Title	Effects of Primary Metronidazole and Clarithromycin Resistance to Helicobacter pylori on Omeprazole, Metronidazole, and Clarithromycin Triple-Therapy Regimen in a Region with High Rates of Metronidazole Resistance
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MAJOR ARTICLE

Effects of Primary Metronidazole and Clarithromycin Resistance to *Helicobacter pylori* on Omeprazole, Metronidazole, and Clarithromycin Triple-Therapy Regimen in a Region with High Rates of Metronidazole Resistance

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The aim of this study was to investigate the effect of metronidazole resistance (MtzR) and clarithromycin resistance (ClaR) on the eradication rate for omeprazole, clarithromycin, and metronidazole triple-therapy regimen and on the development of posttherapy drug resistance in a region of high rates of MtzR. One hundred ninety-six *Helicobacter pylori* isolates were recovered from patients with duodenal ulcer, gastric ulcer, or nonulcer dyspepsia during upper endoscopy. The prevalences of MtzR, ClaR, and dual resistance were 37.8%, 13.8%, and 8.7%, respectively. The intention-to-treat eradication rates for metronidazole-susceptible (87.2% vs. 67.6%; $P = .001$) and clarithromycin-susceptible (86.4% vs. 40.7%; $P < .001$) strains were significantly higher than the rates for resistant strains. Multiple logistic regression analysis implicated younger age (<40 years old), MtzR, ClaR, and the diagnosis of nonulcer dyspepsia as independent factors that predicted treatment failure. The rates of posttreatment MtzR, ClaR, and dual resistance were 88%, 88%, and 75%, respectively. MtxR and ClaR significantly affected the success of eradication therapy. Posttreatment rates of resistance were high and were related to the presence of pretreatment antibiotic resistance.

Helicobacter pylori plays an important role in the pathogenesis of peptic ulcer disease, gastric maltoma, and adenocarcinoma of the stomach [1]. Effective antimicrobial therapy for *H. pylori* has proven to be effective treatment for peptic ulcer disease [2–5]. At the Asia–Pacific Consensus Conference on the Management of *Helicobacter pylori* Infection (Singapore), the regimens recommended included the use of proton pump inhibitor (PPI)/ranitidine bismuth citrate at a standard dose, plus 2 antibiotics (clarithromycin plus either amoxicillin or metronidazole), each given twice per day for 7 days [1]. However, metronidazole resistance to *H. pylori* is common, especially in developing countries. For example, the prevalence of *H. pylori* resistance to metronidazole is 10%–45% in the United States and Europe and 50%–90% in developing countries [6–13]. Several years ago, some of us reported that approximately one-half of the *H. pylori* strains in Hong Kong were resistant to metronidazole, and the frequency of metronidazole resistance was lower among persons with duodenal ulcer than among asymptomatic control subjects [12]. However, others have not observed

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such trends, which has raised questions concerning the generality or even reproducibility of the trends that we observed [9, 11, 13]. We are drawn to the possibility that metronidazole-resistant strains might be less virulent on average than metronidazole-susceptible strains, especially because of recent findings that most cases of clinically significant metronidazole resistance result from loss-of-function mutations in 1 gene (moderate resistance) or several genes (high resistance) that encode a cellular nitroreductase, which converts metronidazole from a harmless prodrug to bactericidal agent [14, 15]. It is attractive to imagine that the potential metabolic changes, even though obviously not lethal to *H. pylori* (given the high level of metronidazole resistance), might decrease the vigor of its growth and, thereby, its virulence [15]. Studies of the effect of metronidazole resistance on the efficacy of antimicrobial treatment for *H. pylori* infection have shown that the eradication rate is ~90% for susceptible strains but <75% for resistant strains [16–18]. These studies were summarized by a meta-analysis, which found that the effect of nitroimidazole resistance on the efficacy of nitroimidazole-containing anti–*H. pylori* regimens was determined by the treatment duration and the components of the regimen [19].

Pretreatment clarithromycin resistance is one of the most important factors for determining the efficacy of *H. pylori* eradication therapy. It decreases the eradication rate by an average of 55%, according to a meta-analysis [20]. Moreover, the failure of a clarithromycin-based regimen may lead to the development of secondary clarithromycin resistance. In a large, multinational, multicenter, randomized clinical trial that assessed the efficacy of PPI-based triple-therapy regimen for the treatment of *H. pylori* infection [21], secondary resistance to clarithromycin occurred in strains recovered from 12 (11.4%) of 105 patients after treatment failure with a clarithromycin-based regimen [22]. Others have reported that the secondary clarithromycin-resistance rate after receipt of amoxicillin-clarithromycin-omeprazole triple-therapy for 1 week was ~23% [23].

In the present study, we have examined the impact of pretreatment metronidazole resistance and clarithromycin resistance on the efficacy of omeprazole-clarithromycin-metronidazole triple-therapy in a region with a high prevalence of metronidazole resistance. The study aimed to find out (1) whether the prevalence of metronidazole and clarithromycin resistance correlates with clinical manifestation, (2) whether the eradication rate depends on antibiotic resistance and/or other risk factors, and (3) the prevalence of posttreatment antibiotic resistance after failure of eradication.

METHODS

Patient population. Consecutive patients referred to the endoscopy unit of the Department of Medicine, Queen Mary Hospital, University of Hong Kong (Hong Kong, China), for the investigation of dyspepsia were considered for study recruitment. Dyspepsia was defined as persistent or recurrent upper abdominal pain or discomfort during the previous 3-month period, in accordance with the Rome criteria for dyspepsia [24]. Informed written consent was obtained from all patients who participated in the study. Duodenal ulcer and gastric ulcer were determined endoscopically and defined as a break in the mucosa of ⩾3 mm in diameter. Nonulcer dyspepsia was defined as no active lesions found by endoscopy or any lesions suggestive of a previous ulcer, such as an ulcer scar, a deformity, or a mucosal irregularity, and no past history of peptic ulcer diseases. Inclusion criteria included age of 18–80 years and demonstrated *H. pylori* infection. *H. pylori* infection was determined by ⩾2 positive results of a rapid urease test (RUT), a histological test, and/or a ^{13}C-urea breath test (^{13}C-UBT) and positive *H. pylori* culture results. Exclusion criteria included presence of severe concomitant illness, active gastrointestinal bleeding, or histologically proven gastric cancer; receipt of aspirin, other nonsteroidal anti-inflammatory drugs (NSAIDs), antibiotics, H_2 receptor blockers, bismuth, or PPIs in the preceding 4 weeks; and history of eradication of *H. pylori* or previous gastric surgery. This study was approved by the ethics committee of the University of Hong Kong.

Gastric biopsies and histological examination. During upper endoscopy, 3 antral biopsy and 1 corpus biopsy specimens were obtained. One antral biopsy specimen was used for the RUT, one was used for *H. pylori* culture, and the rest were sent for histological examination for *H. pylori* by hematoxylin-eosin and Giemsa staining. *H. pylori* was identified by its curved-shaped morphology, location on the epithelial cell surface (within the gastric pits or in the overlying mucus layer), and positive results of Giemsa staining. Additional ulcer-site biopsy specimens from 4 quadrants were obtained from all patients with gastric ulcer. Specimens were examined by experienced pathologists who were blinded to all clinical information, including the RUT results. In this study, diagnosis of *H. pylori* infection required ⩾2 positive results of the 3 tests (RUT, histological examination, and ^{13}C-UBT). This approach has been validated at our health care center before with an accuracy of 100% [25]. All patients included in this study had ⩾2 positive results for the 3 indirect tests and a positive *H. pylori* culture result.

Culture and antibiotic resistance testing. Antral biopsy specimens were obtained during upper endoscopy and transported to the laboratory immediately. *H. pylori* was cultured from gastric biopsy specimens on selective media (Columbia agar with 7% horse blood and *H. pylori*–selective supplement; Oxoid) under microaerophilic conditions produced by a gas-generating system (CampyGen; Oxoid) for 3–6 days. *H. pylori* was confirmed by Gram staining and by positive urease,

Table 1. Demographic characteristics of study patients and week 6 *Helicobacter pylori* eradication rates.

Variable	Patients with available metronidazole susceptibility data (n = 196)		Patients with available clarithromycin susceptibility data (n = 196)	
	MtzS isolates (n = 122)	MtzR isolates (n = 74)	ClaS isolates (n = 169)	ClaR isolates (n = 27)
Age, mean years	50.2	47.5	49.9	44.5
Sex, no. of patients				
Male	57	32	81	8
Female	65	42	88	19
Diagnosis				
Nonulcer dyspepsia (n = 104)	61	43	87	17
Duodenal ulcer (n = 83)	56	27	74	9
Gastric ulcer (n = 9)	5	4	8	1
H. pylori eradication rate, *n/N* (%)				
ITT analysis	107/122 (87.7)[a]	50/74 (67.6)	146/169 (86.4)[b]	11/27 (40.7)
PP analysis	107/120 (89.2)[a]	50/70 (71.4)	146/165 (88.5)[b]	11/25 (44.0)

NOTE. ClaR, clarithromycin-resistant; ClaS, clarithromycin-susceptible; ITT, intention-to-treat; MtzR, metronidazole-resistant; MtzS, metronidazole-susceptible; PP, per protocol.

[a] $P < .01$, compared with MtzR strains.

[b] $P < .001$, compared with ClaR strains.

oxidase, and catalase test results. Metronidazole and clarithromycin susceptibility testing was performed using the Etest (AB Biodisk). Metronidazole resistance was defined as an MIC of >8 mg/L. Clarithromycin resistance was defined as an MIC of >2 mg/L. Etest results were validated using the agar dilution method in our laboratory. Agreement between Etest and agar dilution results was determined by error-rate bounded analysis to be 95.4% for metronidazole and 100% for clarithromycin [26].

^{13}C-UBT. A ^{13}C-UBT was performed for all patients using 75 mg ^{13}C-urea and analyzed by a mass spectrometer designed mainly for ^{13}C-UBT analysis. In brief, patient fasted for 4 h before the test. No test meal was given, and a predose breath sample was obtained. Seventy-five milligrams of ^{13}C-urea powder dissolved in 50 mL of water was given orally. The second breath sample was obtained 30 min after the dose. The cutoff value used was 5%. All patients were kept in a sitting position during the whole testing period. Samples were analyzed by the purpose-built isotope ratio mass spectrometer. This protocol has been validated in our center and has a sensitivity and a specificity of 96.5% and 97.7%, respectively [27].

Treatment of* H. pylori *infection and outcome. All patients received a standard 1-week course of triple-therapy containing omeprazole (20 mg b.i.d.), clarithromycin (500 mg b.i.d.), and metronidazole (400 mg b.i.d.). Endoscopy (RUT, histological examination, and culture) and ^{13}C-UBT were repeated 6 weeks after completion of drug treatment. Successful eradication was indicated if the results of RUT, histological examination, culture, and ^{13}C-UBT were all negative.

Statistical analysis. Statistical tests used included the χ^2 test, Fisher's exact test, Student's t test, and the Mann-Whitney U test for data with skewed distribution. A P value of $\leq .05$ was considered statistically significant. All P values were 2-sided. The intention-to-treat (ITT) analysis included all patients who had taken ≥ 1 tablet of the drugs. In the per-protocol (PP) analysis, patients with poor drug compliance (<75% intake of doses of any study drugs) and patients who refused follow-up were excluded. Multiple logistic regression analysis was performed to determine the factors (age of <40 years, sex, metronidazole resistance, clarithromycin resistance, and diagnosis of nonulcer dyspepsia) associated with successful eradication of *H. pylori*.

RESULTS

Eighty-three patients with duodenal ulcers, 104 patients with nonulcer dyspepsia, and 9 patients with gastric ulcers who satisfied the inclusion and exclusion criteria were recruited (table 1). There were 89 men and 107 women, with a mean age of 49.2 years (range, 19–78 years). There was no age difference between men and women (49.0 years vs. 49.4 years, respectively; $P = .85$). Most (99.5%) of the patients were ethnic Chinese; 1 patient was Indian. There was no age difference between the duodenal ulcer, nonulcer dyspepsia, and gastric ulcer groups,

but there were significantly more women in the nonulcer dyspepsia group (62%) than in the duodenal ulcer group (45%; $P = .021$).

Pretreatment* H. pylori *culture results. Of the 196 *H. pylori* strains isolated, 74 (37.8%) were metronidazole resistant. The mean age of patients who were infected with metronidazole-resistant strains was similar to the mean age of those who were not (47.5 years vs. 50.2 years, respectively; $P = .21$). There was no statistical difference in the prevalence of metronidazole resistance between men and women from all age groups. The overall prevalence of metronidazole resistance was similar between men (32 [36%] of 89) and women (42 [39%] of 107; $P = .64$). The prevalence of metronidazole resistance was similar between patients with nonulcer dyspepsia (43 [41%] of 104) and those with duodenal ulcers (27 [33%] of 83; $P = .43$).

Of the 196 *H. pylori* strains isolated, 27 (13.8%) were clarithromycin resistant. The mean age of patients who were infected with clarithromycin-resistant strains was similar to the mean age of those who were not (44.5 years vs. 49.9 years, respectively; $P = .08$). There was no statistical difference in the prevalence of clarithromycin resistance between the men and women of all age groups. The overall prevalence of clarithromycin resistance among women (19 [17.8%] of 107) was not significantly different from that among men (8 [9.0%] of 89; $P = .08$). The prevalence of clarithromycin resistance was similar between patients with nonulcer dyspepsia (9 [11.7%] of 77) and those with duodenal ulcers (17 [15.5%] of 110; $P = .60$). The prevalence of metronidazole resistance (4 [44.4%] of 9) and clarithromycin resistance (1 [11.1%] of 9) among patients with gastric ulcers was similar to that for patients with nonulcer dyspepsia and patients with duodenal ulcer. Dual resistance to metronidazole and clarithromycin was found in 17 (8.7%) of the 196 patients (figure 1).

Effect of age. For patients aged 19–49 years, the prevalence of metronidazole resistance (as determined by Etest) was 42%–45% (figure 2). The rate decreased to ~30% for patients aged ⩾50 years (46 [44%] of 105 vs. 28 [31%] of 91 patients; $P = .06$), but the difference was not statistically significant. In contrast, the rate of clarithromycin resistance was 26%–29% for patients aged 19–39 years and decreased significantly to 6%–13% for patients aged ⩾40 years (14 [28%] of 50 vs. 13 [9%] of 146 patients; $P = .001$; figure 2).

MIC distribution. The distribution of metronidazole MIC values is* shown in figure 3. Among patients infected with metronidazole-resistant strains, there was no difference in the mean MIC value between patients with successful eradication versus patients for whom eradication failed (159 mg/L vs. 140 mg/L, respectively; $P = .53$)—that is, the MIC value did not matter once it became >8 mg/L. Furthermore, among patients infected with metronidazole-resistant strains, the eradication rate was similar between patients with high metronidazole resistance values (MIC, ⩾256 mg/L) and patients with low metronidazole resistance values (MIC, <256 mg/L; 67.6% vs. 75%, respectively; $P = .496$). The MIC values for clarithromycin are shown in figure 4 and had a bimodal distribution pattern.

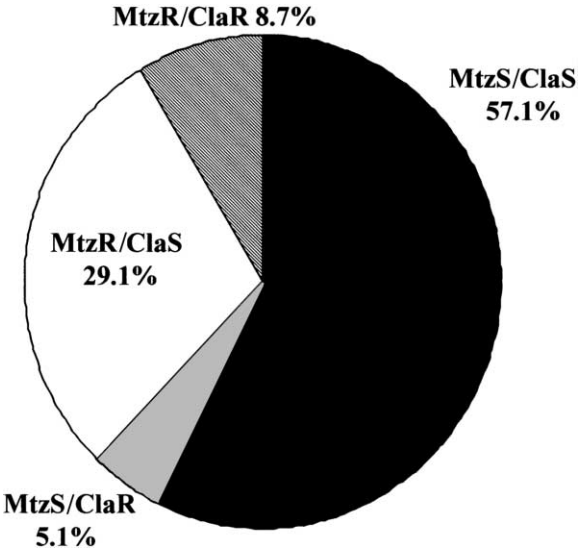

Figure 1. Prevalence of metronidazole susceptibility (MtzS) and clarithromycin susceptibility (ClaS) among 196 *Helicobacter pylori* isolates. ClaR, clarithromycin resistance; MtzR, metronidazole resistance.

Factors affecting eradication rates and the development of posteradication resistance. Six patients refused the week 6 endoscopic examination or were lost to follow-up and were excluded from PP analysis. No patient was excluded because of poor drug compliance (i.e., intake of <75% of doses). There were no hospitalizations or deaths related to treatment. *H. pylori* eradication failed in 33 patients. ITT and PP eradication rates were 80.1% (157 of 196 patients included in the ITT analysis) and 82.6% (157 of 190 patients included in the PP analysis), respectively. All patients with eradicated infection had concordant *H. pylori* test results.

For the 33 patients for whom eradication failed, 20 had concordant *H. pylori* test results (i.e., positive results of RUT, histological examination, culture, and ^{13}C-UBT), 10 had negative culture results only, and 3 had negative results of RUT and histological examination only. The *H. pylori* eradication rates determined by ITT and PP analyses were significantly higher among metronidazole-susceptible strains (ITT analysis, 87.7%; PP analysis, 89.2%) than among metronidazole-resistant strains (ITT analysis, 67.6%; PP analysis, 71.4%) ($P = .001$ and $P = .002$, respectively). Similarly, the *H. pylori* eradication rates determined by ITT and PP analyses were higher among clarithromycin-susceptible strains (ITT analysis, 86.4%; PP analysis, 88.5%) than among clarithromycin-resistant strains (ITT analysis, 40.7%; PP analysis, 44%) ($P < .001$ and $P < .001$, respectively). The ITT eradication rate was signifi-

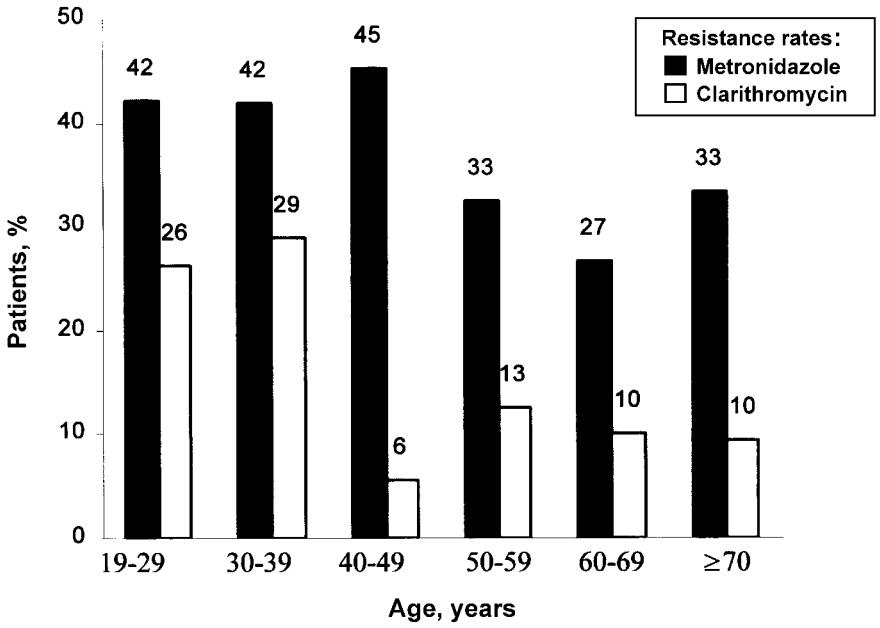

Figure 2. Prevalence of metronidazole and clarithromycin resistance in relation to age

cantly higher in the duodenal ulcer group than in the nonulcer dyspepsia group (88% vs. 75%; $P = .026$).

Patients for whom *H. pylori* eradication failed were significantly younger than were patients with successful eradication (43 vs. 50 years old; $P = .011$). Furthermore, the eradication rate was significantly lower among patients aged <40 years than among patients aged ⩾40 years (63% vs. 87%; $P < .001$). On multiple logistic regression analysis, younger age (<40 years; OR, 3.25; 95% CI, 1.26–8.38; $P = .015$), metronidazole resistance (OR, 3.04; 95% CI, 1.21–7.61; $P = .018$), clarithromycin resistance (OR, 5.78; 95% CI, 1.98–16.9; $P = .001$), and the diagnosis of nonulcer dyspepsia (OR, 2.79; 95% CI, 1.03–7.60; $P = .044$) were independent factors for treatment failure.

Week 6 *H. pylori* culture results were available for 24 of the 33 patients for whom eradication of *H. pylori* failed. The prevalences of posttreatment metronidazole resistance, clarithromycin resistance, and dual resistance were 88% (21 of 24 patients), 88% (21 of 24), and 75% (18 of 24), respectively. Pretreatment metronidazole resistance was present in 14 (67%) of 21 patients with posttreatment metronidazole resistance, and pretreatment clarithromycin resistance was present in 10 (48%) of 21 patients with posttreatment clarithromycin resistance. Month 12 *H. pylori* data (from ^{13}C-UBT) were available for 101 patients in which *H. pylori* had been eradicated; of these patients, only 1 (1%) had positive results at month 12. This patient declined further endoscopic examination.

DISCUSSION

The present study showed that the prevalence of metronidazole-resistant strains was similar between patients with nonulcer dyspepsia and those with duodenal ulcers, and the prevalence was also similar between men and women. The prevalence of metronidazole-resistant strains was lower among patients aged ⩾50 years old. This was different from our previous report [12], in which the frequency of metronidazole resistance (as measured by the disk diffusion method) was lower among persons with duodenal ulcers than among asymptomatic control subjects. Furthermore, the number of culture-positive cases in the previous study was only 69, and the culture-positive women were significantly older than culture-positive men (59.1 vs. 45.8 years; $P = .008$). These 2 differences were resolved in the present study, in which the age distribution was similar between men and women, and the higher number of culture-positive cases may have theoretically decreased the bias because of a small sample size. Metronidazole and clarithromycin susceptibility in this study were measured by Etest, which is highly reliable for testing the antimicrobial susceptibility of *H. pylori* and has been validated in our population [26, 28]. Therefore, we believe that the present report is a better reflection of the clinical situation in Hong Kong.

A higher prevalence of clarithromycin-resistant strains was observed in patients aged <40 years. The exact reason is unclear, but this may be a contributing factor to the lower eradication

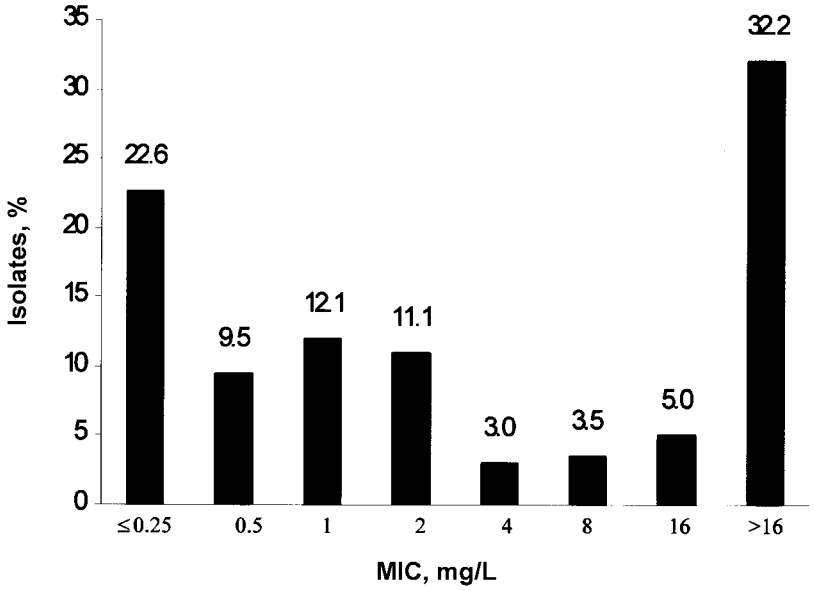

Figure 3. Distribution of MICs of metronidazole for 196 *Helicobacter pylori* isolates

rate observed in patients aged <40 years. A study from France of 2751 patients who received *H. pylori* eradication therapy found that old age, short duration of therapy (i.e., <10 days), and nonulcer dyspepsia were risk factors for treatment failure [29]. In a meta-analysis of short (7-day) versus long (14-day) therapy with a PPI, clarithromycin, and either metronidazole or amoxicillin for the treatment of *H. pylori* infection, an improvement in cure rates of 7%–9% was observed among recipients of the 14-day regimen. However, the ability of a longer duration of therapy to overcome clarithromycin resistance has not been well established [30]. A recent study from Australia also failed to show a beneficial effect associated with 14 days of bismuth triple-therapy over 7-day PPI triple-therapy in a population with a high rate of metronidazole resistance [31].

The ITT *H. pylori* eradication rate was 20.1% higher among metronidazole-susceptible strains than among metronidazole-resistant strains ($P = .001$). The observation of a higher eradication rate for metronidazole-susceptible strains has been well reported [16–19]. However, there have been very few reports on the correlation between the level of metronidazole resistance and the eradication rate. Mégraud et al. [22] performed large-scale antimicrobial susceptibility testing of *H. pylori* recovered

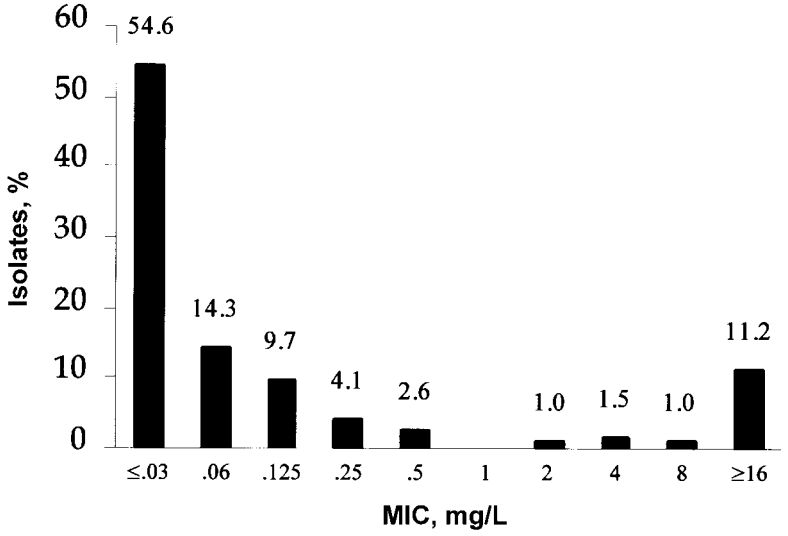

Figure 4. Distribution of MICs of clarithromycin for 196 *Helicobacter pylori* isolates

from patients with duodenal ulcers. MICs of metronidazole of 128 mg/L, 64 mg/L, and 32 mg/L were responsible for a significantly higher risk of failure than was an MIC of 16 mg/L. In contrast, there was no difference in the eradication rate between patients with high-level metronidazole resistance (MIC, $\geq$256 mg/L) and those with low-level metronidazole resistance (MIC, >8 mg/L and <256 mg/L; 67.6% vs. 75%; $P = .496$) in our study. Jeong et al. [15] suggested that high-level metronidazole resistance is due to sequential inactivation of *rdxA* and *frxA* nitroreductase genes and possibly other unknown genes. A possible side effect of these multiple mutations is a decrease in survival fitness of the organism. This may partially explain the findings of our study.

The ITT eradication rate was 45% lower among clarithromycin-resistant strains and correlated well with previous data. Furthermore, 52% of patients for whom clarithromycin-containing eradication therapy failed developed posttreatment resistance, and our results predict that a poor outcome would have occurred if clarithromycin had been readministered for treatment failure [32].

By multiple logistic regression analysis, younger age, metronidazole resistance, clarithromycin resistance, and diagnosis of nonulcer dyspepsia were significant factors for treatment failure. As mentioned above, patients of young age had a higher prevalence of metronidazole and clarithromycin resistance in our cohort. A recent study from the United States suggested an association between metronidazole resistance rate and young age, but older age was significantly associated with clarithromycin resistance [33]. The reason for the opposite trend of clarithromycin resistance in Chinese persons is uncertain but may be associated with the genetic heterogeneity of *H. pylori* strains or a difference in antibiotic prescription patterns. Interestingly, the eradication rate among patients with nonulcer dyspepsia was 13% lower than the rate among patients with duodenal ulcers. This finding has been reported previously [34–37]. The reason was unknown but may be related to differences in *H. pylori* strains harbored by these infected individuals. It has been shown that strains positive for *cagA* (the cytotoxin-associated gene) and *vacA* (vacuolating cytotoxin) were more commonly found in patients with peptic ulcer disease. Cure rates seem to be higher for patients with *cagA*+/*vacA* s1 (signal sequence) *H. pylori* strains, which is consistent with the higher cure rate observed among patients with ulcers than those with nonulcer dyspepsia [38]. Because the same treatment regimen was used, and because almost all subjects were ethnic Chinese, the explanation is likely to be related to the difference in *H. pylori* strains between patients with nonulcer dyspepsia and those with duodenal ulcers. Analyses of these *H. pylori* strains are currently under way.

In conclusion, we have shown that metronidazole resistance, clarithromycin resistance, younger age, and diagnosis of nonulcer dyspepsia significantly affect the success of eradication therapy in an area with a high rate of metronidazole resistance. Rates of posttreatment resistance were high, and this resistance was related to the presence of pretreatment antibiotic resistance.

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