Eradication Rates of *Helicobacter pylori* in Korea Over the Past 10 years and Correlation of the Amount of Antibiotics Use: Nationwide Survey

Woon Geon Shin, Sang Woo Lee, Gwang Ho Baik, Kyu Chan Huh, Sang In Lee, Jun-Won Chung, Woon Tae Jung, Moo In Park, Hye-kyung Jung, Heung Up Kim, Jeong Hwan Kim, Sang Young Seol, Soon Man Yoon, Seong Woo Jeon, Su Jin Hong, Gwang Ha Kim, Dong Ho Lee, Hyun Soo Kim, Sue Kyung Choi, Hee Mo Kang, Joongyub Lee, Gwang Ha Kim, Jung Hwan Kim, Heung Up Kim, Jae Gyu Kim, Dongja Kwon, Jun-Won Chung, Suck Chei Choi, Woon Tae Jung, Woon Geon Shin, Jeong Hwan Kim, Heung Up Kim, Jae Gyu Kim, Division of Gastroenterology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea, E-mail: jjkim@skku.edu

**Abstract**

**Background:** The efficacy of proton-pump inhibitor–amoxicillin–clarithromycin therapy for *H. pylori* eradication has decreased over time.

**Objective:** We assessed the trend of *H. pylori* eradication rates over the last 10 years and the relationship between the eradication rates and the amount of macrolide antibiotic use in a country with a high prevalence of *H. pylori* infection.

**Methods:** This vast nationwide multicenter study was conducted with 34,139 adults treated for *H. pylori* infection from January 2001 to December 2010. The defined daily dose per km² (DSD) of macrolide antibiotics was calculated (*n* = 141,019) using the Health Insurance Review & Assessment data base from 2008 to 2010 in the two cities which had the lowest (Jeju city) or highest (Chunchon city) eradication rate.

**Results:** The eradication rates of proton-pump inhibitor–amoxicillin–clarithromycin therapy ranged 84.9–87.5% from 2001 to 2007, and those of 2008 to 2010 ranged 80.0–81.4% with a decreasing trend (*p* < 0.0001). The decreasing trend of eradication rates for the overall first-line therapy was observed only in three of the seven geographic areas in Korea (*p* < 0.0001). The DSD of macrolide antibiotics was significantly higher in Jeju than Cheunchon city (*0.85 vs 0.52, p < 0.0001*).

**Conclusions:** *H. pylori* eradication rates with clarithromycin-containing triple therapy in Korea showed a decreasing trend over the past 10 years, although the trend varied among geographic areas. This difference may be associated with the amount of macrolide antibiotic use.

Clarithromycin-containing triple therapy, which is combination treatment using a proton-pump inhibitor (PPI)–amoxicillin–clarithromycin (PAC) and is most commonly recommended as one of the first-line *Helicobacter pylori* (*H. pylori*) eradication therapies, now shows unacceptably low treatment success rates. The
Eradication Rates of Helicobacter pylori and Correlation of Antibiotic Use Density

Shin et al.

Efficacy of this triple therapy has decreased over time [1,2], largely due to the increase of clarithromycin resistance, which has had an enormous influence on eradication rates [2]. Most worldwide studies have showed unacceptably low eradication success rates for PAC, with about 60% of studies failing to reach 80% eradication rate in intention-to-treat (ITT) analysis [2]. Therefore, the Maastricht IV/Florence consensus report recommends bismuth-containing quadruple therapy (BCQT) for first-line empirical treatment to avoid clarithromycin use in areas with more than 20% clarithromycin resistance [3].

Although the seroprevalence of H. pylori infection in asymptomatic adult subjects has decreased from 66.9% in 1998 to 59.6% in 2005 [4,5], the high prevalence of H. pylori infection in Korea remains a challenge for the medical community. Since 1998, the Korean College of Helicobacter and Upper Gastrointestinal Research had recommended only 7–14 days PAC treatment as a first-line therapy for H. pylori infection in their first and second edition guidelines [6,7] because of the high metronidazole resistance rate in Korea [8,9].

Although several retrospective Korean studies reported that the eradication rates of PAC from 2000 to 2010 surpassed 80% [10–12], the time trend of eradication rates showed discrepancies among these studies because of the small sample sizes enrolled in individual centers. However, considering the increase in clarithromycin resistance for H. pylori in Korea [13,14], the eradication rate of PAC for H. pylori has likely decreased over the past 10 years, at least in some areas [10], and new strategies are urgently needed to improve the H. pylori eradication rate. It has been unclear which areas in Korea require a different first-line regimen, although the BCQT can be used as a first-line therapy according to the 2013 revised Korean guideline of H. pylori treatment [15]. Thus, we conducted this nationwide and large-scale study to (1) elucidate the time trend of H. pylori eradication rates over the last 10 years according to age, eradication regimens, and geographic area and (2) provide evidence of application of different eradication regimens depending on geographic area in a country with a high prevalence of H. pylori infection.

Antibiotic use is generally accepted as one of the major factors determining the prevalence of antibiotic resistance in a community [16]. Some studies reported a positive relation between antibiotic use and antibiotic resistance [16–18]. And population density is an important factor for the occurrence of antibiotic resistance because dissemination of resistant bacteria and genes among persons further increase the prevalence of antibiotic resistance in a population [16,18]. Therefore, we assessed the difference in the amount of antibiotic use per square kilometer (km²) between the geographic areas with the lowest and highest eradication rates to identify the relationship between antibiotic use and eradication rate.

Methods

Eradication rates over the past 10 years

Study population. This multicenter study was conducted nationwide for adult subjects aged ≥20 treated for H. pylori infection in secondary or tertiary medical centers from January 2001 to December 2010. The search of these patients was performed based on the generic names and doses of H. pylori eradication regimens using each hospital’s electronic medical chart systems. We excluded patients who did not undergo tests to confirm H. pylori eradication within 3 months after the end of H. pylori eradication therapy.

For balanced collection of the data from the national geographic areas, we recruited one medical center per 2.5 million resident population in a province or city. In total, 20 medical centers located in either Seoul or in six different provinces (Chungcheong, Gangwon, Gyeonggi, Gyeongsang, Jeolla, and Jeju) were included.

Cases report form. First, a one-paged CRF, which could be completed by selecting icons on a computer screen with a mouse, was designed using Microsoft Office Access to enhance accuracy and ease of data entry. The form was distributed to the authors along with the data entry guidelines. This CRF included questions on demographic data (e.g., age, sex, and residence), detection methods of H. pylori infection, reasons, regimens, durations, and results of H. pylori eradication. Next, we conducted a preliminary study from January to June 2011 to test interinvestigator agreement using the CRF. We compared the agreement of the preliminary data for the same 20 patients between two data entry physicians in each hospital. Because the introductory data punched in by two physicians coincided with each other for all the variables included in the CRF, the form was used consistently throughout the main data entry period of September 2011 to December 2012 without any corrections.

The Institutional Review Board of each hospital approved the study protocol.

Main outcome. The main outcome was the drift of eradication rates of first- and second-line therapy in rela-
tion to geographic areas and age over the past 10 years. The second-line outcomes were the difference in eradication rates according to eradication regimens and durations, geographic areas, and gastroduodenal diseases. The definition of *H. pylori* eradication success was as follows: (1) negative result in urea breath test (UBT) or (2) negative result in both rapid urease test and histology with hematoxylin–eosin and/or Giemsa stain in the 1- to 3-month follow-up after eradication therapy.

**Population standardization.** In this report, eradication rates were standardized to the mid-year Population of 2010 as a Korean standard population. The standard population provides age distributions to be used in the estimation of age-standardized rates. The mid-year population of 2010 used denominator of the eradication rate was generated using the resident registration population published annually by the Ministry of Government Administration and Home Affairs.

**Measurement of the amount of macrolide antibiotics use**

**Study design.** The lowest eradication rate of PAC used as a first-line therapy for *H. pylori* was 67.3% in Jeju province according to the results of this study. We hypothesized that the possible cause of this high eradication failure rate in Jeju province may be related to high clarithromycin resistance due to antibiotics consumption. Therefore, we proceeded to the next cross-sectional study from June 2013 to June 2014 to compare the amount of antibiotic use from January 2008 to December 2010 between the highest and lowest eradication areas.

The defined daily dose (DDD) is the assumed average maintenance dose per day for a drug used for its main indication in adults. It is used to standardize the comparison of drug usage between different drugs or between different healthcare environments. Thus, we assessed the 3 years’ DDD of macrolide antibiotics consumed per km² per day (DSD) using the Health Insurance Review & Assessment (HIRA) database, which are accessible in the last 5 years, from January 2008 to December 2010 in Jeju city and Chuncheon city, where our eradication data had been collected in Jeju province and Gangwon province, respectively. Chuncheon city is a city located in Gangwon province and had the highest eradication rate (86.2%) in this study (Table S1).

**Results**

**Baseline characteristics and *H. pylori* eradication rates of first-line, second-line, and third-line therapies**

A total of 34,139 patients (31,886, 2108, and 145 patients in the first-, second-, and third-line therapy group, respectively) were included in this analyses. We described detailed baseline characteristics and *H. pylori* eradication rates of first-line, second-line, and third-line therapies according to the reasons for eradication, acid suppressive agent, treatment duration, and regimens in Tables 1 and 2.

**First-line therapy.** In total, 31,886 patients were evaluated for the first-line therapy of *H. pylori* infection (mean age, 52.9 years; male, 63.7%). The mean age of the eradication success group was younger than the eradication failure group (52.68 vs 54.46 years, *p* < .0001). Males had higher eradication rates than...
females (84.6 vs 81.8%, \( p < .0001 \)). The most common reason for *H. pylori* eradication was benign gastric ulcer (BGU) (10,862/31,886, 34.1%). The eradication rates ranged from 78.3% to 86.3% according to gastroduodenal diseases such as gastritis, peptic ulcer, benign gastric neoplasm, gastric cancer, and MALToma and were significantly different among the gastroduodenal diseases (\( p < .0001 \)). Acid suppression agents such as pantoprazole, lansoprazole, rabeprazole, omeprazole, and esomeprazole had significantly different *H. pylori* eradication rates (\( p < .0001 \)). The eradication rates were 82.5–91.7% for treatment durations such as <7, 7, 8–13, 14, and more than 14 days. (\( p < .0001 \)) (Table 1). The most commonly prescribed regimen for first-line therapy was PAC (30,534/31,886, 95.8%). The eradication rates were significantly different according to the treatment regimens such as PAC (83.6%), concomitant therapy (CT) (92.3%), BCQT (89.4%), sequential therapy (ST) (91.9%), and others (82.6%) (\( p < .0001 \)) (Table 2).

**Second-line therapy.** In total, 2108 patients were evaluated for the second-line therapy of *H. pylori* infection (mean age, 55.24 years; male, 57.2%). The mean age showed no differences between the eradication success and failure groups (55.05 vs 56.22 years, respectively, \( p = .122 \)). The eradication rate did not differ according to sex (male, 81.0% vs female, 86.5%, \( p = 1.000 \)). The most common reason for *H. pylori* eradication was BGU (663/2108, 31.5%). The eradication rates were 71.3% to 100% according to gastroduodenal diseases and did not differ among the gastroduodenal diseases (\( p = .145 \)). Acid suppression agents had significantly

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Baseline characteristics and <em>Helicobacter pylori</em> eradication rates of first-, second-, and third-line therapies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>First-line therapies</td>
</tr>
<tr>
<td></td>
<td>Eradication success rates</td>
</tr>
<tr>
<td>Total, n (%)</td>
<td>31,886 (100.0) (83.7)</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td>31,886 (100.0) (83.7)</td>
</tr>
<tr>
<td>Male</td>
<td>20,296 (63.7) (84.6)</td>
</tr>
<tr>
<td>Female</td>
<td>11,590 (36.3) (81.8)</td>
</tr>
<tr>
<td>Reasons for eradication, n (%)</td>
<td>31,886 (100.0) (83.7)</td>
</tr>
<tr>
<td>BGU</td>
<td>10,862 (34.1) (84.1)</td>
</tr>
<tr>
<td>BDU</td>
<td>9796 (30.7) (84.2)</td>
</tr>
<tr>
<td>Gastritis</td>
<td>6977 (21.9) (82.9)</td>
</tr>
<tr>
<td>BGU + BDU</td>
<td>1729 (5.4) (86.3)</td>
</tr>
<tr>
<td>Gastric cancer</td>
<td>1009 (3.2) (84.5)</td>
</tr>
<tr>
<td>Benign gastric neoplasm</td>
<td>354 (1.1) (84.3)</td>
</tr>
<tr>
<td>MALToma</td>
<td>315 (1.0) (85.3)</td>
</tr>
<tr>
<td>Others</td>
<td>844 (2.6) (78.3)</td>
</tr>
<tr>
<td>Acid suppression agent, n (%)</td>
<td>31,784 (100.0) (83.7)</td>
</tr>
<tr>
<td>Pantoprazole</td>
<td>7948 (25.0) (81.3)</td>
</tr>
<tr>
<td>Lansoprazole</td>
<td>6607 (20.8) (82.6)</td>
</tr>
<tr>
<td>Rabeprazole</td>
<td>6173 (19.4) (84.0)</td>
</tr>
<tr>
<td>Omeprazole</td>
<td>5438 (17.1) (85.7)</td>
</tr>
<tr>
<td>Esomeprazole</td>
<td>5618 (17.7) (86.4)</td>
</tr>
<tr>
<td>Duration of treatment, n (%)</td>
<td>31,886 (100.0) (83.7)</td>
</tr>
<tr>
<td>&lt;7</td>
<td>344 (1.1) (91.7)</td>
</tr>
<tr>
<td>7</td>
<td>23,441 (73.5) (82.5)</td>
</tr>
<tr>
<td>8–13</td>
<td>586 (1.8) (85.1)</td>
</tr>
<tr>
<td>14</td>
<td>7486 (23.4) (86.4)</td>
</tr>
<tr>
<td>&gt;14</td>
<td>47 (0.1) (91.5)</td>
</tr>
<tr>
<td>Mean age, years ± SD</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>52.98 ± 12.86</td>
</tr>
<tr>
<td>Eradication success</td>
<td>52.68 ± 12.77</td>
</tr>
<tr>
<td>Eradication failure</td>
<td>54.46 ± 13.17</td>
</tr>
</tbody>
</table>

BGU, benign gastric ulcer; BDU, benign duodenal ulcer; SD, standard deviation.
First-line therapy
Regimens, n (%) | Total | Eradication success rates | p Value |
---|---|---|---|
PAC | 30,534 (95.8) | (83.6) | |
CT | 303 (1.0) | (92.3) | |
BCQT | 186 (0.6) | (89.4) | |
ST | 126 (0.4) | (91.9) | |
Others | 917 (2.9) | (82.6) | |
Second-line therapy regimens, n (%) | 2040 (100.0) | (83.3) | <.0001 |
BCQT | 1612 (79.0) | (88.3) | |
PAC | 160 (7.8) | (49.5) | |
PTM | 70 (3.4) | (90.6) | |
PLM | 44 (2.2) | (74.8) | |
PAM | 1 (0.0) | (100) | |
Others | 153 (7.5) | (67.8) | |
Third-line therapy regimens, n (%) | 139 (100.0) | (81.3) | .001 |
BCQT | 62 (44.6) | (86.0) | |
PAL | 23 (16.5) | (70.6) | |
PAC | 12 (8.6) | (70.5) | |
Others | 42 (30.2) | (82.5) | |

P, proton-pump inhibitor; A, amoxicillin; C, clarithromycin; M, metronidazole; T, tetracycline; L, levofloxacin; CT, concomitant therapy; BQT, bismuth-containing quadruple therapy; ST, sequential therapy.

different H. pylori eradication rates (p = .038). The eradication rates ranged from 81.8% to 100% according to treatment durations (p = .895) (Table 1). The most common regimen prescribed as a second-line therapy was BCQT (1612/2040, 79.0%). The eradication rates ranged from 49.5% to 100% according to treatment regimens and were significantly different among the second-line treatment regimens (p < .0001) (Table 2).

Third-line therapy. In total, 145 patients were evaluated for the third-line therapy of H. pylori infection (mean age, 57.55 years; male, 57.2%). The mean age was no different between the eradication success and failure groups (58.13 vs 55.81 years, respectively, p = .401). The eradication rate did not differ according to sex (male, 70.0% vs female, 81.6%, p = .850). The most common reason for H. pylori eradication was BGU (45/145, 31.0%). The eradication rates ranged from 67.9% to 100% according to gastroduodenal diseases and did not differ among the gastroduodenal diseases (p = .793). Omeprazole had the highest eradication rate (100%) among the various PPIs investigated, although there was no significant difference (p = .061). The eradication rates were 79.9% and 84.2% according to treatment durations of <7 and 7 days, respectively (p = .442) (Table 1). The regimen most commonly prescribed as a third-line therapy was BCQT (62/139, 44.6%). The eradication rates were 70.5% to 86.0% according to treatment regimens and were significantly different among the third-line treatment regimens (p = .001) (Table 2).

Multivariate logistic regression analysis for assessing independent factors of H. pylori eradication success

Multivariate logistic regression analysis was performed including various valuables that could influence on H. pylori eradication rates such as age, sex, gastroduodenal diseases, acid suppression agents, treatment duration, and regimens. Male sex (adjusted odds ratio (AOR), 1.28; 95% confidence interval (CI), 1.20–1.36; p < .0001), BGU (AOR, 1.29; 95% CI, 1.09–1.53; p = .004), BDU (AOR, 1.52; 95% CI, 1.27–1.80; p < .0001), gastritis (AOR, 1.28; 95% CI, 1.07–1.52; p = .007), BGU + BDU (AOR, 1.61; 95% CI, 1.30–1.99; p < .0001), gastric cancer (AOR, 1.31; 95% CI, 1.04–1.65; p = .022), esophageal ulcer (AOR, 1.26; 95% CI, 1.16–1.36; p < .0001), CT (AOR, 2.01; 95% CI, 1.34–3.02; p = .001), BCQT (AOR, 2.02; 95% CI, 1.22–3.33; p = .006), and ST (AOR, 2.40; 95% CI, 1.26–4.55; p = .007) were independent factors of H. pylori eradication success in the first-line therapies. In the second-line therapies, independent factors were BCQT (AOR, 5.36; 95% CI, 3.73–7.70; p < .0001) and PTM (PPI-tetracycline-metronidazole) (AOR, 4.86; 95% CI, 2.18–10.88; p < .0001). Only BCQT (AOR, 5.19; 95% CI, 1.81–14.85; p = .002) was independent factor in third-line therapies (Table 3).

Time trend of H. pylori eradication rates over the last 10 years according to eradication regimens, age, and geographic areas

We depicted the detailed time trend of H. pylori eradication rates over 10 years in relation to the overall first-line therapy, second-line therapy, PAC, BCQT, age, and geographic areas in Figs 1 and 2. The eradication rates of PAC as a first-line therapy ranged from 84.9% to 87.5% from 2001 to 2007, and those of 2008, 2009, and 2010, ranged from 80.0% to 81.4% with a decreasing trend (p < .0001) (Fig. 1A). This decreasing trend was observed in both the ≥60 and <60 years old groups (p < .0001), although the eradication rates from 2004 to 2010 were significantly lower in the ≥60 years group.
The time trend of overall first-line and second-line eradication rates for \textit{H. pylori} have decreased over the
past 10 years in Korea. However, the trends were different in subgroup analysis depending on geographic area. Only three of seven regions, Seoul, Chunchoeng, and Gyeongsang province, showed a decreasing trend in first-line and second-line eradication rates. We cannot find the comparable regional characteristics among these three regions including demographic and geographic factors. However, this result can be partially explained by differences in antibiotics resistance according to geographic area, although drug compliance, bacterial load, and type of strain of H. pylori can impact on eradication rates [19]. One Korean study reported that the resistance rate of clarithromycin prepared by the agar dilution method was 42.1% in Busan city, Gyeongsang province, whereas that of Gangwon province, which did not show any changes in eradication rate in this study, was 12.5% [20]. This result indicates that different guidelines should be applied for H. pylori eradication based on the data for antibiotics resistance for regional areas within the same country or ethnic group [3,15]. Fortunately, BCQT can be recommended as a first-line regimen in these three regions (Seoul, Chunchoeng, and Gyeongsang province) because the eradication rates of BCQT were about >90% and were significantly higher than PAC as shown in Fig. 3.

Surprisingly, the mean eradication rate of PAC used as a first-line therapy in Jeju province for 10 years was only 67.3%, whereas that in Gangwon province was 86.2%. This result is possibly associated with the amount of antibiotics usage and population density, which are closely related to antibiotics resistance [16-18,21]. We postulated that population density might be an important factor for the development of antibiotics resistance because the main route of H. pylori infection,
although still unclear, appears to be interpersonal transmission via the fecal-to-oral route [22]. Therefore, we calculated the DSD (DDD/km²) rather than DID (DDD/1000 inhabitants) in the two cities [16]. Furthermore, we included all kinds of macrolide antibiotics for calculating DSD because it is well known that macrolide antibiotics have cross-resistance with each other [14].

In fact, the DSD of macrolide of Jeju city in Jeju province was statistically higher than that of Chuncheon city in Gangwon province (p < .0001). Especially, there is no doubt that previous exposure to clarithromycin is one of the major causes of resistance development based on some studies reporting that the second-line resistance of clar-

**Figure 2** The time trend of *H. pylori* eradication rates over the last 10 years according to geographic area. The decreasing trend of eradication rates for overall first-line (A) and second-line (B) therapy was observed in three of seven geographic areas: Chungcheong province, Seoul, and Gyeonggi province (p < .0001).

**Table 4** The differences in *Helicobacter pylori* eradication rates according to treatment durations and gastroduodenal diseases

<table>
<thead>
<tr>
<th>Treatment duration, n/N (%)</th>
<th>PAC as a primary therapy</th>
<th>BCQT as a secondary therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Success</td>
<td>Odds (95% CI)</td>
</tr>
<tr>
<td>7 days</td>
<td>24,786/29,792 (83.6)</td>
<td>1</td>
</tr>
<tr>
<td>14 days</td>
<td>18,968/23,102 (82.4)</td>
<td>1.43 (1.32, 1.55)</td>
</tr>
<tr>
<td>Gastric lesions, n/N (%)</td>
<td>5959/7215 (82.7)</td>
<td>1</td>
</tr>
<tr>
<td>Gastric cancer</td>
<td>766/937 (87.9)</td>
<td>1</td>
</tr>
<tr>
<td>Peptic ulcer diseases, n/N (%)</td>
<td>16,670/19,973 (83.8)</td>
<td>1.14 (1.06,1.23)</td>
</tr>
</tbody>
</table>

PAC, Bismuth-containing quadruple therapy; P, proton-pump inhibitor; A, amoxicillin; C, clarithromycin; B, bismuth; M, metronidazole; T, tetracycline; CI, confidence interval; BGU, benign gastric ulcer; BDU, benign duodenal ulcer.
ithromycin for *H. pylori* was significantly higher than the first-line resistance [14,23]. However, it is unclear at this point why Jeju city has increased macrolide use. In summation, as antibiotic use is generally accepted as the main factor determining antibiotics resistance, macrolide-resistant *H. pylori* following previous macrolide exposure might be the main cause of the low eradication rate in Jeju province, although there is still no data on the resistance rate of clarithromycin prepared by the agar dilution method in Jeju province.

Thus, new strategies such as tailored therapy, a pretreatment antimicrobial susceptibility-guided method [24], will be needed to improve the first-line eradication rate in Jeju province after conducting well-designed epidemiologic, experimental, and clinical studies on the prevalence of antibiotics resistance for *H. pylori*, compliance, bacterial load, and type of strain.

The time trend of the first-line eradication rate of *H. pylori* treating PAC decreased especially in the patients aged 60 and older, whereas the second-line eradication rate of BCQT did not change over the 10 years studied. The eradication rates of PAC after 2004 in the older patients (≥60 years) were significantly lower than in the patients <60 years of age. Some previous studies provide evidence for this result [25,26]. However, the evidence is still debated because of conflicting results [27,28]. A higher likelihood of antibiotics exposure, lower compliance, or additional underlying chronic diseases including diabetes [29] in elderly patients may also explain the result. However, taking into consideration of second-line resistance of clarithromycin for *H. pylori* than that of metronidazole, prior macrolide antibiotics exposure may be a possible cause for reduced eradication rate in elderly patients only with PAC not BCQT.

Interestingly, BCQT was most commonly prescribed regimen as a third-line therapy, which was also the most frequently prescribed as a second-line regimen in this study. There is a next therapeutic dilemma in patients with persistent *H. pylori* infection after second-line eradication therapy because no standard third-line therapy has been established in Korea. Some studies reported success of immediate retreatment with the same regimen, although rescue therapies generally consist of two or more antibiotics that were not used previous treatment without knowing the *H. pylori* resistance status. [30,31] In fact, one Korean study reported that the third-line eradication rate of immediately repeated the same treatment of second-line BCQT was 75.0% (95% CI 71.3–78.7%) in PP analysis after the failure of second-line quadruple therapy. [31] This result can be partially explained by the fact that resistance to metronidazole can frequently be overcome by increasing the dose and duration of treatment. One meta-analysis

Table 5 Defined daily doses per km² per day of macrolide and clarithromycin by generic name in Chuncheon and Jeju city from January 2008 to December 2010

<table>
<thead>
<tr>
<th></th>
<th>DSD</th>
<th>Chuncheon city</th>
<th>Jeju city</th>
<th>Difference (Jeju–Chuncheon)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Macrolide</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>0.52 ± 0.08</td>
<td>0.85 ± 0.16</td>
<td>−0.33 ± 0.10</td>
<td>&lt;.0001</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>0.52</td>
<td>0.86</td>
<td>0.34</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Clarithromycin</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>0.27 ± 0.04</td>
<td>0.29 ± 0.05</td>
<td>−0.021 ± 0.03</td>
<td>.006</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>0.27</td>
<td>0.29</td>
<td>−0.02</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

DSD, defined daily doses per km² per day; SD, standard deviation.
reported that nitroimidazole resistance did not significantly influence *H. pylori* eradication rate when quadruple regimens were used for 7 days [32].

On the other hand, quinolone-containing therapy can be used as a third-line therapy. However, the *H. pylori* eradication rates with levofloxacin-containing
resistance from 16.7% during 2003. Likewise, there was a significant increase in ciprofloxacin resistance in regions in Korea. Furthermore, we demonstrated that the use of nationwide data, unlike previous single center results [25,38], is inconclusive because of previous contrasting results [37]. However, this result can be explained by the increasing trend of resistance to quinolone for H. pylori in Korea. Resistance rates to levofloxacin has been reported to be increasing from 4.5% in 2003–2005 to 29.5% in 2007–2009. Similarly, there was a significant increase in ciprofloxacin resistance from 16.7% during 2003–2005 to 34.6% in 2007–2009. In particular, the MIC patterns of ciprofloxacin and levofloxacin showed a bimodal distribution representing typical resistance pattern in 2007–2009 [34]. Therefore, use of quinolone as a third-line therapy has been limited in Korea.

The 14-day PAC treatment regimen had a significantly higher eradication rate than the 7-day regimen (OR, 1.43; 95% CI, 1.32–1.55; p < .0001). Two meta-analyses provide evidence for our result [35,36]. A 14-day treatment improved the eradication rate by 5–9% and showed no difference in the side effects compared to a 7-day treatment. Although the 2013 revised Korean guideline of H. pylori treatment recommends a 7–14 days of treatment duration for PAC [15], extending the treatment duration to 14 days should be considered in the regions with decreased trends in eradication rates.

Benign duodenal ulcer was associated with improved eradication using PAC compared to BGU in this study. Higher eradication rates in patients with BDU have previously been reported [37]. However, this result is inconclusive because of previous contrasting results [25,38–42].

The strength of our study lies in its vast scale and use of nationwide data, unlike previous single center studies that reported discrepancies for the time trend of eradication rates in Korea [10–12]. We found that BCQT can be used as a first-line regimen at three regions in Korea. Furthermore, we demonstrated that the amount of macrolide antibiotics usage was linked to the eradication rate of H. pylori in two geographic areas using the HIRA data for about 140,000 people. Based on this result and taking into account the fact that the eradication rates of both PAC and BCQT in Jeju province were <80%, special recommendations such as tailored therapy may be needed in this region.

There are some limitations in this paper: (1) We could not apply the same cut-off value for the UBT test among the hospitals. This can be a confounding factor. (2) This study has a chance of selection bias because of the retrospective manner for data collection and missing data in the selected secondary or tertiary hospitals. Actually, institutional differences in the eradication rate of H. pylori may be possible because of institutional differences in the antibiotic resistance of H. pylori within the same region [43]. However, we think that the effect of this bias would be minimal because we selected the hospitals in proportion to the population and tried to include all patients treated for H. pylori at the institutions from 2001 to 2010 in our search strategies, mentioned above in the methods section. We also validated our CRF to minimize input error and interinvestigator discrepancy by performing the preliminary study. 3) We investigated the DSD of macrolide only from 2008 to 2010 because HIRA data were accessible in the last 5 years from 2013, even though reduced eradication rates can be a result of prior antibiotic exposure. However, the results of DSD had little bias because of complete enumeration survey in the two cities.

In conclusion, the H. pylori eradication rates of PAC showed decreasing trends over the past 10 years, possibly due to an increase of antibiotics usage in Korea. Reasonable guidelines for H. pylori eradication should be applied based on the data for antibiotics resistance in each regional area because the decreasing trend of H. pylori eradication rate was confined to only three geographic areas.

Acknowledgments and Disclosures

Competing Interests: The authors have no competing interests.

Author Contributions

Jae Gyu Kim and Jae J. Kim are guarantors of article and involved in final approval of the article. Woon Geon Shin, Sang Woo Lee, Hye-kyung Jung, Hee Mo Kang, Joongyub Lee, Jae Gyu Kim, and Jae J. Kim involved in study design. Woon Geon Shin, Sang Woo Lee, Gwang Ho Baik, Kyu Chan Huh, Sang In Lee, Jun-Won Chung, Woon Tae Jung, Moo In Park, Hye-kyung Jung, Heung Up Kim, Jeong Hwan Kim, Sang Young Seol, Soon Man Yoon, Seong Woo Jeon, Su Jin Hong, Gwang Ha Kim, Dong Ho Lee, Hyun Soo Kim, Suck Chei Choi, and Jae Gyu Kim enrolled the subjects and collected the data. AnWoon Geon Shin, Sang Woo Lee, Hye-kyung Jung, Hee Mo Kang, Joongyub Lee, Jae Gyu Kim, Jae J. Kim, Gwang Ho Baik, Kyu Chan Huh, Sang In Lee, Jun-Won Chung, Woon Tae Jung, and Moo In Park took part in analysis and interpretation of the data. Woon Geon Shin drafted the article. Critical revision of the article: Sang Woo Lee, Jae Gyu Kim, and Jae J. Kim, Heung Up Kim, Jeong Hwan Kim, Sang Young Seol, Soon Man Yoon, Seong Woo Jeon, Su Jin Hong, Gwang Ha Kim, Dong Ho Lee, Hyun Soo Kim, and Suck Chei Choi involved in critical revision of the article. All authors approved the final version of the article, including the authorship list.
References


