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Treatment of *Helicobacter pylori* infection: Current status and future concepts

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Abstract

Helicobacter pylori (*H. pylori*) infection is highly associated with the occurrence of gastrointestinal diseases, including gastric inflammation, peptic ulcer, gastric cancer, and gastric mucosa-associated lymphoid-tissue lymphoma. Although alternative therapies, including phytomedicines and probiotics, have been used to improve eradication, current treatment still relies on a combination of antimicrobial agents, such as amoxicillin, clarithromycin, metronidazole, and levofloxacin, and antisecretory agents, such as proton pump inhibitors (PPIs). A standard triple therapy consisting of a PPI and two antibiotics (clarithromycin and amoxicillin/metronidazole) is widely used as the first-line regimen for treatment of infection, but the increased resistance of *H. pylori* to clarithromycin and metronidazole has significantly reduced the eradication rate using this therapy and bismuth-containing therapy or 10-d sequential therapy has therefore been proposed to replace standard triple therapy. Alternatively, levofloxacin-based triple therapy can be used as rescue therapy for *H. pylori* infection after failure of first-line therapy. The increase in resistance to antibiotics, including levofloxacin, may limit the applicability of such regimens. However, since resistance of *H. pylori* to amoxicillin is generally low, an optimized high dose dual therapy consisting of a PPI and amoxicillin can be an effective first-line or rescue therapy. In addition, the concomitant use of alternative medicine has the potential to provide additive or synergistic effects against *H. pylori* infection, though its efficacy needs to be verified in clinical studies.

Core tip: This article provides a review of therapeutic agents and therapies that have been used in the treatment of *Helicobacter pylori* infection. Factors that may affect treatment outcome are described and therapeutic strategy is recommended.

INTRODUCTION

Helicobacter pylori (*H. pylori*), initially named *Campylobacter pyloridis*, was first identified in humans and cultured by Marshall and Warren[1]. It is a microaerophilic, spiral-shaped, Gram negative bacterium, with several polar flagella for mobility. It can only survive at a periplasmic pH of 4.0-8.5 and can only grow at a periplasmic pH of 6.0-8.5. One well-known biochemical characteristic of *H. pylori* is its ability to produce urease, which can hydrolyze gastric urea to liberate ammonia, neutralizing the gastric

acid and increasing the periplasmic pH to 4.0-6.0, thus protecting *H. pylori* from gastric acid[2,3].

The exact routes of *H. pylori* transmission remain unclear. However, epidemiologic studies have shown that exposure of food to contaminated water or soil may increase the risk of *H. pylori* infection, suggesting that person-to-person transmission by oral-oral, fecal-oral, or gastro-oral exposure is the most likely path for *H. pylori* infection[4]. Accordingly, improvements in hygiene and living conditions are important factors in decreasing the prevalence of infection[5]. More than 50% of the world's population has been infected by *H. pylori* and the prevalence of infection in developing countries is greater than 80% in adults over 50 years of age. Infected individuals usually acquire *H. pylori* before 10 years of age and grow up with the infection[6]. In Asia, the prevalence of *H. pylori* infection varies in different countries, the reported overall seroprevalence rates being about 31% in Singapore, 36% in Malaysia, 39% in Japan, 55% in Taiwan, 57% in Thailand, 58.% in China, 60% in South Korea, 75% in Vietnam, 79% in India, and 92% in Bangladesh[7].

H. pylori infection is highly associated with gastrointestinal diseases, including gastric inflammation, peptic ulcer, gastric cancer, and gastric mucosa-associated lymphoid-tissue lymphoma[8-11]. It has been classified as a group 1 carcinogen (*i.e.*, infection with *H. pylori* is carcinogenic in humans) by the International Agency for Research on Cancer consensus group since 1994[12] and many guidelines have been established for treatment of *H. pylori* infection[13-16].

TREATMENT OF *H. PYLORI* INFECTION

Treatment of infection relies on a combination of antimicrobial agents and antisecretory agents, the elevation of the gastric pH by antisecretory agents being required for the bactericidal effect of the antimicrobial agents. Alternatively, although the mechanism of action is not yet clear, phytomedicines and probiotics have been used to improve eradication of *H. pylori*.

The effect of antimicrobial agents and antisecretory agents depends not only on their pharmacological activities, but also on their pharmacokinetic properties. Many antimicrobial agents, including amoxicillin, clarithromycin, levofloxacin, metronidazole, tetracycline, rifabutin, and bismuth-containing compounds, have been used for *H. pylori* therapy, while the main antisecretory agents used are proton pump inhibitors (PPIs).

Antimicrobial agents

The effect of most antimicrobial agents used for *H. pylori* treatment, including clarithromycin, levofloxacin, and metronidazole, is concentration-dependent, *i.e.*, their efficacy is proportional to their plasma concentration[17-19]. In the case of clarithromycin, the breakpoint proposed for susceptible strains is 0.25 μg/mL and that for resistant strains > 0.5 μg/mL[20], while, for levofloxacin and metronidazole, the breakpoints proposed for resistant

strains are > 1 μg/mL and > 8 μg/mL, respectively, as determined by the European Committee on Antimicrobial Susceptibility Testing[21]. In contrast to the effects of the concentration-dependent antibiotics, the bactericidal effect of amoxicillin against *H. pylori* is time-dependent, *i.e.*, its efficacy is proportional to the time that the plasma concentration is higher than the MIC[22-24], and the breakpoint proposed for resistant strains is usually > 0.5 μg/mL, although a more stringent breakpoint (> 0.12 μg/mL) was determined by the European Committee on Antimicrobial Susceptibility Testing for *H. pylori* resistance to amoxicillin[21]. Many bismuth salts are poorly soluble in water and are therefore very weakly absorbed and thus exert their activity by local action in the gastrointestinal tract. The MIC for bismuth to prevent the growth of 90% of *H. pylori* has been reported as 4 to 32 ng/L[25]. A post-antibiotic effect against *H. pylori* has been demonstrated for clarithromycin and levofloxacin[26,27].

In terms of resistance, a change in the properties of penicillin-binding protein, either a decreased affinity for amoxicillin[28] or point mutation in the *pbp1A* gene[29], is the main mechanism leading to amoxicillin resistance of *H. pylori*. Other mechanisms for amoxicillin resistance may include a reduced membrane permeability, leading to low accumulation of amoxicillin[30]. For clarithromycin, the major mechanism for resistance is point mutation in the 23S rRNA gene, the most frequent being at A2143G (69.8%), followed by A2142G (11.7%) and A2142C (2.6%)[31]. Point mutation of *gyrA*, coding for DNA gyrase, in the codons coding for amino acid 87, 88, 91, or 97 has been observed in levofloxacin-resistant isolates[32,33]. For metronidazole, null mutations in the *rdxA* gene, which codes for oxygen-insensitive NADPH nitroreductase (RdxA), have been identified in metronidazole-resistant strains of *H. pylori*. Other genes, such as *frxA* (coding for NADPH flavin oxidoreductase), and *fdxB* (coding for ferredoxin-like enzyme), also play a role in the mechanisms of resistance to metronidazole[34-36]. For rifabutin, *H. pylori* mutants with mutations in codons 524-545 or codon 585 of the *rpo*B gene are resistant to rifabutin[37,38]. Additionally, cross resistance between rifabutin and rifampin has been reported[39]. The prevalence of rifabutin resistance is 1.3% overall, but can be as high as 31% in post-treatment patients[40]. *H. pylori* resistance to bismuth salts is rare[41], and colloidal bismuth subcitrate has been reported to prevent the development of *H. pylori* resistance to nitronidazole[42].

Antisecretory agents-PPI

Although H_2-receptor antagonists can be used as antisecretory agents, PPIs are more effective in increasing the gastric pH. PPIs inhibit the gastric acid pump (H^+/K^+ATPase), which is responsible for the secretion of hydrochloric acid and is located in the canalicular membrane of gastric parietal cells[43]. At low pH, PPIs are protonated, then undergo cyclization to form a tetracyclic sulfonamide, which binds irreversibly to cysteines in the α subunit of the H^+/K^+ATPase and inhibits the $H^+/$

K$^+$ATPase[44]. Thus, the accumulation and action onset of PPIs rely on their acid ionization constant (pK_a), with a higher pK_a allowing greater conversion to the active sulfonamide. Of the PPIs, rabeprazole has the highest pK_a (pKa = 4.9), followed by omeprazole (pKa = 4.13), lansoprazole (pKa = 4.01), and pantoprazole (pKa = 3.96)[45].

Most PPIs are primarily metabolized by the hepatic cytochrome P450 enzymes CYP2C19 and CYP3A4. Thus, their pharmacological effects are influenced by endogenous (*e.g.*, pharmacogenetic polymorphism) and exogenous (*e.g.*, drug-drug interaction) factors. The *CYP2C19* genotype is known to influence the pharmacokinetic properties of PPIs. The ratios of the half-life ($t_{1/2}$) value in CYP2C19 poor metabolizers to that in extensive metabolizers (EMs) is 2.2, 2.1, 1.9, and 1.4 for omeprazole, (-) pantoprazole, lansoprazole, or rabeprazole, respectively, and the corresponding ratios of the area under the curve (AUC) values are 7.4-6.3, 10.7-2.5, 4.3-1.9, and 1.8-1.2[46-51]. While most PPIs are used as racemic mixtures of two optical isomers, esomeprazole, the S-isomer of omeprazole, is available on the market, and an *in vitro* study showed that, compared to omeprazole, it is metabolized to a greater extent by CYP3A4 and to a lesser extent by CYP2C19 and that esomeprazole itself is mainly metabolized by CYP3A4[52]. However, in patients receiving esomeprazole, the *CYP2C19* genotype still plays an important role in the acid-inhibitory effect and *H. pylori* eradication[53,54], and this also applies to patients taking dexlansoprazole, the R-isomer of lansoprazole[55].

PPIs also have a direct antimicrobial activity against *H. pylori*. Nakao and Malfertheiner[56] compared the growth inhibitory activity of omeprazole, lansoprazole, and pantoprazole against 58 clinical isolates of *H. pylori*. and found that the MIC$_{90}$ for lansoprazole was 6.25 μg/mL, lower than that of omeprazole (25 μg/mL) or pantoprazole (100 μg/mL). Kawakami *et al*[57] compared the anti-*H. pylori* activity of rabeprazole, rabeprazole thioether, lansoprazole, omeprazole, and three antibiotics (amoxicillin, clarithromycin, and metronidazole) and found MIC$_{90}$ values of 0.5 μg/mL for rabeprazole, 0.25 μg/mL for rabeprazole thioether, 1 μg/mL for lansoprazole, 16 μg/mL for omeprazole, 0.031 μg/mL for amoxicillin, 1 μg/mL for clarithromycin, and 16 μg/mL for metronidazole.

ALTERNATIVE THERAPIES FOR *H. PYLORI* INFECTION

While antibiotics are the main agents used in the therapy of *H. pylori* infection, the development of resistance has limited their application. Also, administration of antibiotics perturbs the microbiota, the microorganisms that colonize the human gastrointestinal tract, and thus causes side effects, such as diarrhea. Because of this, alternative therapies, including the use of phytomedicines and probiotics, have been used for the treatment of *H. pylori* infection.

Phytomedicines
There is increasing evidence that traditional Chinese medicines (TCMs) are efficacious in the treatment of various diseases. The efficacy and safety of TCMs for the treatment of *H. pylori* have been reviewed and the average eradication rate was found to be about 72%[58], suggesting that TCMs may not be a stand-alone therapy for *H. pylori* infection Nevertheless, the role of TCMs in *H. pylori* treatment remains to be clarified. In addition to TCMs, other phytomedicines that have been used for the treatment of *H. pylori* infection are green tea catechins, garlic extract, cranberry juice, and propolis[59]. For example, it has been demonstrated that a combination of catechins and sialic acid can effectively prevent *H. pylori* infection in animals and improve the eradication rate[60,61]. As catechins and sialic acid have different anti-bacteria actions, the additive or synergistic effects caused by such a combination may provide a potential strategy for treating *H. pylori* infection in the future. However, since most studies have been carried out *in vitro* or in animals, the efficacy of phytotherapy in humans needs to be verified by suitable clinical trials.

Probiotics
Probiotics are living organisms that are administered orally to confer a health benefit on the host. In recent years, the application of probiotics in the treatment of *H. pylori* infection has become an active research field. Several probiotics, including *Saccharomyces boulardii* (*S. boulardii*) and *Lactobacillus* strains, have been combined with antibiotic-containing therapies to treat infection. Compared to standard triple therapy, although addition of *S. boulardii* significantly reduced the incidence of antibiotic-associated diarrhea, it did not significantly improve the eradication rate of *H. pylori*[62-64]. Likewise, addition of *Lactobacillus GG* significantly reduced the incidence of diarrhea, but did not improve the eradication rate of triple therapy[62,65]. Addition of *Lactobacillus acidophilus* was reported to significantly increase treatment outcome of triple therapy[66], but, in another study, addition of the combination of *Lactobacillus acidophilus* and *Bifidobacterium lactis* failed to show an improvement in *H. pylori* eradication[62]. Intriguingly, in contrast to the capsule/sachet-based probiotic preparations, fermented milk-based probiotics have been reported to improve *H. pylori* eradication rates by about 5%-15%[67], possibly because some of contain additional components (*e.g.*, lactoferrin and glycomacropeptide) that may inhibit *H. pylori*.

GUIDELINES AND THERAPEUTIC REGIMENS

Various combinations of PPIs and antimicrobial agents have been designed to treat *H. pylori* infection. These regimens include triple therapy, bismuth-containing quadruple therapy, sequential therapy, and concomitant

Treatment	Asia-Pacific region[13]	Developing countries[14]	Europe[15]	United States[16]
First-line	Triple therapy (PPI + CLA + AMO/MET) BIS-based quadruple therapy (PPI + BIS + MET + TET)	Triple therapy (PPI + CLA + AMO/FUR) Quadruple therapy (PPI + CLA + AMO + BIS/MET or PPI + BIS + MET + TET) Sequential therapy (PPI + AMO and PPI + CLA + NIT)	Triple therapy (PPI-CLA-containing regimen) BIS-based quadruple therapy (for high clarithromycin resistance) Sequential therapy (for high clarithromycin resistance)	Triple therapy (PPI + CLA + AMO/MET) BIS-based quadruple therapy (BIS + MET + TET + RAN) Sequential therapy (PPI + AMO and PPI + CLA + TIM)
Second-line	BIS-based quadruple therapy (PPI + BIS + MET + TET) LEV-based triple therapy (PPI + LEV + AMO) RIF-based triple therapy (PPI + RIF + AMO)	BIS-based quadruple therapy (PPI + BIS + TET + MET/FUR) LEV-based triple therapy: (PPI + LEV + BIS/FUR/AMO)	BIS-based quadruple therapy LEV-based triple therapy	BIS-based quadruple therapy (PPI + TET + BIS + MET) LEV-based triple therapy (PPI + AMO + LEV)
Third-line	RIF-based triple therapy (PPI + RIF + AMO)	LEV-based or FUR-based triple therapy (PPI + AMO + LEV/RIF or PPI + FUR + LEV)	Guided by antimicrobial susceptibility testing	

Table 1 Treatment regimens proposed for the management of *Helicobacter pylori* infection in different geographic areas

AMO: Amoxicillin; BIS: Bismuth; CLA: Clarithromycin; FUR: Furazolidone; LEV: Levofloxacin; MET: Metronidazole; NIT: Nitronidazole; RAN: Ranitidine; RIF: Rifabutin; TET: Tetracycline; TIM: Timidazole; PPI: Proton pump inhibitor.

therapy (non-bismuth quadruple therapy). The Maastricht I Consensus Report recommended that treatment regimens should achieve an eradication rate of at least 80% and proposed a standardized report card to be used to evaluate the outcome of new therapeutic regimens for *H. pylori* infection[68], on which the efficacy of an anti-*H. pylori* regimen is graded as A or excellent if the eradication rate is 95%-100% in the intention-to-treat analysis, while an eradication rate of 90%-95% is considered as B or good, 85%-89% as C or fair, 81%-84% as D or poor, and ⩽ 80% as F or unacceptable.

Guidelines for the management of *H. pylori* infection are still evolving and, depending on the geographic areas, first-line, alternative first-line, second-line, or even third-line therapies have been proposed. Recent guidelines proposed for Asia-Pacific regions, developing countries, Europe, and United States are summarized in Table 1. Despite these guidelines being proposed for different areas, the regimens suggested for first-line and rescue treatments are generally similar.

First line treatments
According to current guidelines, standard triple therapy containing a PPI and two antibiotics, clarithromycin and amoxicillin/metronidazole, is the first-line regimen for treatment of *H. pylori* infection[13-16]. The recommended therapeutic duration of standard triple therapy is 7 d in Europe and Asia, but 10-14 d in the United States. Although triple therapy is considered to be a standard first-line therapy, the most recent data show that the efficacy of standard triple therapy is decreasing and that the eradication rate of standard triple therapy in some areas is less than 80%[32,69]. To improve the eradication rate of triple therapy, Furuta *et al*[70] proposed a tailored regimen based on *CYP2C19* genotype and bacterial susceptibility to clarithromycin, and showed a 96% intention-to-treat

eradication rate. Although this pharmacogenomics-based strategy is promising, it requires genotype testing in advance and the cost-effectiveness remains to be verified. Alternatively, the new version of the Maastricht IV/Florence Consensus Report[15] has updated the recommendations for first-line therapy, and bismuth-containing quadruple therapy has been officially substituted for standard triple therapy in areas in which the clarithromycin resistance rate is over 15%-20%. However, due to side effects, bismuth is no longer available in many countries, including Japan, Malaysia, and Australia, and, as a result, bismuth-containing therapy is not used in these areas, so sequential treatment or a non-bismuth quadruple therapy (concomitant treatment) is recommended as the alternative first-line treatment in high clarithromycin resistance area.

Ten-day sequential therapy, with an eradication rate of 98%, was proposed in 2000[71]. It consists of 5-d dual therapy (PPI plus amoxicillin), followed by 5-d triple therapy [PPI plus clarithromycin and a nitronidazole (metronidazole or tinidazole)]. Compared to 7-d standard triple therapy, sequential therapy was found to result in higher eradication rates (intention-to-treat 92% *vs* 75%; per-protocol 95% *vs* 77%)[72]. A meta-analysis of 10 randomized controlled trials with 3011 patients calculated eradication rates of 91.0% (95%CI: 89.6-92.1) for sequential therapy and 75.7% (95%CI: 73.6-77.7) for standard triple therapy[73]. Using the suggested report card classification, sequential therapy was scored as B or good, while standard triple therapy was only scored as an F or unacceptable[68]. Sequential therapy is therefore recommended as an alternative to standard triple therapy for *H. pylori* infection[14-16]. Nonetheless, a study conducted at 7 Latin American sites demonstrated that 14-d triple therapy was superior to 10-d sequential therapy in eradication of *H. pylori* infection[74], suggesting that the application of
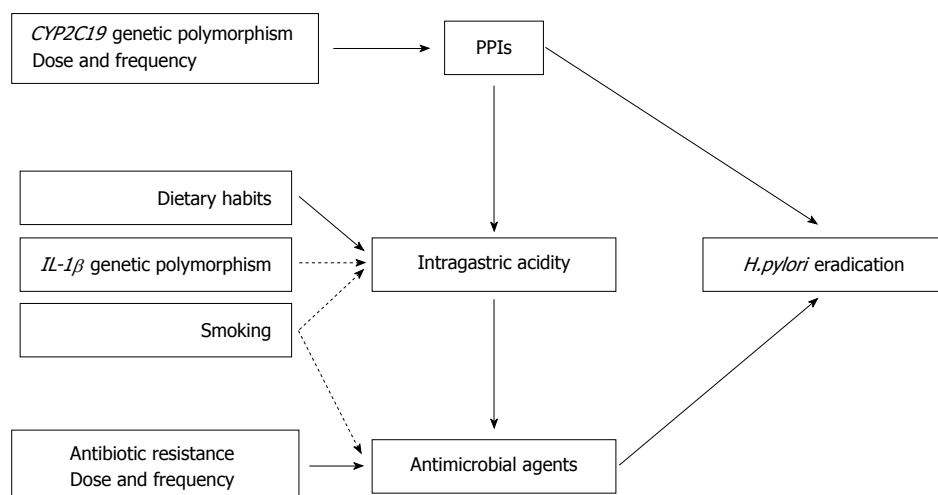
Figure 1 Factors that may affect treatment outcome for eradication of *Helicobacter pylori* infection. The dotted lines indicate a probable positive association. PPI: Proton pump inhibitor; *H. pylori*: *Helicobacter pylori*; IL: Interleukin.

sequential therapy as first-line therapy still requires validation in certain areas.

Although containing two dosing periods, sequential therapy is basically a quadruple therapy consisting of one PPI and three antibiotics. In 1998, before sequential therapy was proposed, two groups of investigators reported the use of a non-bismuth based quadruple therapy (*i.e.*, concomitant quadruple therapy) containing omeprazole, amoxicillin, metronidazole, and clarithromycin/ roxithromycin for 5 d or 1 wk and showed an eradication rate higher than 90%[75,76]. The result of meta-analysis of randomized controlled trials conducted during 1998 and 2007 showed that concomitant quadruple therapy was superior to standard triple therapy in terms of intention-to-treat and per-protocol[77]. Compared to sequential therapy, concomitant quadruple therapy has been demonstrated to be safe and equally effective in eradication of *H. pylori* infection[78], and the same study demonstrated that dual resistance to clarithromycin and metronidazole did not influence the eradication rate of concomitant quadruple therapy, but did significantly affect that of sequential therapy.

Rescue therapy

After failure of first-line therapy for *H. pylori* infection, in addition to bismuth-containing quadruple therapy, levofloxacin-based triple therapy is recommended as rescue therapy. The efficacy of one-week levofloxacin-based triple therapy containing a PPI plus levofloxacin and amoxicillin/nitroimidazole (metronidazole or tinidazole) was first evaluated as a first-line treatment in 2000, and a high eradication rate of 90%-92% was observed[79]. However, when it was compared to 7-d clarithromycin-based triple therapy as either a first-line or rescue therapy in a cross-over design study[80], when used as first-line treatment, clarithromycin-based triple therapy gave a significantly higher eradication rate than levofloxacin-based triple therapy (83.7% *vs* 74.2%, *P* = 0.015); however,

when used as rescue treatment, levofloxacin-based triple therapy achieved a higher eradication rate than clarithromycin-based triple therapy (76.9% *vs* 60%, *P* = 0.154). In addition, the overall eradication rate of clarithromycin-based triple therapy followed by levofloxacin-based triple therapy was significantly higher than that achieved using the reverse sequence (93.0% *vs* 85.3%, *P* = 0.01). These findings suggest that levofloxacin-based triple therapy should be used as second-line treatment, rather than first-line treatment.

FACTORS THAT AFFECT THE MANAGEMENT OF *H. PYLORI* INFECTION

In addition to patient adherence, a number of other factors can influence treatment outcome; these include antibiotic resistance, genotypes [*CYP2C19* and IL: Interleukin (*IL*)*1-β* polymorphisms], and intragastric acidity. Since PPIs and antibiotics are the major agents used to eradicate *H. pylori*, factors that affect the pharmacokinetics (*e.g.*, *CYP2C19* polymorphism for PPIs) or pharmacodynamics (*e.g.*, drug resistance or time/concentration-dependency of antibiotics) of these drugs can determine the evolution of the management of *H. pylori* infection (Figure 1). The impact of *CYP2C19* genotype on the pharmacokinetics and pharmacodynamics of PPIs in *H. pylori* treatment has been reviewed previously[81].

The major effect of PPIs in the treatment of *H. pylori* infection is to increase the intragastric pH, as the intragastric pH is important not only for the efficacious effect of antibiotics, but also for the growth of *H. pylori*. In two studies[81,82], the mean percentage of time that the intragastric pH was higher than 4 was found to be longer in patients cured of *H. pylori* infection than in those who were not cured (84% ± 11% *vs* 58% ± 9%, *P* < 0.001), and patients who were cured had a mean 24-h intragastric pH higher than 5.5. Factors that can influence the intragastric pH include *CYP2C19* genotype, *IL-1β* genotype,

Table 2 Prevalence of antibiotic resistance in different regions[89,95,101-109]

	Africa	Asia	Europe	United States
Amoxicillin	17.8%	1.9%	0.5%	2.2%
Clarithromycin	13.4%	21.0%	11.1%	29.3%
Metronidazole	86.2%	38.1%	17.0%	44.1%
Levofloxacin	NA	14.0%	24.1%	NA

NA: Not available.

and dose frequency of PPIs. When 40 mg rabeprazole was given once daily, the median intragastric pH was 4.3, 4.7, and 5.9 in patients who were CYP2C19 EMs, intermediate metabolizers (IMs), and PMs, respectively[83]. On the other hand, a regimen of rabeprazole 10 mg four times daily maintained the intragastric pH at a value higher than 6.5 regardless of *CYP2C19* genotype[83,84], showing that a dose frequency of four times daily is beneficial in providing sufficient inhibition of acid production in patients whose *CYP2C19* genotype is not known. However, *CYP2C19* polymorphism is not the only factor to consider, as it has been shown that *H. pylori*-infected patients with the *IL-1β-511 T/T* genotype have higher mucosal levels of IL-1β[85], a potent inhibitor of gastric acid secretion, which leads to an increase in the gastric pH, which plays a role in the therapy of *H. pylori* infection. The *IL-1β-511 T/T* genotype has been found to be related to a better outcome of standard triple therapy using omeprazole, lansoprazole, or rabeprazole[86,87].

In terms of the effects of antibiotics, as described in previous sections, the dose and frequency of dosing of antimicrobial agents should be determined by whether their efficacy is time- or concentration-dependent. For time-dependent antibiotics (*e.g.*, amoxicillin), it is more important to prolong the time that the plasma concentration is higher than the MIC, rather than achieve higher drug levels. On the other hand, for concentration-dependent antibiotics (*e.g.*, clarithromycin, levofloxacin, and metronidazole), it is more important to achieve higher plasma levels, within a reasonable range. A regimen chosen by considering these characteristics can improve treatment outcome. In addition to the dosing regimen, the increase in *H. pylori* resistance to antibiotics has also become an important factor in the efficacy of therapeutic regimens. The resistant rates of *H. pylori* to amoxicillin, clarithromycin, metronidazole, and levofloxacin are different among geographic areas (Table 2). Among these, the most important one is probably the resistance to clarithromycin, which is the key component of many regimens. The prevalence of clarithromycin resistance is more than 20% in China, Japan, and most countries in Europe[69,88-90]. Between 1998 and 2008, the clarithromycin resistance rates in Europe and Japan increased, respectively, from 9% to 17.5% and from 6.4% to 27.1%[88,91,92]. A meta-analysis showed that clarithromycin resistance caused a 66% reduction in the eradication rate of standard triple therapy containing a PPI, clarithromycin, and amoxicillin[93].

In addition to clarithromycin resistance, resistance to metronidazole is also important. The metronidazole resistance rate varies greatly in different geographical areas, being 92.4% in Africa, 44.1% in America, 37.1% in Asia, and 17.0% in Europe[89]. The prevalence of metronidazole resistance in developing countries is much higher than in developed countries, possibly due to the common use of metronidazole to treat parasitic infections in developing countries[94]. Metronidazole resistance also affects the efficacy of standard triple therapy containing a PPI, clarithromycin, and metronidazole. In metronidazole-susceptible strains, the eradication rate of triple therapy was found to be 97%, much higher than the value of 72.6% for metronidazole-resistant strains[3,93]. In contrast to clarithromycin and metronidazole resistance, the prevalence of amoxicillin resistance is usually less than 1%[69], and the impact of amoxicillin resistance on treatment outcome is still unclear. On the other hand, although the use of quinoline antibiotics, such as levofloxacin, has resulted in sufficiently satisfactory therapeutic outcomes to allow its use instead of clarithromycin in standard triple therapy regimen, the rapid acquisition of levofloxacin resistance may reduce its effectiveness and should be taken into account[15].

PAST AND FUTURE USE OF HIGH DOSE DUAL THERAPY

The high resistance rate of *H. pylori* to clarithromycin and metronidazole can significantly affect the efficacy of any regimens containing these medications. In contrast, worldwide primary amoxicillin resistance of *H. pylori* is generally low and secondary resistance to amoxicillin is also rare, even though it is a common medication in standard triple therapy[95-97], and it is therefore advantageous to use amoxicillin in the treatment of *H. pylori* infection. Dual therapy using the combination of a PPI (omeprazole) and amoxicillin was first investigated in 1989 and resulted in a better eradication rate (62.5%) than treatment with either PPI alone (0%) or amoxicillin alone (14.2%)[98]. High dose dual therapy consisting of 40 mg omeprazole and 750 mg amoxicillin given three times daily was first proposed in 1995 and gave an eradication rate for *H. pylori* infection greater than 90%[99]. In contrast to regular dual therapy, in high dose dual therapy, the PPI is given three or four times daily, rather than once or twice daily (Table 3). High dose dual therapy also seems to ameliorate the impact of *CYP2C19* genotype. Furuta *et al*[100] evaluated the eradication rate for *H. pylori* in patients with different *CYP2C19* genotypes receiving rabeprazole (10 mg) and amoxicillin (500 mg) four times daily and found eradication rates of 100% in both the EM and IM groups.

Despite the advantage of the low resistance rate to amoxicillin, the eradication rate of high dose dual therapy has been found to vary in different studies. There have only been a few randomized, large scale prospective studies examining the efficacy, adverse events, and patient ad-

Table 3 Use of different high dose dual therapies for *Helicobacter pylori* infection

Author	Role	Regiment	Patients, *n*	Eradication rate				
				ITT	PP	CYP2C19		
						EM	IM	PM
Bayerdörffer *et al*[99]	1st	OME 40 mg and AMO 750 mg *tid* for 14 d	139	89.0%	90.6%			
Miehlke *et al*[110]	2nd	OME 40 mg and AMO 750 mg *qid* for 14 d	41	75.6%	83.8%			
Furuta *et al*[100]	2nd	RAB 10 mg and AMO 500 mg *qid* for 14 d	12		100.0%	100.0%	100%	
Furuta *et al*[111]	2nd	LAN 30 mg and AMO 500 mg *qid* for 14 d	32		96.9%	95.7%	100%	100%
Shirai *et al*[112]	2nd	RAB 10 mg and AMO 500 mg *qid*	66	90.9%	93.8%			
Graham *et al*[113]	1st	ESO 40 mg and AMO 750 mg *tid* for 7 d	36	72.2%	74.2%			
Kim *et al*[114]	1st	LAN 30 mg and AMO 750 mg *tid* for 14 d	104	67.3%	78.4%			
Goh *et al*[115]	2nd	RAB 20 mg and AMO 1 g *tid* for 14 d	149	71.8%	75.4%			

ITT: Intention-to-treat; PP: Per-protocol; OME: Omeprazole; AMO: Amoxicillin; RAB: Rabeprazole; LAN: Lansoprazole; ESO: Esomeprazole; *tid*: Three times daily; *qid*: Four times daily; 1st: First-line treatment; 2nd: Rescue treatment; EM: Extensive metabolizer; IM: Intermediate metabolizer.

herence of high dose dual therapy as first-line or rescue regimen for *H. pylori* eradication and more are required to explain the discrepancies in the eradication rate; factors to be considered may include intragastric pH and dose frequency. As described above, an intragastric pH of 5 or higher is important for treatment outcome, and this is controlled by a number of factors, including PPI dose frequency, *CYP2C19* genotype, and *IL-1β* genotype. In addition, since the bactericidal effect of amoxicillin is time-dependent, the strategy for therapy is to increase duration of exposure, rather than increase the maximum concentration. Thus, for maximal pharmacodynamic effect, it is better to give amoxicillin in smaller and more frequent doses (*e.g.*, 500 mg four times daily), rather than higher and less frequent doses. In this regard, an optimized high dose dual therapy (*e.g.*, both PPI and amoxicillin given four times daily) has the potential to be used as first-line or rescue therapy for treatment of *H. pylori* infection. Alternatively, to improve patient compliance, sustained-release dosage forms could be used.

CONCLUSION

Eradication of *H. pylori* infection is important because of its high prevalence and implications in other diseases. Combinations of antisecretory agents and antimicrobial agents have been proposed as first-line or second-line therapy for its treatment. However, treatment outcome depends on many factors, including intragastric acidity and resistance to antimicrobial agents. While intragastric acidity can be controlled by PPIs, resistance to various antimicrobial agents is increasing. Of the antimicrobial agents frequently used to treat *H. pylori* infection, resistance to amoxicillin is generally low. Although dual therapy containing a PPI and amoxicillin has been reported to result in different eradication rates, its efficacy can be improved by adjusting the dose and dose frequency. In addition, although clinical use of alternative medicines has still to be evaluated, phytomedicines or probiotics may have the potential to provide additive or synergistic effects against *H. pylori* because they exert different effects. Further studies are required to examine the applica-tion of optimized high dose dual therapy and alternative medicines as first-line or rescue treatment for *H. pylori* infection.

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