Efficacy of Seven-day High-dose Esomeprazole-based Triple Therapy versus Seven-day Standard Dose Non-esomeprazole-based Triple Therapy as the First-line Treatment of Patients with Helicobacter pylori Infection

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Background/Aims: The rates of Helicobacter pylori (H. pylori) eradication have declined with the use of proton pump inhibitor-amoxicillin-clarithromycin as the first-line triple therapy. On the other hand, several studies have suggested that high gastric pH levels could affect the H. pylori eradication rate by enhancing the efficacy of antimicrobials. This study compared the efficacy of seven-day high-dose esomeprazole-based triple therapy (7-HEAC) for first-line H. pylori eradication with the seven-day standard dose non-esomeprazole-based triple therapy (7-NEAC) to identify the risk factors related to eradication failure.

Methods: This study included 223 patients who were diagnosed with a H. pylori infection and received 7-HEAC or 7-NEAC between June 2016 and January 2017. The H. pylori eradication rates, as well as demographic and clinical factors, were investigated retrospectively. H. pylori eradication was confirmed by a 13C-urea breath test or rapid urease test at least 4 weeks after the completion of therapy.

Results: The eradication rates were 67.7% (105/155; 95% CI 59.5-74.8%) in the 7-NEAC group and 80.9% (55/68; 95% CI 69.9-89.8%) in the 7-HEAC group (p=0.045). The adverse event rates were 5.8% (9/155) in the 7-NEAC group and 7.4% (5/68) in the 7-HEAC group (p=0.661). Multivariate analysis revealed being female (OR 2.08; 95% CI 1.15-3.76) to be associated with the failure of H. pylori eradication therapy.

Conclusions: The eradication rate of the 7-HEAC group was higher than that of the 7-NEAC group. Nevertheless, more effective first-line therapies may be necessary for H. pylori eradication in the near future. (Korean J Gastroenterol 2020;76:142-149)

Key Words: Helicobacter pylori; Disease eradication; Esomeprazole; Proton pump inhibitors

INTRODUCTION

Standard triple therapy, containing a proton pump inhibitor (PPI), amoxicillin, and clarithromycin, is one of the most popular regimens as a first-line eradication therapy for a H. pylori infection. On the other hand, the efficacy of standard triple
therapy is decreasing worldwide. This trend has also been noticed in Korea, and the reported eradication rates of *H. pylori* using standard triple therapy were 84.9-87.5% from 2001 to 2007 and 80.0-81.4% from 2008 to 2010 (p<0.0001), showing a declining tendency over the past 10 years in Korea. Therefore, a potent first-line regimen is required for successful *H. pylori* eradication.

Several components influence successful eradication, including antibiotic resistance of *H. pylori*, compliance of the patients, and host and bacterial factors. Acid suppression is also a critical factor in eradication. Thus, the possibility that the type of PPI could affect the eradication rate was suggested. Among the PPIs, esomeprazole, which is the S-isomer of omeprazole, was the first PPI available for clinical use as an optical isomer. Esomeprazole is less metabolized by cytochrome P450 2C19 (CYP2C19) than omeprazole. Therefore, it has a higher bio-availability and greater gastric acid suppression than omeprazole. The metabolic advantage of esomeprazole is that it enhances the plasma concentration, leading to a higher area under the curve.

Recent studies using potassium-competitive acid blockers (P-CABs) reported a rapid onset of action and dose-dependent effects on acid production, but P-CABs are not available outside Asia, Europe, and the United States. Therefore, this study compared the efficacy of a seven-day high-dose esomeprazole-based triple therapy as a first-line *H. pylori* eradication treatment with a seven-day standard dose non-esomeprazole-based triple therapy. In addition, the risk factors associated with eradication failure were identified.

**SUBJECTS AND METHODS**

1. Study population

This retrospective study included patients who visited Kosin University Gospel Hospital from June 2016 and January 2017 and were diagnosed with a *H. pylori* infection, for which they received first-line PPI-containing triple therapy. *H. pylori* positivity was verified by a rapid urease test or a 13C-urea breath test. Before the 13C-urea breath test or a rapid urease test was performed, the patients discontinued PPI or histamine (H2) receptor antagonist treatment for at least 2 weeks.

2. *H. pylori* eradication therapy and follow-up

The seven-day high-dose esomeprazole-based triple therapy or seven-day standard dose non-esomeprazole-based triple therapy was prescribed for patients undergoing first-line *H. pylori* eradication therapy. High-dose esomeprazole-based triple therapy consisted of 40 mg of esomeprazole, 1 g of amoxicillin, and 0.5 g of clarithromycin twice daily for seven days (7-HEAC). The standard dose non-esomeprazole-based triple therapy included a standard dose of PPI except esomeprazole, 1 g of amoxicillin, and 0.5 g of clarithromycin twice daily for seven days (7-NEAC). The standard dose non-esomeprazole PPIs was comprised of rabeprazole 20 mg and lansoprazole 30 mg.

Subsequently, a 13C-urea breath test or a rapid urease test was performed to assess the extent of *H. pylori* eradication at least 4 weeks after completing the treatment. Before the 13C-urea breath test or a rapid urease test was performed, the patients discontinued PPI or histamine (H2) receptor antagonist treatment for at least 2 weeks.

3. Rapid urease test

Endoscopic biopsy of the gastric mucosa was conducted to identify a *H. pylori* infection with the rapid urease test (CLO test®, Delta West, Bentley, Australia). The antrum and corpus were the sites of the gastric mucosal biopsy, and normal or...
near-normal gastric mucosa with minimal atrophy or intestinal metaplasia was acquired. The tissue sample was immersed in the rapid urea reagent. The result was deemed positive when the reagent color changed from yellow to red at least 12 hours later. The result was deemed negative if there was no change in reagent color.

4. $^{13}$C-urea breath test

The patients fasted for at least 4 hours before collecting the first breath sample. The patients then consumed tablets containing 100 mg of $^{13}$C-urea (UBITkit™, Otsuka Pharmaceutical, Tokyo, Japan) with 100 mL of water orally. The second breath sample was collected 20 min after taking the tablets. The breath samples obtained were analyzed using a $^{13}$C-urea breath test (UBIT-IR300™; Otsuka Electronics, Osaka, Japan). The cut-off value of the procedure was set to 2.5‰.

5. Statistical analyses

All statistical analyses were conducted using the Statistical Package for the Social Sciences software version 20.0 (SPSS, Chicago, IL, USA). The $H.\ pylori$ eradication rate was evaluated through per-protocol (PP) analysis. The categorical variables and continuous variables were analyzed using a Chi-square ($\chi^2$) test and a Student’s t-test, respectively. The results of univariate and multivariate logistic regression analyses of the

![Fig. 1. Helicobacter pylori eradication rates of 7-HEAC and 7-NEAC](image)

**Fig. 1.** Helicobacter pylori eradication rates of 7-HEAC and 7-NEAC ($p=0.045$). 7-NEAC, 7-day standard dose non-esomeprazole-based triple therapy; 7-HEAC, 7-day high-dose esomeprazole-based triple therapy.

| Table 1. Baseline Characteristics of the Subjects | 7-day Standard dose non-esomeprazole-containing triple therapy (n=155) | 7-day High-dose esomeprazole-containing triple therapy (n=68) | p-value |
|---|---|---|---|
| Age (years) | 54.1±10.3 | 53.9±11.8 | 0.907 |
| Gender | | | 0.560 |
| Male | 91 (58.7) | 37 (54.4) | |
| Female | 64 (41.3) | 31 (45.6) | |
| Residence | | | 0.761 |
| Rural | 27 (17.4) | 13 (19.1) | |
| Urban | 128 (82.6) | 55 (80.9) | |
| Cigarette smoking | 30 (19.4) | 14 (20.6) | 0.856 |
| Alcohol intake | 61 (39.4) | 36 (52.9) | 0.078 |
| Diabetes mellitus | 16 (10.3) | 10 (14.7) | 0.369 |
| Hypertension | 29 (18.7) | 23 (33.8) | 0.017<sup>a</sup> |
| Endoscopic diagnosis | | | 0.067 |
| Gastric ulcer | 43 (27.7) | 19 (27.9) | |
| Duodenal ulcer | 69 (44.5) | 28 (41.2) | |
| Gastric ulcer+Duodenal ulcer | 2 (1.3) | 3 (4.4) | |
| Post ESD due to adenoma or EGC | 28 (18.1) | 7 (10.3) | |
| Others<sup>a</sup> | 13 (8.4) | 11 (16.2) | |

Values are presented as mean±standard deviation or n (%).
SD, standard deviation; ESD, endoscopic submucosal dissection; EGC, early gastric cancer; MALT lymphoma, mucosa-associated lymphoid tissue lymphoma.
<sup>a</sup>Others include MALT lymphoma, dyspepsia, gastric polyp and gastritis; <sup>b</sup>Indicates statistical significance.
risk factors were expressed as the odds ratios (ORs) and 95% Cl. p-values<0.05 were considered significant.

### RESULTS

1. Patient characteristics

Two hundred twenty-three patients were finally enrolled in the current study. Among them, 155 patients were treated with 7-NEAC, which consisted of 144 patients in the lansopra-

| Table 2. Side Effects after the Eradication Therapies |
|------------------------------------------------------|
| **7-day standard dose** non-esomeprazole-containing triple therapy (n=155) | **7-day high-dose esomeprazole-containing triple therapy (n=68)** | **p-value** |
| **Diarrhea** | 4 (2.6) | 2 (2.9) | 0.878 |
| **Bloating or abdominal pain** | 0 (0.0) | 1 (1.5) | 0.130 |
| **Nausea or vomiting** | 2 (1.3) | 0 (0.0) | 0.347 |
| **Skin rash** | 1 (0.6) | 1 (1.5) | 0.547 |
| **Others** | 2 (1.3) | 1 (1.5) | 0.914 |
| **Total** | 9 (5.8) | 5 (7.4) | 0.765 |

Values are presented or n (%).

### Table 3. Related Factors regarding Eradication Failure of Eradication Therapies

| **Eradication success** (n=160) | **Eradication failure** (n=63) | **Univariate p-value** | **Multivariate p-value** | **Adjusted OR (95% CI)** |
|--------------------------------|-----------------------------|------------------------|--------------------------|--------------------------|
| **Age** | | | | | |
| <50 | 46 (74.2) | 16 (25.8) | 0.615 | 0.913 | 1.04 (0.52-2.09) |
| ≥50 | 114 (70.8) | 47 (29.2) | | | |
| **Gender** | | | 0.014* | 0.015* | 2.08 (1.15-3.76)* |
| Male | 100 (78.1) | 28 (21.9) | | | |
| Female | 60 (63.2) | 35 (36.8) | | | |
| **Residence** | | | 0.614 | 0.703 | 1.17 (0.52-3.46) |
| Rural | 30 (75.0) | 10 (25.0) | | | |
| Urban | 130 (71.0) | 53 (29.0) | | | |
| **Cigarette smoking** | | | 0.364 | 0.578 | 1.30 (0.51-3.32) |
| No | 126 (70.4) | 53 (29.6) | | | |
| Yes | 34 (77.3) | 10 (22.7) | | | |
| **Alcohol intake** | | | 0.055 | 0.295 | 0.67 (0.32-2.14) |
| No | 84 (66.7) | 42 (33.3) | | | |
| Yes | 76 (78.4) | 21 (21.6) | | | |
| **Diabetes mellitus** | | | 0.533 | 0.312 | 0.59 (0.21-1.66) |
| No | 140 (71.1) | 57 (28.9) | | | |
| Yes | 20 (76.9) | 6 (23.1) | | | |
| **Hypertension** | | | 0.417 | 0.317 | 1.46 (0.70-3.05) |
| No | 125 (73.1) | 46 (26.9) | | | |
| Yes | 35 (67.3) | 17 (32.7) | | | |

Values are presented or n (%).

OR, odds ratio; CI, confidence interval.

*Logistic model including terms of age, gender, residence, cigarette smoking, alcohol intake, diabetes mellitus and hypertension; *Indicates statistical significance.
zole group and 11 patients in the rabeprazole group, and 68 patients were treated with 7-HEAC.

In terms of the baseline characteristics, the proportion of patients with hypertension (33.8% vs. 18.7%, p=0.017) was significantly higher in the 7-HEAC group. Otherwise, there were no significant differences in age, gender, residence, history of smoking or alcohol use, and diabetes mellitus between the two groups. The endoscopic diagnosis showed no significant differences in the rates of gastric ulcers, duodenal ulcers, gastroduodenal ulcer, post-endoscopic submucosal dissection status, and other endoscopic findings between the two groups (Table 1).

2. H. pylori eradication rates

Fig. 1 presents the eradication rate of H. pylori according to each eradication regimen. In PP analysis, the eradication rates were 67.7% (105/155; 95% CI 59.5-74.8%) and 80.9% (55/68; 95% CI 69.9-89.8%) in the 7-NEAC and 7-HEAC groups, respectively (p=0.045). According to the type of PPIs, the eradication rates were 69.4% (100/144; 95% CI 61.5-76.3%) and 45.5% (5/11; 95% CI 12.5-76.9%) in the lansoprazole and rabeprazole groups using PP analysis, respectively.

3. Adverse effects of eradication therapy

Adverse events were recorded in nine patients (5.8%) in the 7-NEAC group and five patients (7.4%) in the 7-HEAC group (p=0.765). The most common adverse events were diarrhea (4/155, 2.6%), nausea or vomiting (2/155, 1.3%), and skin rash (1/155, 0.6%) in the 7-NEAC group, and diarrhea (2/68, 2.9%), bloating or abdominal pain (1/68, 1.5%), and skin rash (1/68, 1.5%) in the 7-HEAC group. The adverse events were mild in all patients, with no significant differences between the two groups (Table 2).

4. Factors associated with eradication failure

Table 3 lists the factors related to eradication failure. Univariate and multivariate analyses indicated that only female gender (OR, 2.08; 95% CI 1.15-3.76; p=0.015) was significantly associated with eradication failure. No statistically significant relationship was observed between eradication failure and other factors, including age, residence, history of smoking or alcohol use, diabetes mellitus, and hypertension.

**DISCUSSION**

In the current study, the H. pylori eradication rates associated with the 7-NEAC and 7-HEAC regimens were 67.7% and 80.9%, respectively, and adverse events were noted in 5.8% of the 7-NEAC group and 7.4% of the 7-HEAC group. Therefore, the 7-HEAC group had a significantly higher eradication rate than the 7-NEAC group, and the adverse effects of 7-HEAC were similar to those of 7-NEAC. In addition, being female contributed to eradication failure.

These results are in agreement with previous studies comparing the H. pylori eradication rates associated with high-dose PPI-based triple therapy and standard-dose PPI-based triple therapy. A high-dose of PPI refers to a double-dose of PPI. A prospective Greek study showed that the eradication rate of high-dose (40 mg b.i.d.) esomeprazole-based triple therapy was significantly higher than that of the standard dose (20 mg b.i.d.) omeprazole-based triple therapy. In particular, the eradication rate was 96% (95% CI 91-99%) in the high-dose esomeprazole-based triple therapy group. Another study from Taiwan reported that the eradication rate of esomeprazole-containing triple therapy (40 mg b.i.d.) was significantly higher than that of pantoprazole-containing triple therapy (40 mg b.i.d.). Meta-analysis also evaluated the benefits of high-dose PPI in seven-day standard triple therapy. A total of 1,703 patients from the six studies were included, and a mean intention-to-treat (ITT) eradication rate of 82% was found in the high-dose PPI group compared to the 74% in the standard dose PPI group (risk ratio 1.09; 95% CI 1.01-1.07). Therefore, the meta-analysis showed that high-dose PPI was more efficient than standard-dose PPI in standard triple therapy.

Some studies reported different results from the present study. Eradication rates of triple therapy based on four different PPIs (omeprazole 20 mg b.i.d., pantoprazole 40 mg b.i.d., rabeprazole 20 mg b.i.d., and esomeprazole 40 mg b.i.d.) were similar in a Korean study (p=0.517). The eradication rates in the omeprazole, pantoprazole, rabeprazole, and esomeprazole groups were 64.9%, 69.3%, 69.3%, and 72.9%, respectively. A recent Italian study reported that according to ITT and PP analyses, there were no differences in the eradication rate between standard dose PPI-containing triple therapy (esomeprazole 20 mg b.i.d.) and high-dose PPI-containing triple therapy (esomeprazole 40 mg b.i.d.) groups (ITT analysis, 73.9% vs. 81.9%, p=0.25; PP analysis, 78.2% vs. 85.5%,
to transcriptomics studies, the genes underlying at neutral pH compared to acidic pH (pH 4.5).16 Because the division and cell wall synthesis showed elevated transcription above, esomeprazole has higher bio-availability and greater eradication rates by the persistent anti-histamine compared to other conventional PPIs, which affect the antibiotic control and a more rapid onset of acid suppression.4,14 Therefore, esomeprazole is less affected by the CYP2C19 genotype and has little interaction with other drugs.13 As mentioned above, esomeprazole has higher bio-availability and greater acid suppression effect in the stomach.3,4 In contrast, rabeprazole is metabolized prominently through a non-enzymatic pathway with a minor CYP2C19 association. Thus, rabeprazole is less affected by the CYP2C19 genotype and has little interaction with other drugs.13 Among them, PPIs are catalyzed mainly by CYP2C19 and cytochrome P450 3A4 (CYP3A4). Therefore, a CYP2C19 polymorphism could be a major factor in the treatment of PPIs.13 The degree of PPIs metabolism via CYP2C19 varies according to the types of PPIs. Omeprazole, lansoprazole, and pantoprazole are metabolized extensively by CYP2C19.13 In contrast, rabeprazole is metabolized primarily through a non-enzymatic pathway with a minor CYP2C19 association. Thus, rabeprazole is less affected by the CYP2C19 genotype and has little interaction with other drugs.13 As mentioned above, esomeprazole has higher bio-availability and greater acid suppression effect in the stomach.3,4 In addition, esomeprazole therapy leads to fewer inter-individual variations in acid control and a more rapid onset of acid suppression.4,14 Therefore, esomeprazole is an effective and powerful acid inhibitor compared to other conventional PPIs, which affect the eradication rates by the persistent anti-H. pylori effect. The role of acid suppression in eradication therapy is based on the following: 1) the direct antibacterial activity of PPI, 2) inhibition of urease activity, and 3) enhanced activity and stability of antibiotics.22-25 Among them, increased activity and antibiotic stability via acid suppression are the most notable because they are associated with the H. pylori bioenergetics.15 According to transcriptomics studies, the genes underlying H. pylori cell division and cell wall synthesis showed elevated transcription at neutral pH compared to acidic pH (pH 4.5).16 Because the antibiotic effects of amoxicillin and clarithromycin are determined by bacterial growth and cell envelope synthesis, their bactericidal effect is activated in dividing bacteria.16 Sugimoto et al.17 used 24 hours intragastric pH monitoring to determine if gastric acid suppression affected eradication therapy. The median 24 hours gastric pH values were 6.4 and 5.2 in patients with and without successful eradication, respectively (p<0.0131), and successful eradication rates were associated significantly with the degree of acid suppression.17 The eradication rates of the study were still unsatisfactory. An eradication rate higher than 90% is considered as the optimal cut-off therapy for PP analysis.18 On the other hand, a meta-analysis showed that the overall eradication rate of standard triple therapy from 1998 to 2013 was 82.0% (95% CI 80.8-83.2%) based on PP analysis in 104 studies with 42,124 Korean patients.19 Between 2017 and 2018, a nationwide prospective multicenter study was conducted in Korea to evaluate the antibiotic resistance rates of H. pylori. Overall, 580 patients were enrolled, and the resistance rates against clarithromycin, metronidazole, levofloxacin, ciprofloxacin, amoxicillin, and tetracycline were 17.8%, 29.5%, 37.0%, 37.0%, 9.5%, and 0%, respectively.20 A recent Korean study conducted in the same region as the current study reported antibiotic resistance rates of clarithromycin, metronidazole, levofloxacin, ciprofloxacin, amoxicillin, and tetracycline of 19.3%, 19.3%, 40.9%, 40.9%, 11.3%, and 0%, respectively.21 Therefore, more effective first-line eradication therapies, including intensive acid suppression, are required in countries showing increased antibiotic resistance, such as Korea. Being female (OR 2.08; 95% CI 1.15-3.76) was associated with H. pylori eradication failure in this study. Several studies reported that female gender influenced H. pylori eradication.22-25 Moayyedi et al.26 speculated that the gastric physiology probably differed between males and females. A Korean study that investigated clarithromycin mutation rates using the point mutation of the 23S rRNA gene reported that females were infected predominantly with clarithromycin-resistant H. pylori carrying the A2143G mutation (p<0.005).27 Therefore, females with this point mutation in the 23S rRNA of H. pylori strains contributed to the failure of PPI-containing triple therapy, including clarithromycin. Another Korean study, however, found no significant difference in clarithromycin-resistant H. pylori between males and females based on point mutations in the 23S rRNA gene (p=0.087).25 Therefore, gender differences in the eradication of H. pylori need to be evaluated in the future. The study limitations relate to the lack of a histological diagnosis of H. pylori before and after eradication therapy. A few patients underwent both a rapid urease test and a 13C-urea breath test for the confirmation of H. pylori.
These limitations influence the eradication rate. On the other hand, compared to the 80% sensitivity of \textit{H. pylori} based on histology, the sensitivity and specificity of the rapid urease test ranged from 90% to 95% and 95% to 100%, respectively. Furthermore, the sensitivity and specificity of the $^{13}$C-urea breath test were 95% to 97% and 91% to 94%, respectively. The accuracy of both tests is high and very convenient for clinical use. Thus, the absence of histology is unlikely to have affected the study significantly.

In conclusion, treatment with high doses of an esomeprazole-containing triple-drug combination for seven days leads to a higher eradication rate than the standard dose non-esomeprazole-containing triple-drug regimen for seven days, and the adverse effects of both regimens are acceptable. Being female is associated with a higher risk of eradication failure. On the other hand, low eradication rates of \textit{H. pylori} are still under consideration. Therefore, further well-designed and large-scale studies examining the efficacy of first-line eradication therapies for \textit{H. pylori} are required in Korea, including studies with potent acid suppression.

REFERENCES

1. Yeo YH, Shiu SI, Ho HJ, et al. First-line Helicobacter pylori eradication therapies in countries with high and low clarithromycin resistance: a systematic review and network meta-analysis. Gut 2018;67:20-27.

2. Shin WG, Lee SW, Baik GH, 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;21:266-278.

3. Lindberg P, Keeling D, Fryklund J, Andersson T, Lundborg P, Carlsson E. Review article: esomeprazole--enhanced bio-availability, specificity for the proton pump and inhibition of acid secretion. Aliment Pharmacol Ther 2003;17:481-488.

4. Hsu PI, Lai KH, Wu CJ, et al. High-dose versus low-dose esomeprazole-based triple therapy for Helicobacter pylori infection. Eur J Clin Invest 2007;37:724-730.

5. Shin JM, Kim N. Pharmacokinetics and pharmacodynamics of the proton pump inhibitors. J Neurogastroenterol Motil 2013;19:25-35.

6. Oshima T, Miwa H. Potent potassium-competitive acid blockers: a new era for the treatment of acid-related diseases. J Neurogastro-enterol Motil 2018;24:334-344.

7. Choi HS, Park DI, Hwang SJ, et al. Double-dose, new-generation proton pump inhibitors do not improve Helicobacter pylori eradication rate. Helicobacter 2007;12:638-642.

8. Anagnostopoulos GK, Tsiakos S, Margantinis G, Kostopoulos P, Arvanitidis D. Esomeprazole versus omeprazole for the eradication of Helicobacter pylori infection: results of a randomized controlled study. J Clin Gastroenterol 2004;38:503-506.

9. Hsu PI, Lai KH, Lin CK, et al. A prospective randomized trial of esomeprazole- versus pantoprazole-based triple therapy for Helicobacter pylori eradication. Am J Gastroenterol 2005;100:2387-2392.

10. Villoria A, Garcia P, Calvet X, Gisbert JP, Vergara M. Meta-analysis: high-dose proton pump inhibitors vs. standard dose in triple therapy for Helicobacter pylori eradication. Aliment Pharmacol Ther 2008;28:868-877.

11. De Franceso V, Ridola L, Hassan C, et al. Two-week triple therapy with either standard or high-dose esomeprazole for first-line \textit{H. pylori} eradication. J Gastrointestin Liver Dis 2016;25:147-150.

12. Gisbert JP, Dominguez-Munoz A, Dominguez-Martín A, Gisbert JL, Marcos S. Esomeprazole-based therapy in Helicobacter pylori eradication: any effect by increasing the dose of esomeprazole or prolonging the treatment?. Am J Gastroenterol 2005;100:1935-1940.

13. Ishizaki T, Horai Y. Review article: cytochrome P450 and the metabolism of proton pump inhibitors--emphasis on rabeprazole. Aliment Pharmacol Ther 1999;13 Suppl 3:27-36.

14. Scott LJ, Dunn CJ, Mallarkey G, Sharpe M. Esomeprazole: a review of its use in the management of acid-related disorders. Drugs 2002;62:1503-1538.

15. Scott DR, Sachs G, Marcus EA. The role of acid inhibition in Helicobacter pylori eradication. F1000Res 2016;5:F1000 Faculty Rev-1747.

16. 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. Aliment Pharmacol Ther 2012;36:972-979.

17. Sugimoto M, Furuta T, Shirai N, et al. Evidence that the degree and duration of acid suppression are related to Helicobacter pylori eradication by triple therapy. Helicobacter 2007;12:317-323.

18. Graham DY, Lu H, Yamaoka Y. A report card to grade Helicobacter pylori therapy. Helicobacter 2007;12:275-278.

19. Gong EJ, Yun SC, Jung HY, 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;29:704-713.

20. Lee JH, Ahn JY, Choi KD, et al. Nationwide antibiotic resistance mapping of Helicobacter pylori in Korea: a prospective multicenter study. Helicobacter 2019;24:e12592.

21. Ong S, Kim SE, Kim JH, et al. Helicobacter pylori eradication rates with concomitant and tailored therapy based on 23S rRNA point mutation: a multicenter randomized controlled trial. Helicobacter 2019;24:e12654.

22. Osato MS, Reddy R, Reddy SG, Penland RL, Malaty HM, Graham DY. Pattern of primary resistance of Helicobacter pylori to metronidazole or clarithromycin in the United States. Arch Intern Med 2001;161:1217-1220.

23. Cai W, Zhou L, Ren W, Deng L, Yu M. Variables influencing outcome of Helicobacter pylori eradication therapy in South China. Helicobacter 2009;14:91-96.

24. Kim SE, Park MI, Park SJ, et al. Trends in Helicobacter pylori eradication rates by first-line triple therapy and related factors in eradication therapy. Korean J Intern Med 2015;30:801-807.

25. Chang YW, Ko WJ, Oh CH, et al. Clarithromycin resistance and fe-
male gender affect Helicobacter pylori eradication failure in chronic gastritis. Korean J Intern Med 2019;34:1022-1029.
26. Moayyedi P, Chalmers DM, Axon AT. Patient factors that predict failure of omeprazole, clarithromycin, and tinidazole to eradicate Helicobacter pylori. J Gastroenterol 1997;32:24-27.
27. Kim T, Song HJ, Shin SY, et al. Clarithromycin-resistant Helicobacter pylori associated with 23S rRNA point mutations in Jeju Island. Korean J Gastroenterol 2013;61:252-258.
28. Mégraud F, Lehours P. Helicobacter pylori detection and antimicrobial susceptibility testing. Clin Microbiol Rev 2007;20:280-322.
29. Versalovic J. Helicobacter pylori. Pathology and diagnostic strategies. Am J Clin Pathol 2003;119:403-412.
30. Ferwana M, Abdulmajeed I, Alhajiahmed A, et al. Accuracy of urea breath test in Helicobacter pylori infection: meta-analysis. World J Gastroenterol 2015;21:1305-1314.
31. Gatta L, Vakil N, Ricci C, et al. Effect of proton pump inhibitors and antacid therapy on 13C urea breath tests and stool test for Helicobacter pylori infection. Am J Gastroenterol 2004;99:823-829.
32. Leodolter A, Wolle K, Malfertheiner P. Current standards in the diagnosis of Helicobacter pylori infection. Dig Dis 2001;19:116-122.