

# Antibiotic Resistance of *Helicobacter pylori* and Eradication Rate in Japanese Pediatric Patients

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## Abstract

*Helicobacter pylori* (*H. pylori*) eradication rates achieved with a proton pump inhibitor (PPI), amoxicillin and clarithromycin have recently decreased to about 75% because of the increase in clarithromycin resistance in Japan. In the present study, *H. pylori* resistance rates against clarithromycin, amoxicillin and metronidazole were investigated in pediatric patients and eradication rates were evaluated when tailored antibiotics regimens based on antibiotic sensitivity data were used. We isolated *H. pylori* endoscopically from 77 pediatric patients suffering from abdominal symptoms. The susceptibility tests of *H. pylori* strains to clarithromycin, amoxicillin and metronidazole were examined and eradication therapy was tailored using the appropriate antibiotics. Seventy-seven patients were treated with a mean age of  $12.16 \pm 3.34$  years (range, 4.92 - 19.75) consisting of 40 males and 37 females. The average resistance rates between 1998 and 2016 to clarithromycin, amoxicillin and metronidazole were 54.5% (42 of 77), 6.5% (5 of 77) and 5.2% (4 of 77) respectively. The prevalence of clarithromycin resistance increased significantly over time to reach 88.9% by 2013-2016. Successful eradication rates using tailored antibiotic treatment was 93.8% (61 of 65). Clarithromycin-based eradication therapy rate reached 92.6% against clarithromycin-sensitive strains. Metronidazole-based initial eradication therapy also had a high successful rate (97.0%) to clarithromycin-resistant strains. Although high rates of clarithromycin resistant *H. pylori* reaching about 90% were observed in Japanese children, tailored eradication therapy using the appropriate antibiotic agents were highly successful. *H. pylori* sensitivity testing and eradication therapy with appropriate antibacterial agents may contribute to accomplishment of high initial eradication rates and consequently reducing the incidence of developing gastric cancer.

## Keywords

Resistance, Eradication Rate, Susceptibility Test, Clarithromycin, Metronidazole

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## 1. Introduction

*Helicobacter pylori* (*H. pylori*) is a microaerophilic Gram-negative spiral bacterial pathogen that resides in the human stomach in close association with the gastric epithelium. *H. pylori* is one of the most prevalent global pathogens and colonizes an estimated 50% of the world's population [1]. *H. pylori* infection is generally acquired in childhood and typically persists for life. *H. pylori* infection induces chronic gastric mucosal inflammation that contributes to the development of gastric cancer. Additionally, many strains of *H. pylori* produce the CagA oncoprotein [2]. In 1994, *H. pylori* was declared a class I definite human carcinogen by the WHO [3] and this classification was confirmed in 2012 [4]. Eradication therapy against *H. pylori* infection can lead to significant improvement of gastric atrophy and may prevent the development of gastric cancer [5]-[10]. However, successful rates of eradication therapy are declining and antibiotic resistance is thought to be a main cause of eradication failure [11] [12] [13]. In this study, we investigated the *H. pylori* resistance rate against clarithromycin (CAM), amoxicillin (AMPC) and metronidazole (MNZ) in pediatric patients in Japan, and evaluated eradication rates with tailored antibiotics regimens that were designed based on the results of antibiotic susceptibility tests.

## 2. Methods

### 2.1. Patients and Samples

Patients in this study were evaluated and treated at Juntendo University Hospital between 1998 and 2016. Seventy-seven patients suffering from abdominal symptoms such as epigastralgia, nausea and vomiting and from whom *H. pylori* could be isolated were included in this study. The Gastric biopsy samples for bacterial culture were taken endoscopically from both the antrum and the corpus of the stomach when evidence of gastritis or gastroduodenal ulcer was detected by esophagogastroduodenoscopy (EGDs). All patients had no history of *H. pylori* eradication therapy. A signed informed consent was obtained from the parents of all children before assessment with EDGs.

### 2.2. Susceptibility Testing

Antibiotic sensitivity of *H. pylori* isolates to CAM, AMPC and MNZ were examined using the dilution method with Mueller-Hinton agar plates containing 5% horse blood. The minimal inhibitory concentration (MIC) breakpoints were defined as follows;  $\geq 1$   $\mu\text{g/mL}$  for CAM [14],  $>0.125$   $\mu\text{g/mL}$  for AMPC [15] and  $>8$   $\mu\text{g/mL}$  for MNZ [15].

### 2.3. Eradication Therapy

Patients infected with CAM-sensitive strains were administered the CAM-based regimen for 7 - 14 days, which consisted of a proton pump inhibitor (PPI), AMPC (50 mg/kg per day) and CAM (20 mg/kg per day). Patients infected with CAM-resistant strains were administered the MNZ-based regimen for 7 - 14 days, which consisted of PPI, AMPC (50 mg/kg per day) and MNZ (20 mg/kg per day). We used levofloxacin for the patients with MNZ-resistant strains and minocycline for the patients with AMPC-resistant strains. *H. pylori* eradication was confirmed by <sup>13</sup>C-urea breath test or a monoclonal stool antigen test using an enzyme-linked immuno-sorbent assay performed at least 8 weeks after treatment.

### 2.4. Statistical Analysis

Statistical analyses were performed using the chi-square test to evaluate the difference between proportions. A p-value of less than 0.05 was accepted as statistically significant.

### 2.5. Conflicts of Interest

No specific industry was linked to our study. The authors declare no conflicts of interest.

## 3. Results

### 3.1. Patient Characteristics

*H. pylori* was isolated from 77 patients with a mean age of  $12.16 \pm 3.34$  years (range, 4.92 - 19.75) consisted of 40 males and 37 females. The characteristics of these 77 patients are presented in **Table 1**. Antibiotic sensitivity testing was performed for CAM, AMPC and MNZ. A subset of 65 patients then underwent eradication therapy using an antibiotics regimen custom tailored for each patient based on the results of the antibiotic sensitivity tests performed on the *H. pylori* isolated from their own stomach.

### 3.2. Resistance Rate to Antibiotic Agents

The average resistance rates to CAM, AMPC and MNZ were 54.5% (42 of 77), 6.5% (5 of 77) and 5.2% (4 of 77) respectively (**Table 2**). However, when patient isolates are grouped into blocks of 4 to 5 years, the increased incidence of CAM-resistant strains becomes more obvious (**Table 3**). The prevalence of CAM

**Table 1.** Characteristics of 77 pediatric patients.

	Number of patients	Mean age and range (year)
Total	77	12.16 ± 3.34 (4.92 - 19.75)
Gender		
Male	40	12.49 ± 3.29 (4.92 - 19.75)
Female	37	11.80 ± 3.39 (5.00 - 17.17)

**Table 2.** Antibiotic resistance rate.

	Number of patients	Mean age and range (year)
Total	77	12.16 ± 3.34 (4.92 - 19.75)
CAM	42 (54.5%)	11.55 ± 3.27 (4.92 - 16.33)
AMPC	5 (6.5%)	12.35 ± 3.01 (7.67 - 15.50)
MNZ	4 (5.2%)	13.92 ± 2.59 (11.33 - 17.17)

Clarithromycin, CAM; amoxicillin, AMPC; metronidazole, MNZ.

**Table 3.** Alteration of antibiotic resistance rate.

	Number of patients	Number of CAM resistance	Number of AMPC resistance	Number of MNZ resistance
1998-2002	14	3 (21.4%)	0 (0%)	2 (14.3%)
2003-2007	27	15 (55.6%)	0 (0%)	1 (3.7%)
2008-2012	18	8 (44.4%)	1 (5.6%)	1 (5.6%)
2013-2016	18	16 (88.9%)	4 (22.2%)	0 (0%)

Clarithromycin, CAM; amoxicillin, AMPC; metronidazole, MNZ.

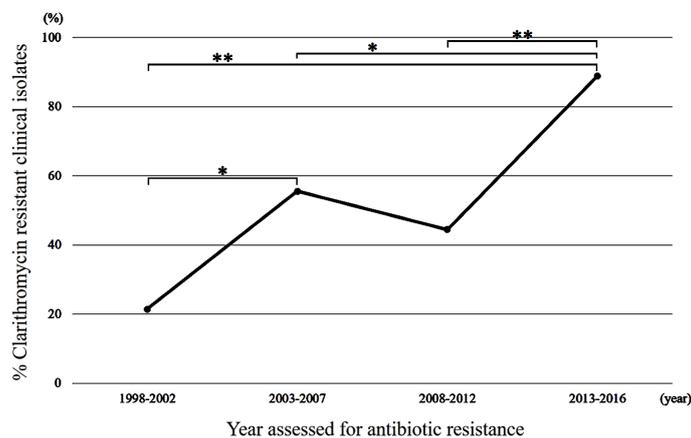
resistant strains increased significantly over time as illustrated **Figure 1**. The percentage of CAM resistant strains more than doubled between the 1998-2002 and 2003-2007 time blocks ( $P < 0.05$ ). The prevalence in the most recent block, 2013 to 2016 was 88.9%, significantly higher than the other periods. The prevalence of AMPC and MNZ resistance are showed in **Figure 2** and **Figure 3**, respectively. A small increase in AMPC resistance is observed, maximizing 22.2% in the most recent time frame (2013-2016), but this increase was not found to be significant. MNZ resistance displayed no significant changes over time.

### 3.3. Eradication Rate

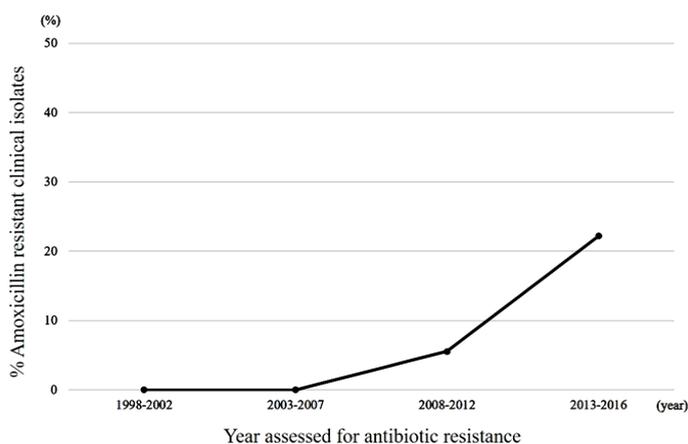
We performed tailored eradication therapy for 65 patients based upon the results of our antibiotic sensitivity testing (**Table 4**). Twelve patients that received eradication therapy in other hospitals or in whom the results of eradication therapy were unknown were excluded. The overall initial eradication success rate using tailored therapy was 93.8% (61 of 65). The eradication rate among patients infected with CAM-sensitive strains and using the CAM-based regimen was 92.6% (25 of 27). The eradication rate among patients infected with CAM-resistant strains and employing the MNZ-based regimen was 97.0% (32 of 33). Side effects were observed in 10 patients (15.4%). The most common side effect was diarrhea in 5 cases (7.7%). No severe side effect required discontinuation of eradication therapy or hospitalization.

## 4. Discussion

Although *H. pylori* infection is the main risk factor for developing gastric cancer and gastric or duodenalulcer, success in eradication therapy may lead to pre-

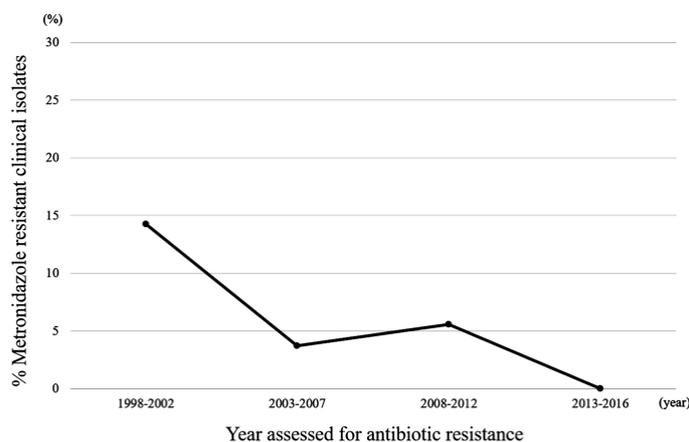


**Figure 1.** Incidence of clarithromycin resistant *H. pylori* in pediatric patients over time (Percentage of clarithromycin resistant clinical isolates of *H. pylori* from pediatric patients assessed from 1998-2016 as determined by in vitro minimal inhibitory concentration (MIC) breakpoints on Mueller-Hinton blood agar plates. Significant differences between year groups were determined by chi-square analysis (\* $P < 0.05$ , \*\* $P < 0.01$ ).



**Figure 2.** Incidence of amoxicillin resistant *H. pylori* in pediatric patients over time (Percentage of amoxicillin resistant clinical isolates of *H. pylori* from pediatric patients assessed from 1998-2016 as determined by in vitro minimal inhibitory concentration (MIC) breakpoints on Mueller-Hinton blood agar plates. Significant differences between year groups were determined by chi-square analysis.).

vention of these diseases [16] [17] [18]. In addition, eradication therapy for *H. pylori* infection is important for prevention of the spread of infection and may contribute to the reduction in medical expenditure on gastric diseases in the future. *H. pylori* eradication therapy results in improvement in gastric mucosal inflammation and atrophy, and prevention of progression of intestinal metaplasia [19]-[28], and reduces the incidence of gastric cancer [5]-[10]. On the other hand, eradication therapy does not prevent the development of metachronous gastric cancer completely [29]. Moreover, the risk of gastric cancer rises with the progress of atrophy [30] [31] [32], and Kato *et al.* [33] showed that gastric atrophy could develop in Japanese children of an average age of 12 years with *H. pylori* infection. In addition, we have shown significant over expression of several



**Figure 3.** Incidence of metronidazole resistant *H. pylori* in pediatric patients over time (Percentage of metronidazole resistant clinical isolates of *H. pylori* from pediatric patients assessed from 1998-2016 as determined by in vitro minimal inhibitory concentration (MIC) breakpoints on Mueller-Hinton blood agar plates. Significant differences between year groups were determined by chi-square analysis.).

**Table 4.** Eradication rates of each resistant *H. pylori* strains.

	Number of patients	Eradication rate
Total	65	93.8%
Mean age (y): 11.82 ± 3.18		
Range (y): 4.92 - 19.25		
CAM: S, AMPC: S, MNZ: S (PPI + AMPC + CAM therapy)	27	92.6%
CAM: R, AMPC: S, MNZ: S (PPI + AMPC + MNZ therapy)	31	97.0%
CAM: R, AMPC: S, MNZ: R (PPI + AMPC + LVFX therapy)	1	100%
CAM: R, AMPC: R, MNZ: S (PPI + MINO + MNZ therapy)	3	75.0%

Year, y; Sensitive, S; Resistant, R; Clarithromycin, CAM; Amoxicillin, AMPC; Metronidazole, MNZ; Levofloxacin, LVFX; Minocycline, MINO.

carcinogenic molecules in the *H. pylori* infected gastric mucosa in childhood [34]. Since eradication therapy prior to the severe expansion of atrophy was shown to be significantly beneficial to prevent gastric cancer [18] [31] [33] [35], early eradication therapy especially from childhood may contribute to reduction of the incidence of gastric cancer. However, we also need careful follow-up endoscopy over the long term following *H. pylori* eradication to exclude the development of metachronous gastric cancer.

Antibiotic resistance is an important factor in treatment success. Hashinaga *et al.* showed the tendency for an increase in resistance rates of *H. pylori* to CAM in adult patients in Japan (18.9% in 2002, 21.1% in 2003, 31% from 2010 to 2011

and 38.5% from 2013 to 2014) [36]. Similar high resistance rates to CAM have also been documented in children in Japan, and increasing rate of primary CAM resistance has been reported. The prevalence of CAM resistance in young patients ranges from 29% - 43.4% in Japan [37] [38] [39] [40] [41]. Kato *et al.* showed increasing rates of CAM resistance from 29% to 36.1% with the extension of the period for 5 years [37] [38]. Okamura *et al.* reported significantly higher CAM resistance rates in 2012-2013 in the young group of less than 31 years old (57.9%) comparing to the elder group of more than 50 years old (35.1%) [40]. In this report, a high prevalence of CAM resistance (54.5%) was also observed, similar to past studies. However, this rate had increased significantly, and reached about 90% in most current period.

On the other hand, the prevalence of MNZ resistance rates in Japan is still low, about 3% in 2013-2014 [36]. The present study also showed a low MNZ resistance rate (5.2%) and it seemed to decrease over time. The lower rate of MNZ resistance as comparing with other countries may result from the limited use of MNZ in Japan. However, it has been pointed out that the increasing use of MNZ may lead to an increase in the incidence of MNZ resistant strains. MNZ resistance is isolated to specific geographic region with high MNZ usage [42]. Several reports suggested that excessive use of MNZ may have contributed to the increase in the emergence of MNZ resistance [43] [44]. Indeed, the acquisition of MNZ resistance after eradication therapy was suggested in a nationwide survey in Japan. The survey reported higher prevalence of MNZ resistant strains, 13.3% resistance after primary eradication therapy with PPI, AMPC and CAM and 52.4% resistance after secondary eradication therapy with PPI, AMPC and MNZ [36]. Okamura *et al.* had reported the existence of a region with a higher *H. pylori* resistance rate to MNZ in Japan. The population of infected patients had a MNZ resistance rate of 40.2% [40]. Although it is difficult to explain why this region has such a high incidence of MNZ resistant strains, it raises the possibility that increased MNZ resistance may be detected in the future, and cautious observation of susceptibility of *H. pylori* should be performed.

*H. pylori* eradication rates achieved with a first-line regimen of PPI, AMPC and CAM have recently fallen to about 75% because of the increasing incidence of CAM resistance in Japan [11] [13]. In addition, the *H. pylori* eradication rate decreases in patients infected with CAM resistant strains to about 40%. Indeed, eradication rates in children treated with a first-line regimen of PPI, AMPC and CAM are also decreasing related to increased antibiotic resistance especially to CAM. In the past, multicenter studies in Japan reported *H. pylori* eradication rates in children achieving with PPI, AMPC and CAM were 70.6% to 77.4% [39] [41]. Consistent with previous studies in adults, the eradication rate has decreased in pediatric patients infected with CAM resistant strains to 40.0% - 57.1% [37] [39]. Since the goal of treatment is at least a 90% eradication rate on a per-protocol basis at the first attempt [45], recent eradication rate of the first-line therapy with PPI, AMPC and CAM strongly suggests the need for new approaches.

On the other hand, *H. pylori* eradication with a first-line regimen of PPI, AMPC and CAM in the patients infected with CAM sensitive strains showed sufficient success rates [11] [46]. In reports on pediatric patients, high eradication rates with PPI, AMPC and CAM to CAM sensitive strains were seen (91.7% - 97.1%) [37] [39] [40]. The guidelines from the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN), recommend antibiotic sensitivity testing for clarithromycin before initial clarithromycin based triple therapy in areas/populations with a known high resistance rate (>20%) of *H. pylori* to clarithromycin [47]. The present study confirms the efficacy of sensitivity testing and CAM-based regimen to CAM sensitive strains. Similar to published studies, we observed a high eradication success rate (92.6%) with CAM-based initial treatment when applied to CAM sensitive strains. In previous studies, high eradication rates (91.9% - 96.7%) were also obtained with tailored eradication therapy based on CAM sensitivity [40] [46] [48]. Since CAM has been used to treat children with respiratory tract infections and chronic sinusitis in Japan, CAM usage may remain at the same level and induce the development of CAM resistance in *H. pylori* in the future. Therefore, tailored eradication therapy with prior testing for antibiotic susceptibility of *H. pylori* is recommended to improve the eradication success rate.

In conclusion, CAM resistance rates of *H. pylori* in Japanese children are increasing and the high resistance rate may cause a decrease of eradication success rates with first-line therapy with PPI, AMPC and CAM. The present study is limited in geography and in patient numbers. However, these data are consistent with many reports documenting the rise in antibiotic resistant *H. pylori*. Additionally, this study provides compelling evidence for the benefits of antibiotic susceptibility screening prior to eradication therapy in order to significantly increase the efficacy of treatment. Selection of appropriate antibacterial agents with *H. pylori* susceptibility testing may contribute to achieving high primary eradication rates and the prevention of developing gastric cancer.

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