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TOPIC HIGHLIGHT

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Attempts to enhance the eradication rate of *Helicobacter pylori* infection

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Abstract

Increasing rates of antimicrobial resistance to clarithromycin and metronidazole present challenges in maintaining optimal eradication rates. Knowledge of local antibiotic resistance and consumption pattern is important in selecting a reliable regimen. In addition, adverse effect profiles of therapeutic regimens are important and must be addressed to enhance compliance rates. Various methods of enhancing the eradication rates of *Helicobacter pylori* (*H. pylori*) have been investigated, including changing combinations or durations of established drugs, adding adjuvant drugs, or development of new molecules or agents. Bismuth-containing quadruple, sequential, concomitant, and levofloxacin-based triple therapies are replacing the long-standing standard of the triple regimen. Despite the encouraging results of these regimens, individualized approaches like treatment after antibiotics resistance test or CYP2C19 genotyping would be the mainstream of future therapy. Because scientific, economic, and technical problems make these advance therapies unfit for widespread use, future development for *H. pylori* therapy should be directed to overcome individualized antibiotic resistance. Although various novel regimens and additive agents have indicated favorable outcomes, more studies or validations are needed to become a mainstream *H. pylori* therapy.

Key words: *Helicobacter pylori*; Antimicrobial drug resistance; Clarithromycin; Metronidazole; Microbial sensitivity tests

Core tip: There is no uniform and definite therapeutic regimen for the *Helicobacter pylori* (*H. pylori*) eradication currently. Increasing rates of antimicrobial resistance present challenges in maintaining optimal eradication rates. Knowledge of local antibiotic resistance and antibiotic consumption pattern is important in selecting a reliable regimen. In addition, adverse effect profiles of therapeutic regimens are important to enhance compliance rates. Bismuth-containing quadruple, sequential, concomitant, and levofloxacin-based triple therapies are replacing the long-standing standard of the triple regimen. Although various novel regimens and additive agents have indicated favorable outcomes, more studies or validations are needed to become a mainstream *H. pylori* therapy.

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INTRODUCTION

Helicobacter pylori (*H. pylori*) is the most common, but not yet overcome chronic bacterial infection in humans. This can produce diseases of upper gastrointestinal tract such

as gastritis, peptic ulcer, gastric cancer, and marginal zone B-cell lymphoma. Moreover, association with other malignancies including colonic and pancreatic cancer has been proposed and evaluated[1-3]. Recently, various novel extraintestinal associations of *H. pylori* have been investigated for many diseases, including immune thrombocytopenic purpura, refractory iron deficiency anemia, vitamin B12 deficiency, insulin resistance (metabolic syndrome), Henoch-Schönlein purpura, atherosclerosis (coronary heart disease or cerebrovascular disease), Parkinson's disease, chronic idiopathic urticaria, and functional gastrointestinal disorders[4-6].

Despite many studies, there is no uniform and definite therapeutic regimen for the *H. pylori* eradication currently. The continuous rising of antimicrobial resistance is the cause of decreased efficacy for the long-standing used regimen. Recent data showed that decreased eradication rate less than 80% in most countries that is unacceptable regarding infectious disease which could promote severe outcome[7-9]. Various attempts have been made to overcome antimicrobial resistance, from changing medication regimens, increasing dose or extending the duration, adding adjuvant medications, treatment after antimicrobial susceptibility test, and even to the development of vaccine. However, different resistance patterns across geographic areas or individuals make it difficult to apply a uniform anti-*H. pylori* regimen. This article will review the first-line eradication regimens according to the updated consensus guidelines and introduce novel regimens or attempts to enhance the eradication rate of *H. pylori*.

FIRST-LINE THERAPY

Standard triple therapy

The effectiveness of antibiotics is related not only to the antimicrobial strength, but also to cost, side effects, duration, tolerability of drugs, local antibiotic use, and bacterial resistance. The triple therapy with proton pump inhibitor (PPI), clarithromycin and amoxicillin or metronidazole has been the standard first line therapy in most of guidelines until recently. Metronidazole can be used for penicillin allergic patients with equivalent effectiveness to amoxicillin[10]. The regimen is simple and has been used widely for more than a decade. However, the decreasing efficacy of this triple therapy has elicited research about potential causes. Subsequently, increased antibiotic resistance especially to clarithromycin was suspected as the core problem, in addition to compliance issues, type of strains, high bacterial load, and gastric acidity[6]. Resistance rates to clarithromycin ranges from 0% in India to 49.2% in Spain, with an overall rate 17.2% in a survey across 21 countries[11,12] and 17.5% in another study involving 18 European countries[13]. Such research findings, however, require careful interpretation because the prevalence of bacterial resistance and patterns of antibiotic use varies according to geographic areas studied and discordant methods of evaluating the minimal inhibitory concentration (MIC) and resistance of antibiotics[11]. Most notably, the triple therapy as an initial regimen is losing its efficacy in areas with high incidence of clarithromycin resistance (over 15% to 20%). Novel regimens aimed at achieving > 90% per protocol (PP) eradication rates and > 80% intention-to-treat (ITT) eradication are being tested. Current recommended first line therapies are listed in Tables 1 and 2. Among many novel therapeutic regimens, only four treatment options including 7 to 14 d triple therapy, 10 to 14 d bismuth-containing quadruple therapy, 10-d sequential and 10-d concomitant therapy are recommended as the first line options in consensus guidelines[6,14-17].

Bismuth containing quadruple therapy

Bismuth containing quadruple therapy with PPI, bismuth, metronidazole and tetracycline is the first line treatment in areas of high clarithromycin or metronidazole resistance and for patients with recent or repeated exposure to clarithromycin or metronidazole[6,18]. In addition, this regimen is an alternative to standard clarithromycin-containing treatments in areas of low clarithromycin resistance[6,14,15] and is also included as the second line treatment in most guidelines[6,14,15,17]. The main advantage of this regimen is that free of clarithromycin resistance and minimal impact of metronidazole resistance which could be overcome by extended duration[19]. Meta-analysis of studies from either clarithromycin or metronidazole resistant areas have shown improved outcomes for bismuth containing quadruple therapy compared to the standard triple therapy[20]. In countries where tetracycline and bismuth salts are not available, doxycycline or amoxicillin could be substitutes, although the results are conflicting[21-24]. Limited compliance due to the increased number of drugs and frequent dosing (four times daily) have led to the development of combination capsules containing bismuth, metronidazole, and tetracycline[25]. As the decreased number of pills and simplified regimen, quadruple therapy including combination capsules with PPI has shown promising eradication rates[25-27].

Sequential therapy

The 10-d sequential therapy consist of PPI and amoxicillin for 5 d followed by PPI, clarithromycin, and metronidazole (or tinidazole) for 5 subsequent days is an alternative to standard triple therapy in high clarithromycin resistance areas[6,16]. Levofloxacin could be a substitute for clarithromycin in patients with penicillin allergy or in areas of high clarithromycin resistance[28]. Even though clarithromycin is included in this regimen, amoxicillin given earlier causes bacterial wall disruption and prevents development of efflux channels for clarithromycin, which is one of the mechanisms of clarithromycin resistance[29]. However, another explanation is that the large number of antibiotics itself is the cause of effectiveness rather than the sequential administration of the medications. In areas of dual resistance to clarithromycin and metronidazole, tinidazole could be a substitute for metronidazole[30]. Extended duration to 14 d did not improve eradication

Table 1 Treatment regimens for *Helicobacter pylori* eradication

Treatment	Regimens	Duration
Standard triple therapy	PPI (standard dose), amoxicillin (1 g), and clarithromycin (500 mg) twice daily PPI (standard dose), metronidazole (500 mg), and clarithromycin (500 mg) twice daily	7-14 d
Bismuth containing quadruple therapy	PPI (standard dose) twice daily, bismuth (standard dose), metronidazole (500 mg), and tetracycline (500 mg) four times daily	10-14 d
Sequential therapy	PPI (standard dose) and amoxicillin (1 g) twice daily for 5 d, followed by PPI (standard dose), metronidazole (500 mg), and clarithromycin (500 mg) twice daily for 5 d	10 d
Concomitant therapy (Non-bismuth quadruple therapy)	PPI (standard dose), amoxicillin (1 g), metronidazole (500 mg), and clarithromycin (500 mg) twice daily	10 d
Hybrid therapy	PPI (standard dose), amoxicillin (1 g) twice daily for 7 d, followed by PPI (standard dose), amoxicillin (1 g), metronidazole (500 mg), and clarithromycin (500 mg) twice daily for 7 d	14 d
Levofloxacin-based triple therapy	PPI (standard dose), amoxicillin (1 g), and levofloxacin (500 mg) twice daily	10 d
LOAD regimen	Levofloxacin (250 mg) with breakfast, omeprazole (40 mg) before breakfast, nitazoxanide (500 mg) twice daily with meals, and doxycycline (100 mg) at dinner	7 d or 10 d
Rifabutin-based triple therapy	PPI (standard dose), amoxicillin (1 g), and rifabutin (150 mg) twice daily	7-14 d
Furazolidone-based quadruple therapy	Lansoprazole (30 mg), tripotassiumdicitratobismuthate (240 mg), tetracycline (1 g), and furazolidone (200 mg) twice daily	7 d
Novel quadruple therapy	PARC; rabeprazole (20 mg, thrice daily for 10 d), amoxicillin (1000 mg, thrice daily for 10 d), rifabutin (150 mg, starting from day 6, twice daily for 5 d), and ciprofloxacin (500 mg, starting from day 6, twice daily for 5 d) PBRC (allergic to amoxicillin); rabeprazole (20 mg, thrice daily for 10 d), bismuth subcitrate (240 mg, 4 times daily for 10 d), rifabutin (150 mg, twice daily for 10 d), and ciprofloxacin (500 mg, twice daily for 10 d)	10 d
High dose dual therapy	Lansoprazole (30 mg) and amoxicillin (750 mg) thrice daily	14 d

PPI: Proton pump inhibitor.

rates, compared to the 10 d regimen[30]. Several meta-analyses and a pooled analyses indicated that the sequential therapy was beneficial effects when compared to standard triple therapy, although most of the enrolled data were collected in Italy where the rates of clarithromycin resistance are relatively high across the peninsula[30-34]. Recent data from Asian countries expanded these beneficial effects of sequential therapy more clearly[35-37], although some conflicting results continue to remain[38].

Concomitant therapy

A return to the old regimen called for concomitant or non-bismuth quadruple therapy as an alternative option to bismuth containing quadruple therapy in high clarithromycin resistance areas[6]. The regimen consists of PPI, clarithromycin, amoxicillin, and metronidazole for at least 10 d. This relatively short duration (3 to 5 d) therapy was proposed more than 10 years ago and had been abandoned. However, it is making a comeback as the first line therapy[39,40]. Recent randomized clinical trials (RCTs) indicated that concomitant therapy is superior or equivalent to standard triple therapy in antibiotic resistant areas[41,42]. A meta-analysis showed > 90% PP and > 80% ITT eradication rates for concomitant therapy, which was an improvement over the standard triple therapy, although all 5 RCTs included in the analysis had been executed more than 10 years ago[43]. Subsequently, a more recent meta-analysis found ITT eradication rates of 90% with concomitant *vs* 78% with standard triple therapy[44]. Regarding the favorable outcomes despite the short duration of concomitant therapy in enrolled RCTs, extended duration is expected to achieve better results. The eradication rates in one RCT executed in Thailand support this theory (96.4% in 10 d *vs* 89.1% in 5 d concomitant therapy)[45]. The main advantage of concomitant therapy is the efficacy against dual resistance strains (clarithromycin and metronidazole), which is better than that of the sequential therapy[32,42,46]. Another advantage is the higher compliance rates compared to the sequential therapy.

HYBRID THERAPY

Hsu *et al*[47] proposed a hybrid (dual concomitant) therapy consisting of dual therapy with PPI and amoxicillin for 7 d, followed by a concomitant quadruple therapy with PPI, amoxicillin, clarithromycin and metronidazole for another 7 d. The result of eradication rate was excellent with 99% in PP and 97% in the ITT analysis, even when considering dual clarithromycin and metronidazole resistance strains[47]. The main mechanism seems to be the extended use of amoxicillin for 14 d, compared to sequential or concomitant therapy. One RCT indicated that the hybrid therapy had equivalent eradication rates to 14-d concomitant therapy[48,49]; however, more validation is needed.

QUINOLONE-BASED THERAPY

Levofloxacin is the most validated quinolone antibiotics in various combination regimens. Levofloxacin-based triple therapy consists of PPI, levofloxacin, and amoxicillin for 10 d. Based on a large body of published clinical trials, the eradication rate of levofloxacin-based triple therapy has been found to range from 74% to 96%

Table 2 Current recommended first line regimens of *Helicobacter pylori* eradication

Guidelines	Regimens	Duration
Maastricht IV/Florence (2012)[6]	Clarithromycin containing treatments in areas of low clarithromycin resistance (Bismuth-containing quadruple treatment is an alternative)	7-14 d
	Bismuth-containing quadruple treatment in areas of high clarithromycin resistance (if not available, sequential treatment or non-bismuth quadruple treatment is recommended)	-
		-
Asian Pacific (2009)[15]	Standard PPI-based triple therapy	7 d
	(Bismuth-containing quadruple treatment is an alternative)	-
American College (2007)[14]	Standard PPI-based triple therapy OR	14 d
	Bismuth-containing quadruple treatment	10-14 d
	(Sequential therapy may be an alternative)	-
South Korea (2013)[82]	Standard PPI-based triple therapy	7-14 d
	(Bismuth-containing quadruple treatment is an alternative)	7-14 d
Japan (2009)[16]	Standard PPI-based triple therapy	7 d
Canada (2005)[112]	Standard PPI-based triple therapy	14 d
ESPGHAN and NASPGHAN for children (2011)[113]	Standard PPI-based triple therapy	-
	Bismuth-containing quadruple treatment	10-14 d
	Sequential therapy	10 d

PPI: Proton pump inhibitor; ESPGHAN and NASPGHAN: European and North American Societies of Pediatric Gastroenterology Hepatology and Nutrition.

(ITT analysis), which was similar for therapies including moxifloxacin[50]. Moxifloxacin-based triple therapy showed slightly superior efficacy to the bismuth containing quadruple therapy which is statistically insignificant, but when analyzed only as a rescue therapy, showed slightly inferior efficacy[51]. Another regimen consisting of levofloxacin, omeprazole, nitazoxanide, and doxycycline (LOAD regimen) for 7 or 10 d had been introduced. The LOAD regimen demonstrated a higher eradication rate than standard triple therapy as the first line treatment[52]. However, the subsequent results are limited. The eradication success of levofloxacin-based triple therapy seems not to be affected by clarithromycin and/or metronidazole resistance[53-55]. However, this regimen is not generally recommended as the first line treatment because quinolone resistant strains have increased as the consumption of quinolones have increased for infections of respiratory and urogenital tracts[50]. Presently, it might be considered to be an efficient alternative regimen in populations with clarithromycin resistance > 15%-20% and quinolone resistance < 10%. In recently published guidelines, levofloxacin-based triple therapy is considered to be the second line treatment when the first line treatments has failed (standard triple therapy in low clarithromycin resistance areas and bismuth containing quadruple, sequential and concomitant therapy in high clarithromycin resistance areas)[6]. Although a third line treatment is recommended based on the results of individual antibiotic susceptibility tests, levofloxacin-based triple regimen could be used as an empiric salvage treatment after the failures of first and second line therapy in low quinolone resistance areas. Levofloxacin-based quadruple therapy including rabeprazole, bismuth subcitrate, amoxicillin and levofloxacin for 10 d has also shown 84% eradication rate in ITT and PP analysis after the failure of the first-line and second-line treatments[56]. Studies using the novel quinolone, sitafloxacin, demonstrated low antibiotic resistance and promising results as a third line treatment in Japan[57-59]. Garenoxacin and rufloxacin also could be a candidate as rescue regimen, although these quinolones are not yet available in many countries[60,61]. However, selection of quinolone should be based on the results of antibiotics susceptibility test or geographic resistance patterns as shown in a study of gatifloxacin[62] because of rapid increases in resistant strains.

RIFABUTIN-BASED TRIPLE THERAPY

Based on *in vitro* studies, an anti-tuberculous agents, rifabutin, was introduced as part of a rescue therapy for *H. pylori* eradication[63]. A triple regimen that includes amoxicillin, PPI and rifabutin showed encouraging effects as a salvage treatment[64-66]. However, optimal duration of therapy remains unclear (7 d *vs* 10 d *vs* 14 d), and although rare, myelotoxicity is a significant complication which should be overcome for widespread applications[65]. Because of potential for mycobacterial resistance, this regimen should be reserved or used only in rescue treatment. Rifabutin-based triple therapy is listed in recent published guidelines as an empiric third line salvage treatment and could be used in areas where bismuth and tetracycline are not available[6,65].

FURAZOLIDONE-BASED QUADRUPLE THERAPY

Furazolidone-based therapy is another salvage treatment option. In a study, a single week therapy with lansoprazole, tripotassiumdicitratobismuthate, tetracycline and furazolidone after second line treatment failure (Bismuth containing quadruple therapy for 1 wk) had achieved 90% eradication rate in ITT and PP analysis[67]. However problems of cross resistance with metronidazole and high incidence of side effects need to be addressed[68].

NOVEL QUADRUPLE THERAPY

Rifabutin and ciprofloxacin-based novel quadruple therapy was introduced in an Australian study[69]. Rifabutin-based, quinolone of ciprofloxacin added new regimen has achieved eradication rates over 90% in patients having at least one treatment failure. However, this combination regimen was made and introduced according to the results of pre-treatment antibiotics susceptibility test, and it might not be used in the same combination of medications because of different geographic antimicrobial resistance patterns. At this time, this regimen cannot be included in the quinolone based or rifabutin based therapy. It seems to be the one example of culture based therapy.

HIGH DOSE DUAL THERAPY

Based on the fact that sustained intragastric pH > 4.0 is associated with successful *H. pylori* eradication rate, a high-dose dual therapy that consists of PPI and amoxicillin three times a day for 14 d was proposed and evaluated in high clarithromycin resistance areas[70,71]. The eradication rate was 82.8% for standard triple therapy for 14 d and 78.4% for high dose dual therapy, between which the difference was statistically not different[70]. Regarding fewer side effects and better compliance of high dose dual therapy, larger studies are needed before this regimen can be established as a main therapeutic regimen[72].

CULTURE BASED THERAPY

After the failure of second-line treatments, antimicrobial susceptibility test is recommended to guide the following optimal regimen[6]. In one study from Italy, treatments tailored to the results of antimicrobial susceptibility test achieved over 90% eradication rate after second-line therapy failure[73]. However, the sensitivity of antimicrobial susceptibility test is less than 60%[74]. Also, the test cannot detect or reflect the whole geographic or interpersonal variations in antimicrobial susceptibility of *H. pylori*. Another problem is mixed-infections of antibiotic susceptible and resistant *H. pylori* strains[75]. Moreover, the test is expensive and invasive. The dual-priming oligonucleotide-based multiplex PCR (DPO multiplex PCR) test recently introduced showed higher sensitivity and specificity for the detection of *H. pylori* and antimicrobial resistance[76,77]. Recent advancement in third-line empiric regimens could be a prior option for salvage treatment over the ideal culture-based therapy.

CYP2C19 GENOTYPING

PPIs have anti-*H. pylori* effect and increase eradication rates by enhancing the concentration of other antibiotics in the stomach[78]. Metabolism of PPI depends on the cytochrome P450 (CYP450) enzyme of the liver, and *CYP2C19* genotype and multidrug resistance gene 1 (*MDR1*) polymorphism are known to affect the metabolism and efficacy of PPIs[15]. According to the meta-analysis, CYP2C19 polymorphism affects the *H. pylori* eradication rate, especially for omeprazole and less for than lansoprazole and rabeprazole[78]. Extensive PPI metabolizer and MDR T/T genotype are found to have associations with lower eradication rates[78,79]. In Asia, the impact of CYP2C19 polymorphism would be significant because poor metabolizer genotype was estimated in at least 15% of study populations[80,81]. At this time however, choice of PPI and/or dose are preferred than CYP2C19 genotyping tests because evidences for these tests are still lacking and not clinically available in most countries[15,82].

ADJUVANT THERAPY

Probiotics

Probiotics were proposed as an adjuvant therapy to increase the eradication rate and to decrease the side effects of therapeutic regimens, especially antibiotic-associated diarrhea. *Saccharomyces boulardii* and *Lactobacillus* species are the main probiotic strains used, and meta-analysis of this adjuvant therapy showed an increased eradication rate (RR = 1.13 for *Saccharomyces boulardii* and OR = 1.78 for *Lactobacillus* species) and decreased rates of therapy-related adverse effects (RR = 0.46 for *Saccharomyces boulardii* and OR = 0.49 for *Lactobacillus* species)[83,84], although contradictory results remain[85,86]. A more recent trial showed pretreatment with *Lactobacillus gasseri* before therapy regimens improved eradication rates from 69.3% to 82.6% in clarithromycin resistant areas[87]. Also, fermented milk containing probiotics, kefir, was demonstrated to increase eradication rates from 50% to 78%[88]. The exact mechanism behind this improvement is uncertain. Some possible explanation is the competition against the *H. pylori* bacteria and the restoration of normal gut-flora[89].

Statin

HMG-CoA reductase inhibitors are known to have many pleiotropic effects, and were added to the standard triple therapy in one RCT[90]. Better eradication rate was observed for the group treated with the addition of statin (simvastatin). However, only a small number of patients were enrolled in this study, and considerations about lipid have to be overcome.

Histamin-2 receptor blocker

Pretreatment with histamine-2 receptor blocker (ranitidine) followed by standard triple therapy had achieved a slightly higher eradication rate compared to a control group without a pretreatment. However, this difference was not statistically insignificant[91].

Aspirin

A recent study from Turkey demonstrated a higher eradication rate for aspirin plus standard triple therapy, compared to standard therapy alone[92]. However, the trial included a small number of patients, and the eradication rate of the standard therapy was below established stan-

dards for first line therapy. Further large-scale studies are needed to confirm this result.

Vitamin

Vitamin C and E are potent antioxidants that reduce the damage caused by reactive oxygen species in gastric mucosa. Based on this concept, vitamin supplements as adjuvant therapy was evaluated in *H. pylori* eradication. One RCT from Turkey reported improved outcomes for the vitamin supplement group (ITT 63.8%, PP analysis 66.2%) over the standard triple therapy group (ITT 42.5%, PP analysis 44.7%)[93]. However, the result of a meta-analysis did not show beneficial effects from vitamin C or E because of small sample sizes and methodological problems of enrolled studies[94].

Pronase

Pronase is a kind of proteolytic enzyme which is known to cause degradation of gastric mucus and breaking the barrier of the surface mucous gel layer (SMGL)[95,96]. It is widely used premedication for endoscopy to improve endoscopic visibility of gastric mucosa prescribed with sodium bicarbonate. Based on the concepts that *H. pylori* colonizes not only on the apical surface of gastric surface mucous cells but also the SMGL, and pronase has dissolving function of SMGL, the additive effect of pronase combined with standard triple therapy for *H. pylori* eradication were evaluated[97]. Only one RCT revealed that LAMP (lansoprazole once daily, 500 mg of amoxicillin, 250 mg of metronidazole and 18000 tyrosine units of pronase thrice daily for 2 wk) group showed a significant higher eradication rate than LAM group (ITT: 94% *vs* 76.5%, $P = 0.0041$)[97]. Another study which used pronase 18000 tyrosine units twice a day for 2 d showed the potential benefits of pronase on *H. pylori* eradication, although combined with topical anti-*Helicobacter* treatment which is not used now and not a well-designed study to prove the efficacy of pronase[98]. More validation is needed because regimens of these studies are not used now.

PHYTOMEDICINE

Many studies have aimed at finding potent phytomedicine for *H. pylori* infection. *Terminalia macroptera* (*Combretaceae*) root and *Eucalyptus tolleria* leaf with clarithromycin showed anti-*H. pylori* effect, and minimal inhibitory concentration (MIC) was measured from *in vitro* studies[99]. Among *in vitro* studies on phytomedicine, effects on antimicrobial resistant strains were observed for *Combretum molle* and *Sclerocarya birrea*[100,101]. The eupatilin component was found to have anti-*H. pylori* effect as well as anti-inflammatory effect from *in vitro* study, although clinical evidence is limited[102]. The urushiol component in the sap from the Korean lacquer tree (*Rhus verniciflua* Stokes) was found to have a potent anti-*H. pylori* effect in *in vitro* and mouse model studies[103,104]. A traditional Chinese medicine formula, HJZW, had been evaluated using an experimental rodent model, and anti-*H. pylori* property was revealed using the agar dilution method[105]. Continuous efforts to find the additive phytomedicine to the established therapeutic regimens are anticipated. However, the development of clinically available drugs seems to need more time and studies.

IMMUNOTHERAPY

From the results of passive immunization with orally administered bovine antibodies for the prevention and eradication of *H. pylori* in animal studies, a first-line immunotherapy had been performed in human subjects[106], in which the whey protein concentration from milk of *H. pylori*-immunized cows were administered to *H. pylori* infected individuals. However, the immunotherapy was ineffective in reducing *H. pylori* colonization[106].

VACCINE

While most novel approaches focus on overcoming antimicrobial resistance, prevention of infection through active immunization has been studied using animal models. From the promising results of experimental vaccines in preclinical efficacy studies, few clinical trials were performed with urease-based vaccines, administered either as a purified recombinant protein along with mucosal adjuvants or as a *salmonella*-vectored vaccine. Although efficacy was limited, the vaccine showed good immunogenicity and safety profiles in phase I trial. However, lacking financial support from the industrial sector, no further clinical trials are expected at the moment[107,108].

ADHERENCE TO TREATMENT

Patient adherence to treatment is the important factor predicting successful eradication of *H. pylori*. According to the study which evaluated the association between adherence with prescribed regimen and eradication rate, successful eradication was observed in 96% of patients who took more than 60% of medication that is larger than that of who took less[109]. This result is consistent with the study which evaluated the efficacy of two eradication regimens. In that study, 90% of the patients took a full dose of prescribed medication correctly and that was suspected as the cause of encouraging outcomes of this study[110]. To enhance the adherence, one RCT demonstrated that enhanced compliance program (ECP) which is medication counseling (written and oral) from a pharmacist, along with a medication calendar and a minipill-box, as well as a follow-up telephone call after initiation of therapy, increased the number of patients who took more than 90% of the medications[111]. Combination capsule containing bismuth, metronidazole, and tetracycline described in the section of Bismuth containing quadruple therapy is also one of the methods to enhance the adherence of patients[25-27].

CONCLUSION

The standard triple regimen is losing its efficacy for *H. pylori* eradication in many countries. Novel therapies such as bismuth-containing quadruple, sequential, concomitant, and levofloxacin-based triple regimens are replacing the main therapy, although cannot be generalized unanimously. Despite the encouraging results of novel regimens or adjuvant medications, attempts to overcome antibiotic resistance like treatment after antibiotics resistance test or CYP2C19 genotyping are expected to be reliable and promising approaches.

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