved food, etc.
	Spicy food	E.g., Chili, garlic, ginger, Chinese barbecue sauce, etc.
	Sweet food	E.g., Candy, chocolate, sweet bread, sweet cake, red bean soup, etc.
A	Alcohol	E.g., White wine, red wine, beer, etc.
B	Beverages	E.g., Acidic beverages, soda pop, sports drink, etc.
C	Caffeine	E.g., Coffee, tea, cola, soda water, etc.
	Carbonic acid	E.g., Carbonic drinks and carbonic acid in foods
	Cuisines	E.g., Taiwan spicy hot pot, Korean, Thai, Mexico, glutinous-rice foods
	Cigarettes	
D	Dairy products	E.g., Milk, yogurt, cheese, etc.
E	-	Eat too much or frequent
F	Fruits/fruit juice	Citrus fruits (e.g., lemon, orange, tangerine), grapes, pineapple, grapefruit, kiwi fruit, tomato, banana, apple, strawberry, blueberry, cherry, plum, mulberry, etc.
	Fatty foods	
	Fermented foods	
	Fried foods	
G	-	GERD-induced food of your kind
Hp	-	Health products with complex or unknown components

HP: *Helicobacter pylori*, GERD: Gastroesophageal reflux disease

may be needed [38]. Besides, it is less necessary to perform antibiotic sensitivity testing by BCQT given tetracycline resistance is very low and metronidazole resistance can be overcome by long-duration treatment such as 14 days. Above all, BCQT is a good alternative not only for first-line but also rescue eradication regimens, especially in regions with high clarithromycin resistance [9,10].

Weakness of bismuth-containing quadruple therapy

Although increasing the doses and duration of BCQT can partially overcome drug resistance [38], its complicated dosing regimen commonly causes more adverse events and poor drug compliance [39]. For example, in our previous first-line and rescue studies (tetracycline and metronidazole in BCQT), 61% in the first-line group and 68% in the rescue group experienced side effects [9,10]. A recent study from Korea on the efficacy of BCQT as a first-line treatment had an eradication rate of 74% in their ITT analysis and 93% in their PP analysis [39]. In another Korean second-line study by BCQT, the eradication rates were 82.6% by ITT therapy and 93.6% by per-protocol analysis, respectively [40]. However, the side effects were high, causing significant patients to discontinue therapy [39,40]. In contrast, side effects by HDDT are relatively low. In our studies, only 27% in the first line and 29% in the rescue studies, respectively [9,10].

High dose dual therapy versus bismuth-containing quadruple therapy for first-line treatment

According to our study, on ITT analysis, the eradication rate was 94.7% in the HDDT group and 90.6% in the BCQT group (P = 0.146). There was a trend towards a higher eradication rate in HDDT compared to BCQT. By per-protocol analysis, the respective eradication rates were 96.4% and 93.3% (P = 0.199). More BCQT than HDDT patients experienced adverse events (61.1% vs. 27.4%, $P < 0.0001$) [9].

High dose dual therapy versus bismuth-containing quadruple therapy for second-line treatment

With the same HDDT and BCQT regimens, we compared the rescue efficacy of HDDT versus BCQT in another large-scale multi-center trial [10]. Both HDDT and BCQT achieved high eradication rates by ITT analysis (92% vs. 87%, P = 0.0015). By per-protocol analysis, the respective eradication rates were 94% and 88% (P = 0.0006). There was a significant difference in adverse events between these two groups (29% in HDDT vs. 68% in BCQT, $P < 0.001$) [10].

Future hope: roles of bismuth compound and vonoprazan in high dose dual therapy

High-dose dual therapy is suitable for first-line and second-line treatment

In a recent meta-analysis article (2019), both HDDT and BCQT can achieve similar eradication rates for H pylori infection and adherence, and generally, HDDT causes fewer adverse events [41]. In another meta-analysis (2020), HDDT was equivalent to the recommended first-line or rescue regimens (triple therapy, BCQT, and non-bismuth quadruple therapy) with fewer side effects [42]. Similarly, by a network meta-analysis (2021), HDDT for 14 days appeared to be the most optimal primary therapy for *H. pylori* among Asian populations with comparable efficacy and compliance and causing fewer side effects [43].

According to the Maastricht V/Florence guideline, the eradication rate should be over 80% by ITT analysis and over 90% by PP analysis [2]. From our study results, HDDT fulfills Maastricht V requirements both in first-line and second-line treatments [8-10]. HDDT was better than BCQT, in the first-line study, by about 4% on ITT analysis and 3% on PP analysis and in the rescue study by about 5% on ITT analysis and 6% on PP analysis [9,10]. Both HDDT and BCQT proved to be useful for both first-line and second-line treatment for H. pylori eradication. A meta-analysis also showed that HDDT and guideline-recommended rescue therapies (levofloxacin-containing triple therapy, rifabutin or metronidazole triple therapy, and BCQT) achieved similar efficacy [27]. Thus, HDDT has been suggested in the 2017 ACG guideline as a rescue regimen [44].

Adding a bismuth compound to high-dose dual therapy may solve diet restriction

The mechanism of bismuth compounds against *H. pylori* is still not completely understood, although combined use of a bismuth compound in anti-*H. pylori* regimens can increase treatment efficacy [45]. Marcus *et al*. proposed a mechanism with an *in vitro* experiment [46]. They found *colloidal bismuth* subcitrate (CBS) did not act directly on urease or the urea channel but rather impeded proton entry into the bacterial cytoplasm. With cytoplasmic pH remaining within range for increased metabolic activity of *H. pylori*, the efficacy of

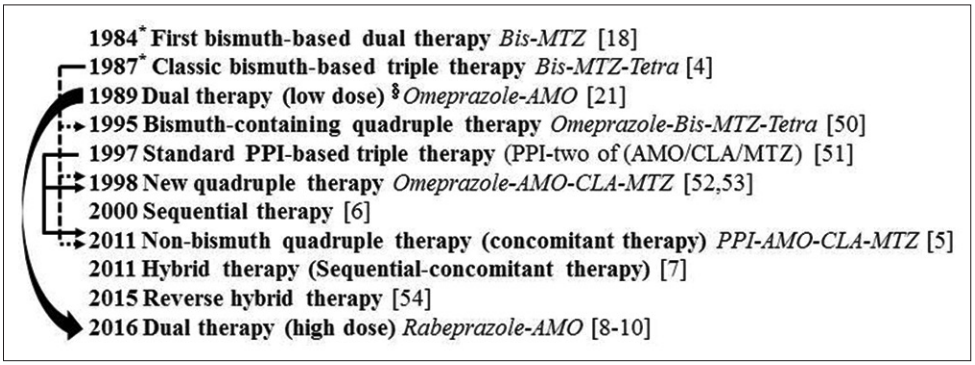

Figure 5: The historical timeline of anti-*Helicobacter pylori* regimens. The dotted arrowed lines show the developmental track from bismuth-based to non-bismuth quadruple therapy. The solid arrowed lines point out how standard PPI-based triple therapy can formulate into new and concomitant therapies by adding three antibiotics to a PPI. The curved arrowed line evinces the long time lag from low dose to high dose dual therapies. *The year in which the regimen was formulated but is not necessarily the published year. §PPIs were developed in the 1980s, with omeprazole being launched in 1988. Bis: Bismuth compound, MTZ: Metronidazole, Tetra: Tetracycline, AMO: Amoxicillin, CLA: Clarithromycin, PPIs: Proton pump inhibitors

growth-dependent antibiotics (e.g., amoxicillin) is increased. In fact, their results showed CBS in combination with ampicillin leads to decreased survival of *H. pylori*. If this phenomenon were also true in the human stomach (*in vivo*), combing bismuth compound with amoxicillin may reduce the necessity of profound intra-gastric acid inhibition for amoxicillin to exert optimal anti-*Hp* efficacy. Wang *et al.* found CBS and related bismuth compounds irreversibly inhibit different types of metallo-β-lactamases [47]. More studies are needed to investigate the interaction between β-lactam antibiotics (e.g. amoxicillin) and bismuth compounds.

As we have reported, no intentional restriction of acidic or spicy foods, heavy alcohol, or tea will influence the efficacy of HDDT [8-10]. According to these evidence, HDDT and bismuth compound used together may minimize the necessity of food restriction during HDDT. To our knowledge, only one study has compared the effect of HDDT with or without bismuth [48]. However, this study is only small-scale (both groups only 80 patients). Clinically, at least one optimum regimen and an alternate are needed to ensure that all or most patients will be cured with a maximum of two regimens [49]. However, each regimen has its own strength and weakness. There is still no large-scale, randomized controlled trial (RCT) comparing the efficacy, adverse effects, and adherence of HDDT with or without bismuth versus amoxicillin-metronidazole BCQT as first-line regimens. The historical timeline of anti-*H. pylori* regimens [50-54], at this time, may raise a more robust HDDT by adding a bismuth compound [Figure 5]. Without the need of diet restriction, we are currently recruiting patients in this RCT (ClinicalTrials.gov: NCT03897244). Hopefully, the results can provide solutions to the most optimal use of HDDT.

Reasons of vonoprazan to be a novel option in high dose dual therapy

Vonoprazan, a novel oral potassium-competitive acid blocker (P-CAB), was launched in Japan in 2015. Like all PPIs, vonoprazan inhibits gastric H^+, K^+-ATPase but it non-covalently binds to the H^+, K^+-ATPase α subunit to compete with potassium binding. Vonoprazan accumulates in parietal cells with its acid-inhibitory effect mostly unaffected by food contents, which is essential to HDDT [55]. It produced more potent and sustained acid-inhibitory action and greater increase in gastric pH than lansoprazole as it accumulated in higher concentrations and was slowly cleared from gastric glands [56]. Thus, vonoprazan, if used in HDDT, does not need to be prescribed in high dosing frequency. Third, vonoprazan provides an environment in which antimicrobials can have greater efficacy. Thus the potential synergy between vonoprazan and the antimicrobials (like amoxicillin) may make *H pylori* more susceptible to antibiotics when it restores its replicative capability at a pH higher than 5.5 [31,57]. Given the three reasons described above, vonoprazan may represent a novel option as a component of HDDT for *H pylori* eradication.

Conclusion

Given the high rates of drug resistance, complicated dosing regimen, and adverse events, BCQT is replaceable by HDDT. In contrast, HDDT is a low-resistance, simple regimen with few side effects. Although HDDT is also effective for first-line and second-line therapies, amoxicillin should be used four times daily. Intra-gastric pH is vulnerable to poor diet control, inadequate dosage, and dosing frequency of PPIs. According to the above-mentioned evidence, adding a bismuth compound to HDDT may eliminate the need of diet restriction. Besides, vonoprazan, a novel oral P-CAB, may override PPIs as the main component of HDDT for *H pylori* eradication.

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Conflicts of interest

There are no conflicts of interest.

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