Hanyang Medical Reviews

Hanyang Med Rev 2017;37:2-9
https://doi.org/10.7599/hmr.2017.37.1.2
pISSN 1738-429X eISSN 2234-4446

Review

The first-line regimens of Helicobacter pylori eradication in Korea

Chan Hyuk Park

Department of Internal Medicine, Hanyang University Guri Hospital, Hanyang University College of Medicine, Guri, Korea

Approximately half of the world's population is infected by Helicobacter pylori, which causes various gastrointestinal diseases including gastritis, peptic ulcer, gastric mucosa-associated lymphoid tissue lymphoma, and gastric cancer. The conventional triple therapy, that consists of proton pump inhibitor (PPI), amoxicillin, and clarithromycin, is widely used in Korea because of high resistance rates of *H. pylori* against metronidazole. Recently, however, clarithromycin-resistance rates have also increased and the eradication rate of conventional triple therapy has been unacceptable. In order to increase the eradication rate of H. pylori, various regimens have been suggested. Understanding *H. pylori* eradication regimens will help select drugs in the management of *H. pylori* infection.

Key words: *Helicobacter pylori*; Proton pump inhibitor; Antibiotics; Eradication

Corresponding Author: Chan Hyuk Park
Department of Internal Medicine, Hanyang University Guri Hospital, Hanyang University College of Medicine, 153 Gyeongchun-ro, Guri, 11923, Korea.
Tel: +82-31-560-2230
Fax: +82-31-553-7369
E-mail: yesable7@gmail.com

Received 13 Jan 2017
Revised 23 Feb 2017
Accepted 27 Mar 2017

INTRODUCTION

Approximately half of the world's population is infected by Helicobacter pylori [1], which causes various gastrointestinal diseases including gastritis, peptic ulcer, gastric mucosa-associated lymphoid tissue lymphoma, and gastric cancer [2,3]. Korean guidelines, which were revised in 2013, by the Korean College of Helicobacter and Upper Gastrointestinal Research strongly recommend that *H. pylori* should be eradicated in patients with peptic ulcer disease, gastric MALT lymphoma, endoscopically treated early gastric cancer, and immune thrombocytopenic purpura [4].

Identification of optimal regimen of *H. pylori* eradication has been a challenge for gastroenterologists. Twenty years ago, one comparative study showed that proton pump inhibitor (PPI)-based triple therapy, that consisted of PPI, amoxicillin, and metronidazole, had superior efficacy for *H. pylori* eradication among various regimens based on PPI, bismuth, amoxicillin, and metronidazole [5]. In addition, conventional triple therapy, that consists of PPI, amoxicillin, and clarithromycin, has been widely used in Korea because of the high resistance rate of *H. pylori* against metronidazole [4,6,7]. This conventional triple therapy for 7-14 days is also a world-wide choice for *H. pylori* eradication [8,9]. However, eradication of conventional triple therapy has decreased over the past 10 years [10,11], caused by resistance against clarithromycin [12]. Alternatively, many eradication regimens including sequential therapy, concomitant therapy, and hybrid therapy have been suggested [4]. Despite of the insufficient eradication rate of the conventional triple therapy, the current Korean guideline still recommends conventional triple therapy as a first-line therapy for *H. pylori* infection because superior efficacy of alternative regimens over the conventional triple therapy has not been fully evaluated [4]. Recently, however, the Maastricht V/Florence Consensus Report stated that PPI-clarithromycin-containing triple therapy without prior susceptibility testing should be abandoned

when the clarithromycin resistance rate in the regions is more than 15% [13]. In other words, alternative regimens should be considered in the clarithromycin-resistant *H. pylori* prevalent regions when treating *H. pylori* infection without prior susceptibility test. Understanding *H. pylori* eradication regimens will help select drugs in the management of *H. pylori* infection.

PROTON PUMP INHIBITOR

PPIs have two major roles in the eradication therapy; one is reducing gastric acid secretion, and the other is increasing bioavailability and activities of antibiotics [14]. In addition, gastric acid secretion is not sufficiently inhibited in extensive metabolizers of PPIs. Therefore, many clinicians wondered whether more potent PPIs would lead to a higher eradication rate. In Taiwan, esomeprazole-based triple therapy showed superior efficacy of *H. pylori* eradication rate compared to omeprazole in the extensive metabolizer subgroup [15]. However, significant difference was not observed between esomeprazole and omeprazole, in all patients including extensive and poor metabolizers. A randomized-controlled trial in Korea also showed that double-dose of new-generation PPIs including esomeprazole and rabeprazole did not affect the *H. pylori* eradication rate [16], compared with 20 mg of omeprazole twice daily. Relatively low proportion of extensive metabolizers in Korea may be a reason for the insignificant difference between different PPIs in terms of *H. pylori* eradication rate. Although several PPIs are not approved for the purpose of *H. pylori* eradication therapy currently, by the Ministry of Food and Drug Safety in Korea, all types of PPIs may be effective for *H. pylori* eradication.

A remarkable thing about *H. pylori* eradication therapy is use of potassium-competitive acid blockers (P-CABs) instead of PPIs. P-CABs inhibit gastric hydrogen/potassium-ATPase in a potassium-competitive and reversible manner [17]. Because P-CAB is highly accumulated and slowly excreted from gastric tissue, it has a potent and a long-lasting anti-secretory effect on gastric acid [18]. In Japan, triple therapy based on vonoprazan, a novel P-CAB, showed favored eradication rate compared to lansoprazole-based triple therapy [19]. The eradication rate was 92.6% (95% confidence interval [CI] 89.2% to 95.2%) and 75.9% (95% CI 70.9% to 80.5%) in vonoprazan- and lansoprazole-based triple therapies, respectively. Although Korean studies are lacking now, P-CAB-based therapy may be one potential option for *H. pylori* eradication. However, resistance against antibiotics remains a matter for concern. In the study on vonoprazan-based triple therapy, eradication rate was still insufficient in patients with clarithromycin-resistant *H. pylori* infection [19-21]. Although P-CAB-based therapy may be a superior regimen over PPI-based therapy, it cannot be recommended in the presence of clarithromycin-resistant infections [22].

CONVENTIONAL TRIPLE THERAPY

Conventional triple therapy usually consists of standard dose of PPI, 1 g of amoxicillin, and 500 mg of clarithromycin, twice daily [4]. As mentioned in the Introduction, metronidazole as a first-line therapy has not been recommended in Korea because of the high resistance of *H. pylori* [4]. The resistance rate of *H. pylori* against metronidazole in Korea has increased from 33.3% in 1994, to 47.7% in 1999, to 66.2% in 2003 [23].

In the rank probability analysis of the world-wide network meta-analysis, conventional triple therapy for 7 days showed relatively good tolerability among various regimens; however, ranking of eradication rate was very poor [24]. Many years ago, prolonged duration of triple therapy was effective for increasing *H. pylori* eradication rate. A randomized-controlled study published in 2001 demonstrated that eradication rate was 74.4%, 80.2%, and 91.9% in the triple therapy for 7 days, 10 days, and 14 days, respectively. However, the high eradication rate of 14 days-triple therapy seems to decrease as times goes on. A randomized-controlled study published in 2007 indicated no difference of eradication rate between 7 days-regimen and 14 days-regimen (intention-to-treat [ITT] analysis: 71.2% and 75.5%, respectively) [25]. Another study published in 2012 also demonstrated no significant difference among 7 days-, 10-days, and 14-days regimens (ITT analysis: 70.4%, 74.7%, and 80.0% respectively, P=0.244) [26]. Although the current guideline still recommends the conventional triple therapy for 7 to 14 days as first-line *H. pylori* eradication therapy, clinicians should be cautious for treating *H. pylori* infection with the conventional triple therapy.

ADDITION OF PROBIOTICS OR MUCOPROTECTIVE AGENTS

In order to increase the conventional triple therapy, various supplements, including probiotics and mucoprotective agents

have been tried [27-31]. Overall, probiotics seemed to have additive effect on *H. pylori* eradication. One study comparing eradication rate between the conventional triple therapy for 7 days and that with probiotics (Bacillus subtilis [$2.5x10^9$ colony-forming unit [CFU]/g] and Streptococcus faecium [$2.25x10^{10}$ CFU/g]) for 8 weeks showed the superior efficacy of probiotics-included regimen (ITT analysis: with probiotics vs. without probiotics, 83.5% vs. 73.3%, *P*=0.020) [27]. Another study demonstrated that eradication rate of the conventional triple therapy for 7 days with Will yogurt®, which contains probiotics (*Lactobacillus acidophilus* [$>10^5$ CFU/mL], *Lactobacillus casei* [$>10^5$ CFU/mL], *Bifidobacterium longum* [$>10^6$ CFU/mL], and *Streptococcus thermophiles* [$>10^8$ CFU/mL]) for at least 3 weeks tended to be higher than the conventional triple therapy only (ITT analysis: 79.2% vs. 72.1%, *P*=0.124) [28]. Another study also showed the superiority of eradication rate in the probiotics group (*Saccharomyces boulardii* [$3x10^{10}$ CFU/g] for 4 weeks) compared to the conventional triple therapy only group (ITT analysis: 80.0% vs. 71.6%, *P*=0.012) [30]. Probiotics-included regimens can be helpful for increasing eradication rate of conventional triple therapy. However, prolonged duration of *H. pylori* eradication may be a disadvantage of this strategy.

In contrast to the results of probiotics, mucoprotective agent seemed to be less effective. In two randomized-controlled trials comparing between conventional triple therapy only vs. conventional triple therapy with ecabet sodium (gliptide®), there was no difference of eradication rate between the groups (ITT analysis: 72.1% vs. 78.9%, P=0.204; 81.4% vs. 86.2%, *P*=0.159) [30,31]. Although there was no significant difference on ITT analyses, per protocol (PP) analysis of one study showed superiority of mucoprotective agent-included therapy (PP analysis: conventional triple therapy only vs. conventional triple therapy with ecabet sodium, 78.8% vs. 88.6%, *P*=0.044) [29]. Given that mucoprotective agent was administered for only 7 days unlike probiotics, prolonged medication of mucoprotective agent may be helpful for increasing the eradication rate of *H. pylori*.

SEQUENTIAL THERAPY

Sequential therapy was first introduced by Zullo *et al*. in 2000 [32]. Standard sequential therapy regimen consists of two phases of treatment. For the first 5 days (or 7 days), standard dose of PPI and 1 g of amoxicillin are administered twice daily. Thereafter, standard dose of PPI, 500 mg of clarithromycin, and 500 mg of metronidazole (or tinidazole) are administered twice daily for the last 5 days (or 7 days). Sequential therapy has been suggested because of inoculum effect and efflux channel of clarithromycin [33,34]. In the first phase of treatment, amoxicillin is aimed to lower the bacterial load in the stomach to improve the efficacy of the immediately subsequent short course of triple therapy that consists of PPI, clarithromycin, and metronidazole [33]. It has been known that amoxicillin is not affected by bacterial factors including CagA status and infection density [33]. In addition, amoxicillin in the first phase of treatment may prevent the development of efflux channels by damaging the cell wall of *H. pylori* [35]. This may help to improve the efficacy of clarithromycin in the second phase of the treatment.

In Korea, the first study on comparison between sequential therapy vs. conventional triple therapy was published in 2008 [36]. In this study standard sequential therapy for 10 days was compared to conventional triple therapy for 7 days. Unfortunately, it did not show difference of eradication rate between the two regimens because of small sample size (ITT analysis: sequential vs. triple therapy, 77.9% vs. 71.6%, *P*=0.361). However, many investigators have been interested in sequential therapy. Actually, head-to-head comparisons between conventional triple and sequential therapies were the most frequently performed designs in Korea among the clinical trials on first-line *H. pylori* eradication regimens. In 2011, sequential therapy for 10 days was shown to be superior to conventional triple therapy for 14 days (ITT analysis: 85.9% vs. 75.0%, *P*=0.006) [37]. In 2012, three studies were published, and two of them demonstrated superior efficacy of sequential therapy compared to conventional triple therapy for 7 days (ITT analysis: 62.2% vs. 77.8%, P=0.002; 63.0% vs. 79.3%, *P*=0.005) [38,39], while the remaining one did not show statistical difference of eradication rate among sequential therapy and various triple therapy regimens (ITT analysis: sequential therapy vs. 7 days-triple therapy vs. 10 days-triple therapy vs. 14 days-triple therapy, 75.6% vs. 70.4% vs. 74.7% vs. 80.0%, *P*=0.416) [26]. In 2016, a nationwide multi-center randomized-controlled trial showed that sequential therapy had better eradication rate than conventional triple therapy as a first-line treatment of *H. pylori* infection (ITT analysis: 82.4% vs. 70.8%, P=0.001) [40].

Overall, sequential therapy seemed to be better than conventional triple therapy in terms of eradication rate. A meta-analysis in Korea also demonstrated that eradication

rate of sequential therapy was superior to that of conventional triple therapy (79.7% vs. 68.1%, P<0.001). However, a 79.7% eradication rate in sequential therapy is still unacceptable according to the report card for scoring the outcome (the reports when scoring the outcomes) of anti-*H. pylori* therapy [21]. On ITT analysis, at least a 85% eradication rate is required to adopt the regimen for *H. pylori* eradication. In addition, some investigators suggested that superior efficacy of sequential therapy may be caused not by sequential use of drugs but use of three antibiotics including amoxicillin, clarithromycin, and metronidazole (or tinidazole) [41]. For these reasons, the regimen that consisted of three antibiotics and PPI, namely concomitant therapy, was introduced.

CONCOMITANT THERAPY

Concomitant therapy consists of all drugs given in sequential therapy, which are standard dose of PPI, 1 g of amoxicillin, 500 mg of clarithromycin, and 500 mg of metronidazole. All drugs are administered twice daily simultaneously. However, durations of concomitant therapy vary from 5 days to 14 days. Until recently, no consensus regarding the optimal duration was established.

In the world-wide network meta-analysis, concomitant therapy was ranked best for eradication rate among various regimens including sequential therapy [24]. However, Korean data do not support this worldwide study. In 2013, there was no difference of eradiation rate between 14 days-sequential therapy and 14 days-concomitant therapy (ITT analysis: 75.6% vs. 80.8%, *P*=0.423) [42]. Two studies published in 2016 also did not show any difference of eradication rate between sequential and concomitant therapy (ITT analysis: 10 days-sequential vs. 10 days-concomitant therapy, 70.6% vs. 77.8%, *P*=0.140; 10 days-sequential vs. 14 days-sequential vs. 10 days-concomitant vs. 14 days concomitant therapy, 77.6% vs. 73.8% vs. 75.6% vs. 77.9%, *P*=0.915) [43,44].

Judging from previously reported Korean randomized-controlled trials, it seems that there was no difference of eradication rate between sequential and concomitant therapies. However, number of studies may be insufficient for reaching a definitive conclusion. In addition, indirect evidence as well as direct evidence should be considered to fully analyze the comparison. For example, there are many studies on the comparison between conventional triple therapy and sequential therapy. In addition, studies comparing conventional triple therapy with concomitant therapy also exist. Based on these studies, indirect evidence between sequential therapy and concomitant therapy can be induced. Because indirect evidence provides additional information upon direct evidence, it may be helpful for increasing statistical power and improving precision of estimates. Korean network meta-analysis on *H. pylori* eradication may be needed for clarifying the comparative efficacy of concomitant therapy.

HYBRID THERAPY

A modified sequential therapy, namely hybrid therapy, was also introduced for increasing eradication rate of H. pylori. It starts with a dual regimen of standard dose of PPI and 1 g of amoxicillin twice daily for 5 days (or 7 days) like sequential therapy. However, quadruple therapy that consists of standard dose of PPI, 1 g of amoxicillin, 500 mg of clarithromycin, and 500 mg of metronidazole twice daily for the next 5 days (or 7 days) is followed. Prolonged administration of amoxicillin is a characteristic of hybrid therapy compared to sequential therapy. It also resembles 10 days- or 14 days-concomitant therapy; however, clarithromycin and metronidazole are not included in the first 5 or 7 days of the treatment.

There are two randomized controlled trials on hybrid therapy compared to either sequential or concomitant therapy in Korea [13,45]. In one study that compared eradication rate of *H. pylori* between 14 days-hybrid therapy and 14 days-sequential therapy, there was no statistical difference (ITT analysis: 81.1% vs. 79.8%, *P*=0.821) [45]. In addition, one study between 10 days-hybrid therapy vs. 10 days-concomitant therapy did not show any difference of *H. pylori* eradication rate (ITT analysis: 78.8% vs. 78.6%, *P*=0.943) [13]. Overall, hybrid therapy seemed to have superiority to neither sequential nor concomitant therapy in terms of *H. pylori* eradication rate.

QUINOLONE-BASED SEQUENTIAL THERAPY

Traditional *H. pylori* eradication regimens include PPI, amoxicillin, clarithromycin, tinidazole (or metronidazole), and bismuth subcitrate. Recently, however, it has been known that quinolone, that inhibits deoxyribonucleic acid gyrase, is effective in the treatment of *H. pylori* infection [46-48]. Additionally, many studies support that quinolone-based sequential therapy is effective in an area with >15% prevalence of clarithromycin resistant *H. pylori* strains [49,50].

Quinolone-based sequential therapy consists of two phases of treatment like standard sequential therapy. For the first 5 days (or 7 days), standard dose of PPI and 1 g of amoxicillin are administered twice daily. Thereafter, standard dose of PPI twice daily, 500 mg of metronidazole (or tinidazole) twice daily, and quinolone (i.e., 400 mg of moxifloxacin once daily or 250 mg of levofloxacin twice daily) are administered for the last 5 days (or 7 days).

Until recently, quinolone-based sequential therapy is the most promising regimen in Korea. One study between moxifloxacin-based sequential therapy for 14 days vs. standard sequential therapy for 14 days showed superiority of moxifloxacin-based sequential therapy in terms of eradication rate (91.3% vs. 71.6%, *P*=0.001) [51]. In addition, eradication rate of moxifloxacin-based sequential therapy for 14 days was higher than that of hybrid therapy for 14 days (91.4% vs. 79.2%, *P*=0.004) [52]. Although data of eradication rate of quinolone-based sequential therapy compared to concomitant therapy is lacking now, indirect estimate may support superior efficacy of quinolone-based sequential therapy over concomitant therapy given that the eradication rate of concomitant therapy was similar to that of sequential or hybrid therapies.

However, one study comparing eradication rate between 10 days-standard sequential therapy vs. 10 days-levofloxacin-based sequential therapy showed no statistical difference (79.0% vs. 78.0%, *P*=0.863). It is not certain that the discrepant results were caused by type of quinolone (moxifloxacin vs. levofloxacin) or duration of treatment (14 days vs. 10 days). More randomized controlled trials in this issue may be needed for reaching a definitive conclusion.

Another concern of quinolone-based regimen in Korea is the potential drug resistance of Mycobacterium tuberculosis, because quinolone is one of the medications for tuberculosis, which is highly endemic in Korea. Additionally, latent tuberculosis infection is also prevalent in Korea. The positive results of tuberculin skin test and whole-blood interferon gamma assay was 51-52% and 4-14%, respectively [53,54], in the young general population in Korea. If quinolone-based regimen is adopted as a primary treatment regimen for *H. pylori* infection, there may be a chance of increasing quinolone resistance of M. tuberculosis. Careful consideration of this issue may be needed for adopting quinolone-based sequential therapy as a first-line eradication regimen for *H. pylori* infection.

BISMUTH-CONTAINING QUADRUPLE THERAPY

Bismuth-containing quadruple therapy consists of standard dose of PPI b.i.d., 120 mg of bismuth q.i.d, 500 mg of metronidazole t.i.d., and 500 mg of tetracycline q.i.d. for 7 to 14 days. Traditionally, bismuth-containing quadruple therapy has been generally used for the second-line regimen of *H. pylori* eradication [55-57]. Although the Korean guideline suggested that bismuth-containing quadruple therapy may be an alternative first-line regimen if clarithromycin-resistance is suspected, evidence of bismuth-containing quadruple therapy as a first-line regimen is insufficient in Korea. The first randomized-controlled trial comparing bismuth-containing quadruple therapy with conventional triple therapy as a first-line regimen was published in 2005 [58]. It did not show difference of eradication rate (ITT analysis: 7 days-bismuth containing quadruple vs. 7 days-conventional triple therapy, 71.6% vs. 78.7%, *P*=0.424). Recently, 14 days-bismuth-containing quadruple therapy was compared to 10 days-sequential therapy in a multi-center, randomized-controlled trial [59]. In this study, there was no difference of eradication rate between the two regimens (ITT analysis: bismuth-containing quadruple vs. sequential therapy, 68.7% vs. 74.9%, P=0.240). In addition, PP analysis showed that eradication rate of bismuth-containing quadruple therapy tended to be lower than that of sequential therapy (76.5% vs. 84.2%, *P*=0.099).

Given that clarithromycin is not included in the bismuth-containing quadruple therapy, this regimen may be an alternative first-line regimen in regions where clarithromycin-resistant *H. pylori* is prevalent. However, more studies are required for clarifying the effectiveness of bismuth-containing quadruple therapy as a first-line treatment of *H. pylori* infection.

CONCLUSION

Currently, various *H. pylori* eradication regimens are available (Table 1). Based on the randomized-controlled trials in Korea, conventional triple therapy is unacceptable for the first-line therapy without prior susceptibility test because of the high clarithromycin-resistance rate. Sequential therapy, hybrid therapy, and concomitant therapy seemed to be more effective than the conventional triple therapy; however, eradication rates of these regimens are also unsatisfactory considering the report card for scoring the outcome (the reports when scoring

Table 1. Eradication regimen for Helicobacter pylori infection

Regimen	Drug
Conventional triple therapy	PPI standard dose b.i.d. + amoxicillin 1g b.i.d. + clarithromycin 500mg b.i.d. for 7-14 days
Conventional triple therapy with probiotics	PPI standard dose b.i.d. + amoxicillin 1g b.i.d. + clarithromycin 500mg b.i.d. for 7 days, probiotics for 4-8 weeks
Conventional triple therapy with mucoprotective agent	PPI standard dose b.i.d. + amoxicillin 1g b.i.d. + clarithromycin 500mg b.i.d. + mucoprotective agent for 7 days
Sequential therapy	First phase: PPI standard dose b.i.d. + amoxicillin 1g b.i.d. for 5-7 days Second phase: PPI standard dose b.i.d. + clarithromycin 500mg b.i.d. + metronidazole 500mg b.i.d. for 5-7 days
Quinolone-based sequential therapy	First phase: PPI standard dose b.i.d. + amoxicillin 1g b.i.d. for 5-7 days Second phase: PPI standard dose b.i.d. + moxifloxacin 400mg q.d. (or levofloxacin 250mg b.i.d.) + metronidazole 500mg b.i.d. for 5-7 days
Concomitant therapy	PPI standard dose b.i.d. + amoxicillin 1g b.i.d. + clarithromycin 500mg b.i.d. + metronidazole 500mg b.i.d. for 5-14 days
Hybrid therapy	First phase: PPI standard dose b.i.d. + amoxicillin 1g b.i.d. for 5-7 days Second phase: PPI standard dose b.i.d. + amoxicillin 1g b.i.d. + clarithromycin 500mg b.i.d. + metronidazole 500mg b.i.d. for 5-7 days
Bismuth-containing quadruple therapy	PPI standard dose b.i.d. + bismuth 120 mg q.i.d. + metronidazole 500mg t.i.d. + tetracycline 500mg q.i.d. for 7-14 days

PPI, proton pump inhibitor

the outcomes) of anti-*H. pylori* therapy [21]. Current evidence supports the quinolone-based sequential therapy may be a good choice as first-line therapy in Korea. However, this narrative review cannot provide a definitive conclusion because there are many head-to-head trials among various regimens, and only direct evidence was considered here. Indirect estimates should be considered for clarifying the comparative efficacy of various *H. pylori* eradication regimens. Network meta-analysis based on Korean randomized-controlled trials may be helpful for guiding selection of eradication regimen in patients with *H. pylori* infection in Korea.

REFERENCES

1. Hunt RH, Xiao SD, Megraud F, Leon-Barua R, Bazzoli F, van der Merwe S, et al. Helicobacter pylori in developing countries. World Gastroenterology Organisation Global Guideline. J Gastrointestin Liver Dis 2011;20:299-304.
2. McColl KE. Clinical practice. Helicobacter pylori infection. N Engl J Med 2010;362:1597-604.
3. de Martel C, Ferlay J, Franceschi S, Vignat J, Bray F, Forman D, et al. Global burden of cancers attributable to infections in 2008: a review and synthetic analysis. Lancet Oncol 2012;13:607-15.
4. Kim SG, Jung HK, Lee HL, Jang JY, Lee H, Kim CG, et al. Guidelines for the diagnosis and treatment of Helicobacter pylori infection in Korea, 2013 revised edition. J Gastroenterol Hepatol 2014;29:1371-86.
5. Lee DH, Park HJ, Song SY, Lee SJ, Choi W, Lee YC, et al. Evaluation of therapeutic regimens for the treatment of Helicobacter pylori infection. Yonsei Med J 1996;37:270-7.
6. Chung J, Ha M, Yun S, Kim JH, Lee JJ, Kim YJ, et al. Meta-analysis: Sequential therapy is superior to conventional therapy for Helicobacter pylori infection in Korea. Korean Journal of Gastroenterology 2013;62:267-71.
7. Kim N, Kim JJ, Choe YH, Kim HS, Kim JI, Chung IS. [Diagnosis and treatment guidelines for Helicobacter pylori infection in Korea]. Korean J Gastroenterol 2009;54:269-78.
8. Chey WD, Wong BC. American College of Gastroenterology guideline on the management of Helicobacter pylori infection. Am J Gastroenterol 2007;102:1808-25.
9. Fock KM, Katelaris P, Sugano K, Ang TL, Hunt R, Talley NJ, et al. Second Asia-Pacific Consensus Guidelines for Helicobacter pylori infection. J Gastroenterol Hepatol 2009;24:1587-600.
10. Shin WG, Lee SW, Baik GH, Huh KC, Chung J, Jung WT, et al. Eradication Rates of Helicobacter pylori in Korea Over the Past 10 years and Correlation of the Amount of Antibiotics Use: Nationwide Survey. Helicobacter 2016;21:266-78.
11. Gong EJ, Yun SC, Jung HY, Lim H, Choi KS, Ahn JY, et al. Meta-analysis of first-line triple therapy for helicobacter pylori eradication in Korea: is it

time to change? J Korean Med Sci 2014;29:704-13.
12. Lee JW, Kim N, Kim JM, Nam RH, Chang H, Kim JY, et al. Prevalence of primary and secondary antimicrobial resistance of Helicobacter pylori in Korea from 2003 through 2012. Helicobacter 2013;18:206-14.
13. Heo J, Jeon SW, Jung JT, Kwon JG, Lee DW, Kim HS, et al. Concomitant and hybrid therapy for Helicobacter pylori infection: A randomized clinical trial. J Gastroenterol Hepatol 2015;30:1361-6.
14. Marcus EA, Inatomi N, Nagami GT, Sachs G, Scott DR. The effects of varying acidity on Helicobacter pylori growth and the bactericidal efficacy of ampicillin. Alimentary pharmacology & therapeutics 2012;36:972-9.
15. Sheu BS, Kao AW, Cheng HC, Hunag SF, Chen TW, Lu CC, et al. Esomeprazole 40 mg twice daily in triple therapy and the efficacy of Helicobacter pylori eradication related to CYP2C19 metabolism. Alimentary pharmacology & therapeutics 2005;21:283-8.
16. Choi HS, Park DI, Hwang SJ, Park JS, Kim HJ, Cho YK, et al. Double-dose, new-generation proton pump inhibitors do not improve Helicobacter pylori eradication rate. Helicobacter 2007;12:638-42.
17. Shin JM, Sachs G. Long lasting inhibitors of the gastric H,K-ATPase. Expert Rev Clin Pharmacol 2009;2:461-8.
18. Hori Y, Imanishi A, Matsukawa J, Tsukimi Y, Nishida H, Arikawa Y, et al. 1-[5-(2-Fluorophenyl)-1-(pyridin-3-ylsulfonyl)-1H-pyrrol-3-yl]-N-methylmethanamine monofumarate (TAK-438), a novel and potent potassium-competitive acid blocker for the treatment of acid-related diseases. The journal of pharmacology and experimental therapeutics 2010;335:231-8.
19. Murakami K, Sakurai Y, Shiino M, Funao N, Nishimura A, Asaka M. Vonoprazan, a novel potassium-competitive acid blocker, as a component of first-line and second-line triple therapy for Helicobacter pylori eradication: a phase III, randomised, double-blind study. Gut 2016;65:1439-46.
20. Matsumoto H, Shiotani A, Katsumata R, Fujita M, Nakato R, Murao T, et al. Helicobacter pylori Eradication with Proton Pump Inhibitors or Potassium-Competitive Acid Blockers: The Effect of Clarithromycin Resistance. Dig Dis Sci 2016;61:3215-20.
21. Graham DY, Lu H, Yamaoka Y. A report card to grade Helicobacter pylori therapy. Helicobacter 2007;12:275-8.
22. Graham DY. Vonoprazan Helicobacter pylori eradication therapy: ethical and interpretation issues. Gut 2016.
23. Kim JM. [Antibiotic resistance of Helicobacter pylori isolated from Korean patients]. Korean J Gastroenterol 2006;47:337-49.
24. Li BZ, Threapleton DE, Wang JY, Xu JM, Yuan JQ, Zhang C, et al. Comparative effectiveness and tolerance of treatments for Helicobacter pylori: systematic review and network meta-analysis. BMJ 2015;351:h4052.
25. Kim BG, Lee DH, Ye BD, Lee KH, Kim BW, Kim SG, et al. Comparison of 7-day and 14-day proton pump inhibitor-containing triple therapy for Helicobacter pylori eradication: neither treatment duration provides acceptable eradication rate in Korea. Helicobacter 2007;12:31-5.
26. Choi HS, Chun HJ, Park SH, Keum B, Seo YS, Kim YS, et al. Comparison of sequential and 7-, 10-, 14-d triple therapy for Helicobacter pylori infection. World J Gastroenterol 2012;18:2377-82.
27. Park SK, Park DI, Choi JS, Kang MS, Park JH, Kim HJ, et al. The effect of probiotics on Helicobacter pylori eradication. Hepatogastroenterology 2007;54:2032-6.
28. Kim MN, Kim N, Lee SH, Park YS, Hwang JH, Kim JW, et al. The effects of probiotics on PPI-triple therapy for Helicobacter pylori eradication. Helicobacter 2008;13:261-8.
29. Kim HW, Kim GH, Cheong JY, Yang US, Park SK, Song CS, et al. H pylori eradication: a randomized prospective study of triple therapy with or without ecabet sodium. World Journal of Gastroenterology 2008;14:908-12.
30. Song MJ, Park DI, Park JH, Kim HJ, Cho YK, Sohn CI, et al. The effect of probiotics and mucoprotective agents on PPI-based triple therapy for eradication of Helicobacter pylori. Helicobacter 2010;15:206-13.
31. Seo JY, Kim MJ, Ko KH, Kim DH, Lim DS, Chon HR. Efficacy of Ecabet Sodium for Helicobacter pylori Eradication, Combined with Lansoprazole-Based Triple Regimen: A Prospective Study. Korean J Med 2011;80:546-52.
32. Zullo A, Rinaldi V, Winn S, Meddi P, Lionetti R, Hassan C, et al. A new highly effective short-term therapy schedule for Helicobacter pylori eradication. Aliment Pharmacol Ther 2000;14:715-8.
33. Gisbert JP, Calvet X, O'Connor A, Megraud F, O'Morain CA. Sequential therapy for Helicobacter pylori eradication: a critical review. J Clin Gastroenterol 2010;44:313-25.
34. De Francesco V, Margiotta M, Zullo A, Hassan C, Troiani L, Burattini O, et al. Clarithromycin-resistant genotypes and eradication of Helicobacter pylori. Ann Intern Med 2006;144:94-100.
35. Murakami K, Fujioka T, Okimoto T, Sato R, Kodama M, Nasu M. Drug combinations with amoxycillin reduce selection of clarithromycin resistance during Helicobacter pylori eradication therapy. Int J Antimicrob Agents 2002;19:67-70.
36. Choi WH, Park DI, Oh SJ, Baek YH, Hong CH, Hong EJ, et al. [Effectiveness of 10 day-sequential therapy for Helicobacter pylori eradication in Korea]. Korean J Gastroenterol 2008;51:280-4.
37. Kim YS, Kim SJ, Yoon JH, Suk KT, Kim JB, Kim DJ, et al. Randomised clinical trial: the efficacy of a 10-day sequential therapy vs. a 14-day standard proton pump inhibitor-based triple therapy for Helicobacter pylori in Korea. Aliment Pharmacol Ther 2011;34:1098-105.
38. Park HG, Jung MK, Jung JT, Kwon JG, Kim EY, Seo HE, et al. Randomised clinical trial: a comparative study of 10-day sequential therapy with 7-day standard triple therapy for Helicobacter pylori infection in naive patients.

Aliment Pharmacol Ther 2012;35:56-65.
39. Oh HS, Lee DH, Seo JY, Cho YR, Kim N, Jeoung SH, et al. Ten-day sequential therapy is more effective than proton pump inhibitor-based therapy in Korea: a prospective, randomized study. Journal of gastroenterology and hepatology 2012;27:504-9.
40. Kim JS, Kim BW, Hong SJ, Kim JI, Shim KN, Kim JH, et al. Sequential Therapy versus Triple Therapy for the First Line Treatment of Helicobacter pylori in Korea: A Nationwide Randomized Trial. Gut Liver 2016;10:556-61.
41. Gisbert JP, Calvet X. Review article: non-bismuth quadruple (concomitant) therapy for eradication of Helicobater pylori. Alimentary pharmacology & therapeutics 2011;34:604-17.
42. Lim JH, Lee DH, Choi C, Lee ST, Kim N, Jeong SH, et al. Clinical outcomes of two-week sequential and concomitant therapies for Helicobacter pylori eradication: a randomized pilot study. Helicobacter 2013;18:180-6.
43. Chung J, Han JP, Kim KO, Kim SY, Hong SJ, Kim TH, et al. Ten-day empirical sequential or concomitant therapy is more effective than triple therapy for Helicobacter pylori eradication: A multicenter, prospective study. Digestive and liver disease 2016;48:888-92.
44. Park SM, Kim JS, Kim BW, Ji JS, Choi H. A randomised clinical trial comparing 10- or 14-day sequential therapy and 10- or 14-day concomitant therapy for the first line empirical treatment of Helicobacter pylori infection. J Gastroenterol Hepatol 2016.
45. Oh DH, Lee DH, Kang KK, Park YS, Shin CM, Kim N, et al. Efficacy of hybrid therapy as first-line regimen for Helicobacter pylori infection compared with sequential therapy. Journal of gastroenterology and hepatology 2014;29:1171-6.
46. Gisbert JP, Morena F. Systematic review and meta-analysis: levofloxacin-based rescue regimens after Helicobacter pylori treatment failure. Alimentary pharmacology & therapeutics 2006;23:35-44.
47. Peedikayil MC, Alsohaibani FI, Alkhenizan AH. Levofloxacin-based first-line therapy versus standard first-line therapy for Helicobacter pylori eradication: meta-analysis of randomized controlled trials. PLoS One 2014;9:e85620-e.
48. Saad RJ, Schoenfeld P, Kim HM, Chey WD. Levofloxacin-based triple therapy versus bismuth-based quadruple therapy for persistent Helicobacter pylori infection: a meta-analysis. The American journal of gastroenterology 2006;101:488-96.
49. Romano M, Cuomo A, Gravina AG, Miranda A, Iovene MR, Tiso A, et al. Empirical levofloxacin-containing versus clarithromycin-containing sequential therapy for Helicobacter pylori eradication: a randomised trial. Gut 2010;59:1465-70.
50. Zullo A, De Francesco V, Hassan C, Ridola L, Repici A, Bruzzese V, et al. Modified sequential therapy regimens for Helicobacter pylori eradication: a systematic review. Digestive and liver disease 2013;45:18-22.
51. Hwang JJ, Lee DH, Lee AR, Yoon H, Shin CM, Park YS, et al. Efficacy of moxifloxacin-based sequential therapy for first-line eradication of Helicobacter pylori infection in gastrointestinal disease. World J Gastroenterol 2015;21:5032-8.
52. Hwang JJ, Lee DH, Yoon H, Shin CM, Park YS, Kim N. Efficacy of moxifloxacin-based sequential and hybrid therapy for first-line Helicobacter pylori eradication. World J Gastroenterol 2015;21:10234-41.
53. Kang YA, Lee HW, Yoon HI, Cho B, Han SK, Shim Y, et al. Discrepancy between the tuberculin skin test and the whole-blood interferon gamma assay for the diagnosis of latent tuberculosis infection in an intermediate tuberculosis-burden country. JAMA: the Journal of the American Medical Association 2005;293:2756-61.
54. Lee K, Han MK, Choi HR, Choi C, Oh Y, Lee SD, et al. Annual incidence of latent tuberculosis infection among newly employed nurses at a tertiary care university hospital. Infection control and hospital epidemiology 2009;30:1218-22.
55. Chung JW, Lee JH, Jung HY, Yun SC, Oh TH, Choi KD, et al. Second-line Helicobacter pylori eradication: a randomized comparison of 1-week or 2-week bismuth-containing quadruple therapy. Helicobacter 2011;16:289-94.
56. Lee BH, Kim N, Hwang TJ, Lee SH, Park YS, Hwang J, et al. Bismuth-containing quadruple therapy as second-line treatment for Helicobacter pylori infection: effect of treatment duration and antibiotic resistance on the eradication rate in Korea. Helicobacter 2010;15:38-45.
57. Yoon JH, Baik GH, Kim YS, Suk KT, Shin WG, Kim KO, et al. Comparison of the Eradication Rate between 1- and 2-Week Bismuth-Containing Quadruple Rescue Therapies for Helicobacter pylori Eradication. Gut and liver 2012;6:434-9.
58. Jang HJ, Choi MH, Kim YS, Seo YA, Baik KH, Baik IH, et al. [Effectiveness of triple therapy and quadruple therapy for Helicobacter pylori eradication]. Korean J Gastroenterol 2005;46:368-72.
59. Lee JY, Kim N, Park KS, Kim HJ, Park SM, Baik GH, et al. Comparison of sequential therapy and amoxicillin/tetracycline containing bismuth quadruple therapy for the first-line eradication of Helicobacter pylori: a prospective, multi-center, randomized clinical trial. BMC Gastroenterol 2016;16:79.