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...
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].

**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 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: Clarithromycin, MTZ: Metronidazole, LEV: Levofloxacin, AMO: Amoxicillin, BCQT: Bismuth containing quadruple therapy](image1)

![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)](image2)
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) 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].

**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 is inevitable.
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                    |                                                                                                                                          |
|           | Cigarettes                  | E.g., Taiwan spicy hot pot, Korean, Thai, Mexico, glutinous-rice foods                                                                     |
| 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,                                                                          |
|           | Fatty foods                 | grapefruit, kiwi fruit, tomato, banana, apple, strawberry, blueberry, cherry, plum, mulberry, etc.                                           |
|           | 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

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

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Conflicts of interest

There are no conflicts of interest.

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