# Pretreatment Antimicrobial Susceptibility-Guided Vs. Clarithromycin-Based Triple Therapy for *Helicobacter pylori* Eradication in a Region With High Rates of Multiple Drug Resistance

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OBJECTIVES: **_Helicobacter pylori_ eradication rates with clarithromycin-based triple therapy are declining, and an alternative strategy is needed urgently. We sought to compare the efficacy of pretreatment antimicrobial susceptibility-guided vs. clarithromycin-based triple therapy for _H. pylori_ eradication in a region with high rates of multiple drug resistance.**

METHODS: **Consecutive _H. pylori_-infected patients with gastric epithelial neoplasms were randomized to receive antimicrobial susceptibility-guided therapy or clarithromycin-based triple therapy for 7 days. In patients in whom the infection was not eradicated, antibiotics were given according to an initial antimicrobial susceptibility test as a second-line therapy in both groups. Eradication rates, antibiotics resistance rates, and drug compliance owing to adverse effects were compared between the groups.**

RESULTS: **In total, 114 patients were enrolled, and 112 completed the protocols. Drug compliance and side effects were similar between the groups. The intention-to-treat eradication rates were 94.7% (95% confidence interval (CI)=88.8–100%, 54/57) in the antimicrobial susceptibility-guided group and 71.9% (95% CI=60.2–83.5%, 41/57) in the clarithromycin-based triple therapy group after the initial treatment ($P$=0.002), whereas the per-protocol (PP) eradication rates were 96.4% (95% CI=91.5–100%, 54/56) in the antimicrobial susceptibility-guided group and 73.2% (95% CI=61.5–84.8%, 41/56) in the clarithromycin-based triple therapy group ($P$=0.001). In _H. pylori_ with clarithromycin resistance, the eradication failure rate with first-line treatment was lower in the susceptibility-guided therapy group (0%, 0/12) compared with the clarithromycin-based triple therapy group (80.0%, 95% CI=59.7–100%, 12/15) by PP analysis ($P$<0.001).**

CONCLUSIONS: **Pretreatment antimicrobial susceptibility-guided therapy is more effective than clarithromycin-based triple therapy for _H. pylori_ eradication in a region with high rates of multiple drug resistance.**

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## INTRODUCTION

*Helicobacter pylori* is one of the most common human pathogens, infecting an estimated 50% of the global population. *H. pylori* infection is the most consistent risk factor in noncardiac gastric cancer (1–4). There is strong evidence that *H. pylori* eradication reduces the risk of gastric cancer development (5–14). Its elimination is thus the most promising strategy to reduce the incidence of gastric cancer.

In selected populations at very high risk of developing gastric cancer, *H. pylori* eradication should be reimbursed to prevent subsequent cancer and to reduce health-care costs (12). There is an absolute indication for *H. pylori* eradication in patients with previous gastric epithelial neoplasm (GEN) including dysplasia and early gastric cancer already treated by endoscopic or surgical resection (3). Treatment regimens containing a proton pump inhibitor (PPI) and a combination of two antibiotics, such

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as amoxicillin, clarithromycin, and metronidazole, have been considered to be the most efficacious. The conventional triple therapy has shown eradication rates of *H. pylori* of 60–90% (15). However, antibiotic resistance in *H. pylori*, especially clarithromycin, has been increasing, and resistance is the most important factor responsible for the recent fall in the success rates of *H. pylori* eradication treatment (16,17). This may be a serious problem in the future even in countries with low antibiotic resistance. Several studies have evaluated the relationship between pretreatment antibiotic resistance and eradication rates using different standard treatments and performing a susceptibility test before the initiation of a therapeutic regimen (18–21). Accumulating evidence suggests that antibiotic sensitivity testing results in improved eradication rates (22–27). Nevertheless, the effects remain controversial (28–30). In addition, there are few data on pretreatment antimicrobial susceptibility-guided therapy, including clarithromycin, metronidazole, and levofloxacin, for *H. pylori* eradication in regions with high rates of multiple drug resistance. Levofloxacin-based therapy has been recently reported to have higher and more consistent eradication rates as a first-line therapy in *H. pylori* eradication (10–12). However, levofloxacin resistance is increasingly undermining the efficacy of eradication treatment. It may be asked whether levofloxacin-based therapy can be used effectively without a susceptibility test in regions with high rates of multiple drug resistance.

In this study, we aimed to compare the efficacy of pretreatment antimicrobial susceptibility-guided vs. clarithromycin-based triple therapy for *H. pylori* eradication in a region with high rates of multiple drug resistance.

## METHODS

### Patients and study protocol

H. *pylori*-positive patients with GEN were enrolled in this clinical study from November 2011 to October 2012. Patients were randomized to receive antimicrobial susceptibility-guided therapy or triple therapy (proton pump inhibitor, amoxicillin, and clarithromycin) for 7 days. Patients were allocated to one or the other treatment by the drawing of sequentially numbered envelopes, each containing a previously determined, randomly selected assignment based on a table of random numbers. Exclusion criteria included age <18 years, prior eradication treatment, severe concomitant disease, history of allergy to any of the substances used in the study, previous gastric surgery, pregnancy or lactation, chronic use of corticosteroids or nonsteroidal anti-inflammatory drugs, and triple drug resistance in the bacterial culture and antimicrobial susceptibility testing (resistance to clarithromycin, metronidazole, and levofloxacin).

Patients were considered to have demonstrated good or adequate compliance if they took at least 90% of their medications. Compliance was evaluated with residual medication counts. Infection with *H. pylori* was assessed at endoscopy. Gastric mucosal biopsy specimens were taken from the antrum and the corpus; one antral specimen and one corpus biopsy specimen were used for the rapid urease test (ASAN Helicobacter Test, Asan Pharmaceutical, Seoul, Korea), and two antral and two corpus biopsies were used for the bacterial culture; they were soaked in 0.2 ml of Brucella broth (BD Biosciences, San Jose, CA). The diagnosis of *H. pylori* infection was confirmed based on positivity in the rapid urease test. In all patients, the *H. pylori* status was checked 4 weeks after the end of treatment using the $^{13}$C-urea breath test.

This study was approved by the Chonnam National University Hospital Institutional Review Board and was conducted with the approval of the Institutional Ethical Standard Committee. All patients provided written informed consent before endoscopy.

### Isolation of *H. pylori*

*H. pylori* was isolated from the gastric antrum and corpus. Briefly, biopsy specimens were homogenized using pipette tips. They were seeded on chocolate agar plates (Hanil Comed, Seongnam, Gyeonggi, Korea). The plates were then incubated in a multigas incubator (microaerobic atmosphere: 10% $CO_2$, 5% $O_2$, 85% $N_2$, 37 °C) for 3–7 days. If *H. pylori* was not isolated after 7 days of incubation, the plates were incubated for 14 days. An isolate was identified as *H. pylori* on the basis of colony morphology, microscopic image of Gram-negative helix-shaped bacterial morphology, and urea degradation capability.

### Antimicrobial susceptibility testing

Minimum inhibitory concentrations (MICs) were determined by the agar dilution method using Mueller-Hinton agar (BD Biosciences) with 5% sheep blood and 1% (v/v) IsoVitaleX (BD Biosciences) containing one of the following drug concentrations: 2–32 μg/ml of metronidazole, 0.25–4 μg/ml of clarithromycin, 0.125–2 μg/ml of amoxicillin, 0.125–2 μg/ml of levofloxacin, and 1–16 μg/ml of tetracycline. All antibiotics used in this investigation were purchased from Sigma (St Louis, MO), except for clarithromycin that was from Abbott Laboratories (Abbott Park, IL). *H. pylori* ATCC 43526 (Manassas, VA) was used as a quality control organism. The antibiotic concentrations used were based on the cutoff levels related to the breakpoint for resistance. All MICs were interpreted using CLSI (Clinical and Laboratory Standards Institute) clinical breakpoints. Antibiotic resistance was defined as follows: amoxicillin, MIC ≥0.5 μg/ml; clarithromycin, MIC >1.0 μg/ml; metronidazole, MIC >8 μg/ml; tetracycline, MIC >4 μg/ml; and levofloxacin, MIC >1 μg/ml (31).

### Therapeutic regimens

Patients treated with triple therapy received 40 mg nongeneric pantoprazole (Pantoloc) or 30 mg lansoprazole (Lanston) twice daily, 1 g amoxicillin twice daily, and 500 mg clarithromycin twice daily (PAC) for 7 days. Patients whose eradication regimen was chosen on the basis of the results of pretreatment antimicrobial susceptibility testing received 40 mg pantoprazole or 30 mg lansoprazole twice daily, 1 g amoxicillin twice daily, and 500 mg clarithromycin twice daily (PAC) for 7 days if the *H. pylori* strains

were sensitive to clarithromycin. In the case of resistance to clarithromycin, we used 1 g amoxicillin twice daily plus 500 mg metronidazole twice daily (PAM) if the *H. pylori* strains were sensitive to metronidazole. When *H. pylori* strains were resistant to both clarithromycin and metronidazole, patients received 1 g amoxicillin twice daily plus 400 mg levofloxacin once daily (PAL) if the *H. pylori* strains were sensitive to levofloxacin. In those patients who failed to eradicate the infection with triple therapy, antibiotics were given according to antimicrobial susceptibility test as second-line therapy in both groups. In those patients who failed to eradicate the infection with the first susceptible antibiotics, different susceptible antibiotics were given according to the initial antimicrobial susceptibility test as second-line therapy. When *H. pylori* strains were sensitive to metronidazole, patients took 40 mg pantoprazole or 30 mg lansoprazole twice daily, 500 mg tetracycline four times daily, 500 mg metronidazole three times daily, and 125 mg bismuth subcitrate four times daily (PMTB) for 7 days. If *H. pylori* stains were sensitive to levofloxacin, patients received 40 mg pantoprazole or 30 mg lansoprazole twice daily and 1 g amoxicillin twice daily plus 400 mg levofloxacin once daily (PAL) for 7 days. Owing to the open design, the practitioners could give whichever PPI they chose personally.

### Statistical analysis

We calculated the sample size needed to detect a difference of 25% in the eradication rate between the antimicrobial susceptibility-guided therapy group (assumed to have an eradication rate of 95%) and the conventional triple therapy group (assumed to have an eradication rate of 70%), with a power of 90% and a significance level of 0.05 ($\alpha = 0.05$, two sided). We anticipated a dropout rate of 10%. The final calculated sample size was at least 52 patients per group. Intention-to-treat and per-protocol (PP) analyses were performed to compare *H. pylori* eradication rates between the two groups. Categorical variables are reported as numbers and percentages and compared using the $\chi^2$ or Fisher's exact test. Continuous variables are reported as means±s.d. and were compared using *t*-tests. All statistical analyses were performed using the SPSS software (ver. 19.0; SPSS, Chicago, IL). The *P* values of 0.05 were considered to indicate statistical significance.

## RESULTS

### Patients

In total, we screened 237 consecutive patients who were positive for rapid urease and had GEN from November 2011 to October 2012. Among them, 88 patients were excluded owing to culture failure and 35 patients were excluded owing to triple drug resistance. Thus, in total, 114 patients were enrolled, with 57 in the susceptibility-guided therapy group and 57 in the clarithromycin-based triple therapy group. Of the 114 patients, 112 patients completed the study: 56 in each group. One patient in the susceptibility-guided therapy group dropped out because of vomiting, and one patient in the clarithromycin-based triple therapy group dropped out because of abdominal pain. They are indicated in **Figure 1**. The baseline characteristics of the patients in the two groups are shown in **Table 1**. There were no significant differences between the two groups with respect to age, gender, histological type, location of the lesions, resection specimen size, or primary antibiotic resistance rates.

### Compliance and adverse events

Adequate compliance with the first-line eradication regimen between the clarithromycin-based triple therapy group and susceptibility-guided therapy group was the same (56/57, 98.2%, 95% confidence interval (CI) = 94.7–100%). Adverse effects of the first-line eradication regimens between the groups were also similar (8.8%, 95% CI = 1.4–16.1% vs. 7.0%, 95% CI = 0.3–13.6%; $P = 1.000$; **Table 2**). The adverse effects were abdominal pain, nausea, vomiting, bitter taste, and diarrhea.

### *H. pylori* eradication rates

For the first-line treatment, antibiotics were chosen according to antimicrobial susceptibility testing in the susceptibility-guided therapy group as follows: (i) PAC (78.9%, 45/57), (ii) PAM (10.5%, 6/57), and (iii) PAL (10.5%, 6/57). By intention-to-treat analysis, the eradication rates were found to be 94.7% (95% CI = 88.8–100%, 54/57) in the antimicrobial susceptibility-guided group and 71.9% (95% CI = 60.2–83.5%, 41/57) in the clarithromycin-based triple therapy group after initial treatment ($P = 0.002$, **Figure 2**). By PP analysis, the eradication rates were 96.4% (95% CI = 91.5–100%, 54/56) and 73.2% (95% CI = 61.5–84.8%, 41/56), respectively ($P = 0.001$, **Figure 2**).

For second-line treatment, antibiotics were selected according to susceptibility testing in both groups. Six patients in the clarithromycin-based triple therapy group were excluded because of follow-up loss. One patient in the susceptibility-guided therapy group was excluded because of follow-up loss. The second regimen of antibiotics in the clarithromycin-based triple therapy group was as follows: (i) PAL (40.0%, 4/10) and (ii) PMTB (60.0%, 6/10). The second regimen of antibiotics in the susceptibility-guided therapy group was as follows: (i) PAM (50.0%, 1/2) and (ii) PMTB (50.0%, 1/2). After second-line treatment, overall eradication rates were similar between the susceptibility-guided therapy group (100%, 56/56) and the clarithromycin-based triple therapy group (98.0%, 95% CI = 94.1–100%, 50/51) by PP analysis ($P = 0.477$, **Figure 3**).

In patients with clarithromycin-resistant and metronidazole-sensitive *H. pylori* isolates, the eradication failure rate after first-line treatment was significantly lower in the susceptibility-guided therapy group (0%, 0/6) than the standard empirical triple therapy group (75.0%, 95% CI = 50.5–99.5%, 9/12) by PP analysis ($P = 0.009$, **Table 3**). In patients with clarithromycin-resistant, metronidazole-resistant, and levofloxacin-sensitive *H. pylori* isolates, the eradication failure rate after first-line treatment was significantly lower in the susceptibility-guided therapy group (0%, 0/6) compared with the clarithromycin-based triple therapy group (100%, 3/3) according to PP analysis ($P = 0.012$, **Table 3**). In patients with primary clarithromycin-resistant *H. pylori* isolates, the eradication failure rate after first-line treatment was significantly lower in the susceptibility-guided therapy group (0%, 0/12) compared with

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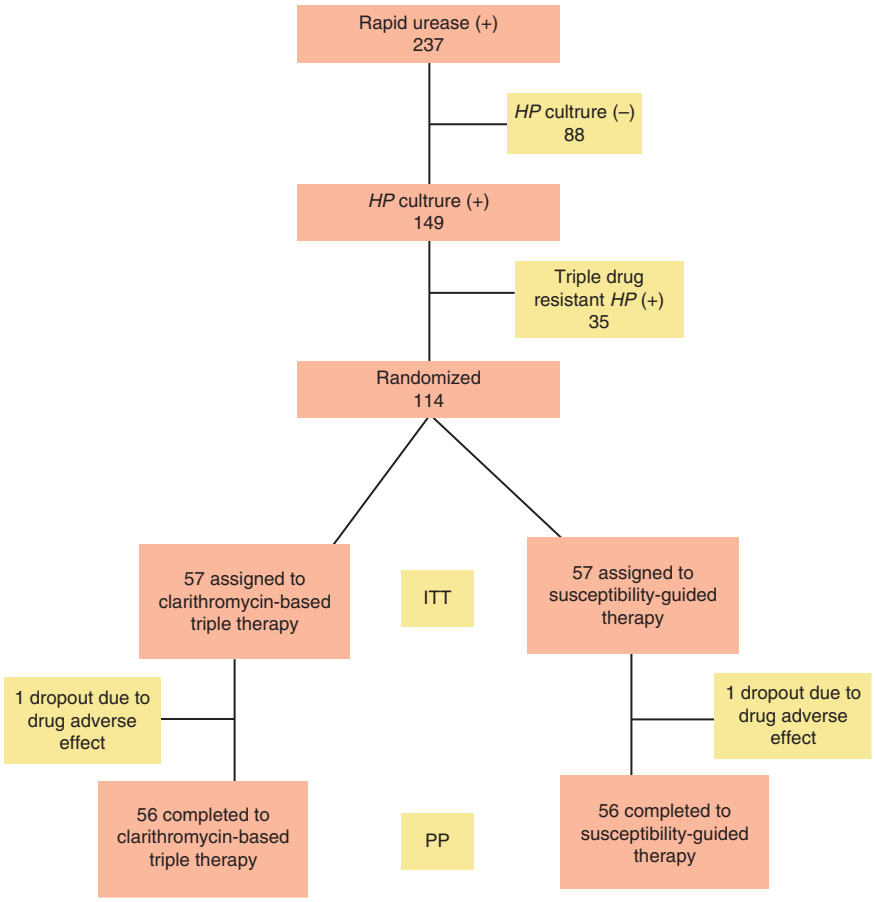


**Figure 1.** Flowchart showing entries and withdrawals from the study. *HP*, *Helicobacter pylori*; ITT, intention-to-treat analysis; PP, per-protocol analysis; triple drug resistance, resistance to clarithromycin, metronidazole, and levofloxacin.

the clarithromycin-based triple therapy group (80.0%, 95% CI = 59.7–100%, 12/15) according to PP analysis ($P < 0.001$, **Table 4**).

## DISCUSSION

This study is the first reported prospective, open-label, randomized trial for *H. pylori* eradication exclusively in patients with GEN, including adenoma and adenocarcinoma. Patients with GEN do not represent the majority of patients who require *H. pylori* eradication therapy. However, patients with GEN are one important group who will benefit from *H. pylori* eradication therapy. In addition, patients with GEN are a "good" cohort who can undergo long-term follow-up endoscopic examinations after *H. pylori* eradication. Long-term follow-up examinations will widen our knowledge about *H. pylori* infection and the clinical significance of *H. pylori* reinfection. Finally, the results for the patients with GEN can be applied to the majority of patients who require *H. pylori* eradication therapy. Thus, patients with GEN are a good model for the study of *H. pylori* infection and eradication generally.

This study is a prospective, open-label, randomized trial comparing the efficacy of pretreatment antimicrobial susceptibility-guided vs. clarithromycin-based triple therapy for *H. pylori* eradication in a region with high rates of multiple drug resistance. It showed that in both PP and intention-to-treat analyses, pretreatment antimicrobial susceptibility-guided therapy resulted in significantly higher eradication rates in comparison with clarithromycin-based triple therapy. It also confirmed that the main cause of eradication failure was antibiotic resistance. According to the Maastricht IV Consensus Report, PPI–clarithromycin-containing triple therapy should be abandoned when the clarithromycin resistance rate in the region is >15–20%. The clarithromycin resistance rate in this study appears to be close to 25% (28/114). It may be simpler and more cost effective to simply abandon clarithromycin-based first-line therapy here. Second, bismuth-containing quadruple therapies are recommended for first-line empirical treatment. Levofloxacin-containing triple therapy is recommended for second-line empirical treatment, and third-line treatment should be guided by antimicrobial susceptibility testing after failure of second-line treatment (3). This protocol has some disadvantages in regions with high rates of multiple drug resistance. First, this study shows that levofloxacin-containing triple therapy cannot be recommended for second-line therapy because the levofloxacin resistance rate (36.8%, 42/114) was higher than the clarithromycin resistance

**Table 1. Baseline clinical characteristics of the patients**

| | Clarithromycin-based triple therapy (*n*=57) | Susceptibility-guided therapy (*n*=57) | *P* value |
|---|---|---|---|
| Age (mean±s.d.), years | 61.8±9.1 | 62.3±10.5 | 0.761 |
| Gender (male/female) | 40/17 | 32/25 | 0.174 |
| *Histological type,* n *(%)* | | | 0.459 |
| Low-grade dysplasia | 17 (29.8) | 20 (35.1) | |
| High-grade dysplasia | 11 (19.3) | 12 (21.0) | |
| Differentiated EGC | 29 (50.9) | 25 (43.9) | |
| *Location of lesion* | | | 0.621 |
| Antrum, *n* (%) | 34 (59.6) | 35 (61.4) | |
| Angle, *n* (%) | 5 (8.8) | 7 (12.3) | |
| Body, *n* (%) | 16 (28.1) | 14 (24.6) | |
| Cardia, *n* (%) | 2 (3.5) | 1 (1.8) | |
| Resection specimen size (mm) | 38.1±12.9 | 39.4±11.2 | 0.588 |
| *Primary antibiotics resistance* | | | |
| Amoxicillin, *n* (%) | 5 (8.8) | 6 (10.5) | 1.000 |
| Clarithromycin, *n* (%) | 16 (28.1) | 12 (21.1) | 0.514 |
| Metronidazole, *n* (%) | 25 (43.9) | 28 (49.1) | 0.707 |
| Tetracycline, *n* (%) | 1 (1.8) | 2 (3.5) | 1.000 |
| Levofloxacin, *n* (%) | 18 (31.6) | 24 (42.1) | 0.332 |

EGC, early gastric cancer.

**Table 2. Adverse effects of first-line treatment**

| | Clarithromycin-based triple therapy (*n*=57) | Susceptibility-guided therapy (*n*=57) | *P* value |
|---|---|---|---|
| *Total,* n *(%)* | 5/57 (8.8) | 4/57 (7.0) | 1.000 |
| Abdominal pain | 1/57 (1.8) | 0/57 | |
| Nausea | 0/57 | 1/57 (1.8) | |
| Vomiting | 0/57 | 1/57 (1.8) | |
| Bitter taste | 0/57 | 1/57 (1.8) | |
| Diarrhea | 2/57 (3.5) | 1/57 (1.8) | |
| Skin rash | 1/57 (1.8) | 0/57 (0) | |
| Dizziness | 1/57 (1.8) | 0/57 (0) | |
| *Treatment regimen* | | | 0.562 |
| PAC, *n* (%) | 5/57 (8.8) | 3/45 (6.7) | |
| PAM, *n* (%) | 0 | 0/6 (0) | |
| PAL, *n* (%) | 0 | 1/6 (16.7) | |

PAC, proton pump inhibitor, amoxicillin, and clarithromycin; PAL, proton pump inhibitor, amoxicillin, and levofloxacin; PAM, proton pump inhibitor, amoxicillin, and metronidazole.

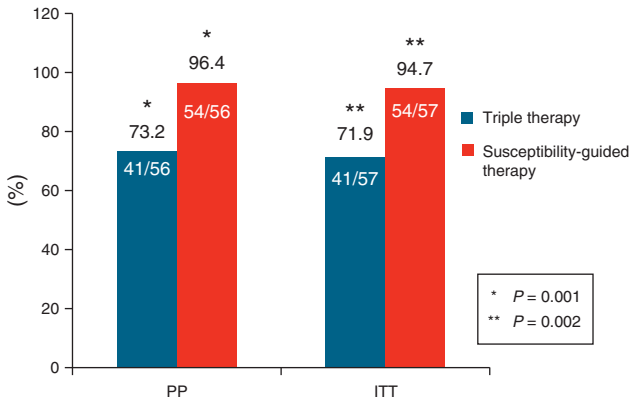


**Figure 2.** *Helicobacter pylori* eradication in the standard triple therapy group and in the susceptibility-guided therapy group after first-line treatment. ITT, intention-to-treat analysis; PP, per-protocol analysis.

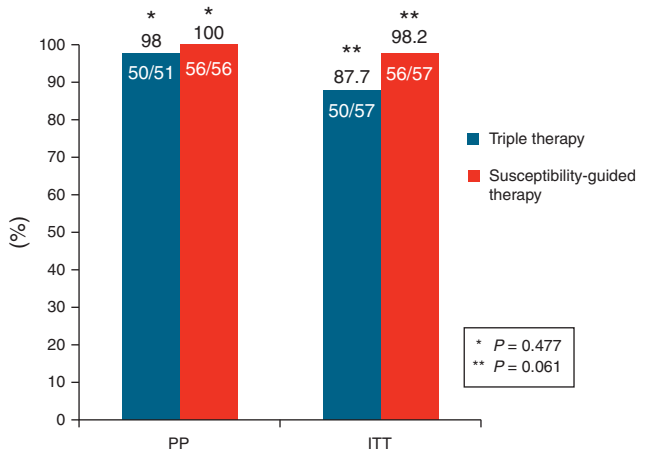


**Figure 3.** *Helicobacter pylori* eradication in the clarithromycin-based triple therapy group and in the susceptibility-guided therapy group after overall treatment. ITT, intention-to-treat analysis; PP, per-protocol analysis.

rate (24.5%, 28/114) in our region. Second, the role of antimicrobial susceptibility testing for third-line treatment might be very limited because there are few reliable drugs for third-line treatment. Third, antimicrobial resistance could be increased after first-line and second-line antibiotic use. The incidence of secondary resistance is dependent on the type of primary eradication therapy used. Fourth, it could be more difficult to get a culture of *H. pylori* after first-line and second-line treatments. Thus, our study suggests that first-line treatment should be guided by pretreatment antimicrobial susceptibility test in regions with high rates of multidrug resistance. This study also provides strong evidence for the hypothesis that initial and overall eradication failure rates can be lowered to ideal values (<5%) by pretreatment antimicrobial susceptibility-guided therapy. The ideal low rate of eradication failure by pretreatment antimicrobial susceptibility-

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guided therapy might contribute to the prevention of the emergence of antibiotic resistance, including multidrug resistance. In addition, the ideal low rate of *H. pylori* eradication failure might decrease the incidence of metachronous gastric cancer in patients with GEN.

This is the first reported study to include amoxicillin, clarithromycin, metronidazole, and levofloxacin as antibiotics used in antimicrobial susceptibility-guided therapy. Previous studies analyzed antimicrobial susceptibility using amoxicillin, metronidazole, clarithromycin, and tetracycline (25,27). A levofloxacin-based regimen (PAL) is an alternative second-line treatment, based on results obtained in recent years (32,33). However, the rapid acquisition of resistance may jeopardize its efficacy. This study included a levofloxacin susceptibility test in addition to amoxicillin, metronidazole, and clarithromycin susceptibility tests. The ideal rate of eradication (100%) was achieved with PAL when *H. pylori* strains were sensitive to levofloxacin in this study. Pretreatment levofloxacin susceptibility-guided therapy might prevent the rapid acquisition of levofloxacin resistance when using an empirical levofloxacin regimen for levofloxacin-resistant *H. pylori* strains. This study suggested that an ideal selection model of antibiotics according to antimicrobial susceptibility testing should be determined for the successful eradication of *H. pylori*. In this study, the selection of antibiotics was decided depending on antibiotic resistance; the antibiotics selected included clarithromycin, metronidazole, and levofloxacin, in that order. PAC was selected if *H. pylori* strains were sensitive to clarithromycin. In the case of resistance to clarithromycin, PAM was selected if *H. pylori* strains were sensitive to metronidazole. When *H. pylori* strains were resistant to both clarithromycin and metronidazole, PAL was used if *H. pylori* strains were sensitive to levofloxacin. According to this selection method of the regimen, a high rate of initial eradication was achieved in the susceptibility-guided therapy group, and high rates of overall eradication were achieved in both groups.

Pretreatment antimicrobial susceptibility-guided therapy has some benefits. First, clarithromycin-based regimen can still be used in areas of high clarithromycin resistance if *H. pylori* strains sensitive to clarithromycin are identified. Second, an appropriate second-line regimen can be selected if *H. pylori* can be cultured and antimicrobial susceptibility testing can be performed. Third, 1 week of treatment may be enough for successful eradication. In this study, 1 week of PAC, PAM, or PAL, according to antimicrobial susceptibility testing, were highly effective for *H. pylori* eradication. In addition, the short duration of treatment can decrease drug side effects and increase compliance.

Our study has some limitations. First, it was a single-center study. To confirm our results, larger, multicenter studies are needed. Second, the culture rate of our study was relatively low (62.8%). A more effective method should be developed to increase the culture rate. Indeed, without the development of highly effective culture method, the strategy of pretreatment susceptibility-guided antibiotic selection may be neither practical nor cost effective. An alternative approach is bismuth-containing quadruple therapies for first-line empirical treatment, and then second-line treatment should be guided by antimicrobial susceptibility testing after failure of first-line treatment. Third, we did not perform reculturing of *H. pylori* in patients with treatment failure by first-line and

**Table 3. *Helicobacter pylori* eradication failure rates in both groups after first-line treatment and overall treatment by per-protocol analysis**

| Therapy | Resistant pattern of *H. pylori* isolate Clar–Metro–Levo | Eradication failure rates, *n* (%) First-line Tx | Overall Tx |
|---|---|---|---|
| *SGT* | | | |
| PAC | S–X–X | 2/44 (4.5) | 0/44 (0) |
| PAM | R–S–X | 0/6 (0)* | 0/6 (0) |
| PAL | R–R–S | 0/6 (0)** | 0/6 (0) |
| Total | | 2/56 (3.6)*** | 0/56 (0) |
| *Triple therapy* | | | |
| PAC | S–X–X | 3/41 (7.3) | 1/41 (2.4) |
| | R–S–X | 9/12 (75.0)* | 0/8 (0) |
| | R–R–S | 3/3 (100.0)** | 0/2 (0) |
| Total | | 15/56 (26.8)*** | 1/51 (2.0) |

Clari, clarithromycin; Levo, levofloxacin; Metro, metronidazole; PAC, proton pump inhibitor, amoxicillin, and clarithromycin; PAL, proton pump inhibitor, amoxicillin, and levofloxacin; PAM, proton pump inhibitor, amoxicillin, and metronidazole; R, resistant; S, sensitive; SGT, susceptibility-guided therapy; Tx, treatment; X, sensitive or resistant.
*$P$=0.009, **$P$=0.012, ***$P$=0.001.

**Table 4. *Helicobacter pylori* eradication failure rates according to primary antibiotic resistance in both groups after first-line treatment by per-protocol analysis**

| | Total (*n*=112) | Clarithromycin-based triple therapy (*n*=56) | Susceptibility-guided therapy (*n*=56) | *P* value |
|---|---|---|---|---|
| Amoxicillin-R, *n* (%) | 2/11 (18.2) | 2/5 (40.0) | 0/6 (0) | 0.182 |
| Clarithromycin-R, *n* (%) | 12/27 (44.4) | 12/15 (80.0) | 0/12 (0) | <0.001 |
| Metronidazole-R, *n* (%) | 6/51 (11.8) | 5/24 (20.8) | 1/27 (3.7) | 0.088 |
| Tetracycline-R, *n* (%) | 0/3 (0) | 0/1 (0) | 0/2 (0) | |
| Levofloxacin-R, *n* (%) | 6/41 (14.6) | 5/18 (27.8) | 1/23 (4.3) | 0.070 |

R, resistance.

second-line treatment. However, susceptibility-guided antibiotic selection for second-line treatment had very high efficacy. Fourth, even though rifabutin-containing rescue therapy constitutes an encouraging strategy after multiple previous eradication failures with key antibiotics, such as amoxicillin, clarithromycin, metronidazole, and levofloxacin (34), we did not include rifabutin susceptibility testing in this study. Fifth, the *H. pylori* status was checked 4 weeks after the end of treatment using the $^{13}$C-urea breath test. There is the slight chance of a false negative result. If the $^{13}$C-urea breath test had been repeated a month later, some of the tests would likely be positive. Sixth, it did not state which PPI to use in the randomization envelope. This might have caused some bias to one PPI or another.

In conclusion, pretreatment antimicrobial susceptibility-guided therapy is more effective than clarithromycin-based triple therapy for *H. pylori* eradication in a region with high rates of multiple drug resistance.

## CONFLICT OF INTEREST

**Guarantor of the article:** Chang-Hwan Park, MD, PhD.

**Specific author contributions**. C.-S. Park and C.-H. Park: conception, design, analysis and interpretation of data, drafting of the manuscript, critical revision of article, and final approval given; S.-M. Lee, H.-R. Koh, and C.-H. Jun: conception, design, and analysis and interpretation of data; S.-Y. Park, W.-S. Lee, Y.-E. Joo, and H.-S. Kim: conception, design, drafting of the manuscript, and critical revision of the article; S.-K. Choi and J.-S. Rew: conception, design, analysis and interpretation of data, drafting of the manuscript, critical revision of article, and final approval given.

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**Potential competing interests**: None.

## Study Highlights

### WHAT IS CURRENT KNOWLEDGE

- ✓ *Helicobacter pylori (H. pylori)* eradication rates with clarithromycin-based triple therapy are declining.
- ✓ Antibiotic resistance, especially to clarithromycin, has been increasing, and resistance is the most important factor responsible for the recent fall in the success rates of *H. pylori* eradication treatment.

### WHAT IS NEW HERE

- ✓ The intention-to-treat eradication rates were 94.7% in the antimicrobial susceptibility-guided group and 71.9% in the clarithromycin-based triple therapy group after the initial treatment.
- ✓ In *H. pylori* with clarithromycin resistance, the eradication failure rate with first-line treatment was lower in the susceptibility-guided therapy group (0%) compared with the clarithromycin-based triple therapy group (80.0%).
- ✓ This study suggested that an ideal selection model of antibiotics according to pretreatment antimicrobial susceptibility testing should be determined for the successful eradication of *H. pylori* in a region with high rates of multiple drug resistance.

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