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ORIGINAL ARTICLE

Retrospective Study

Five-year sequential changes in secondary antibiotic resistance of *Helicobacter pylori* in Taiwan

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Institutional review board statement: This retrospective chart review study was approved by both the Institutional Review Board and the Ethics Committee of Chang Gung Memorial Hospital, Taiwan (IRB-104-1245B).

Informed consent statement: The Ethics Committee waived the requirement for informed consent, and each patient's medical records were anonymized and redacted prior to access.

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Abstract

AIM: To determine changes in the antibiotic resistance of *Helicobacter pylori* (*H. pylori*) in southern Taiwan after failure of first-line standard triple therapy.

METHODS: We analyzed 137 *H. pylori*-infected isolates from patients who experienced eradication failure after standard first-line triple therapy from January 2010 to December 2014. The *H. pylori* strains were tested for susceptibility to amoxicillin, clarithromycin, levofloxacin, metronidazole and tetracycline using the E-test method. The minimal inhibitory concentration (MIC) was determined by the agar dilution test.

MIC values of ⩾ 0.5, ⩾ 1, ⩾ 1, ⩾ 4 and ⩾ 8 mg/L were considered to be the resistance breakpoints for amoxicillin, clarithromycin, levofloxacin, tetracycline and metronidazole, respectively.

RESULTS: A high resistance rate was found for clarithromycin (65%-75%) and metronidazole (30%-40%) among patients who failed first-line standard therapy. The resistance levels to amoxicillin and tetracycline remained very low; however, levofloxacin resistance was as high as 37.5% in 2010 but did not increase any further during the past 5 years. The rates of resistance to these antibiotics did not show a statistically significant upward or downward trend.

CONCLUSION: Antibiotic resistance of *H. pylori* remains a problem for the effective eradication of this pathogen and its associated diseases in Taiwan. High clarithromycin resistance indicated that this antibiotic should not be prescribed as a second-line *H. pylori* eradication therapy. Moreover, levofloxacin-based second-line therapy should be used cautiously, and the local resistance rates should be carefully monitored.

Key words: *Helicobacter pylori*; Antibiotic resistance; Five-year sequential changes; Failed first-line therapy; Southern Taiwan

Core tip: Antibiotic resistance of *Helicobacter pylori* (*H. pylori*) is one of the major causes of eradication therapy failure. This study was designed to assess the 5-year sequential changes in antibiotic resistance of *H. pylori* in southern Taiwan after the failure of first-line standard triple therapy. The rates of resistance to antibiotics did not show a statistically significant upward or downward trend. Antibiotic resistance of *H. pylori* has remained a problem in the effective eradication of this type of bacteria in Taiwan. High clarithromycin resistance indicated that this antibiotic should not be prescribed as a second-line therapy for *H. pylori* eradication. Therefore, levofloxacin-based second-line therapy should be used cautiously, and the local resistance rates should be carefully monitored.

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INTRODUCTION

The prevalence of antibiotic resistance of *Helicobacter pylori* (*H. pylori*) varies among countries and may be partly determined by geographical factors. *H. pylori* infects approximately 50% of the global population; its prevalence is approximately 70% in developing nations and approximately 20%-30% in industrialized nations[1]. In Taiwan, the mean seroprevalence rate is approximately 54.5%[2]. The eradication of *H. pylori* is an important issue in the field of preventive medicine. The Maastricht IV/Florence-Consensus Report has recommended that the standard triple therapy should now be avoided in areas where clarithromycin (CAM) resistance is high (> 15%)[3]. Over time, the reported local primary resistance rate to CAM in Taiwan has ranged from 6%-18%[4,5]. In fact, the primary resistance rate to CAM was reported to be as high as 22.7% in patients who lived in rural areas in eastern Taiwan[6]. If the resistance rates continue to rise, the use of first-line *H. pylori* eradication with standard triple therapy, which consists of a proton pump inhibitor (PPI), clarithromycin and amoxicillin, might lead to a poor outcome (< 80%)[7]. Ten years ago, Hsu *et al*[8] reported a > 90% eradication rate of *H. pylori* with the use of first-line standard triple therapy for 7 d in Taiwan.

When first-line therapy fails, the Maastricht IV Consensus Report recommends that bismuth-containing quadruple therapy be a choice for second-line therapy[3]. However, in areas where bismuth is not available, a levofloxacin-containing triple therapy is recommended in areas of both high and low CAM resistance. Unfortunately, growing primary resistance to levofloxacin has been reported worldwide, including in the reports from 1998-2007 in Taiwan[9]. Due to the rapid development of quinolone resistance, the issue of empirical second-line quinolone-based therapy should be further examined. Clearly, antibiotic resistance determines the success of eradication. Our study aimed to investigate the 5-year sequential changes in antibiotic susceptibility of *H. pylori* among patients who failed first-line therapy in southern Taiwan.

MATERIALS AND METHODS

Patients

A retrospective study was conducted on *H. pylori*-infected patients who had failed standard first-line triple therapy (PPI twice daily, 500 mg clarithromycin twice daily, and 1 g amoxicillin twice daily for 7 d) between January 2010 and December 2014 at outpatient clinics at Kaohsiung Chang Gung Memorial Hospital, Taiwan. *H. pylori* eradication failure was defined as a positive ^{13}C-UBT or any two positive rapid urease tests, as well as positive histology and culture after treatment with first-line eradication therapy. However, we *only* recruited those patients with positive *H. pylori* cultures. Among them, a total of 137 *H. pylori* isolates were obtained from gastric biopsy specimens of patients. All isolates from patients who had been previously treated for *H. pylori* infection or who had

Table 1 The trend of annual antibiotic resistance rates in the treatment of *Helicobacter pylori*

		Patient number	Proportion (95%CI) (%)	*P* value (χ^2 test for linear trend)
Amoxicillin	2010	0/24	0 (-)	-
	2011	0/32	0 (-)	
	2012	0/20	0 (-)	
	2013	0/20	0 (-)	
	2014	0/41	0 (-)	
Clarithromycin	2010	17/24	70.8 (51.2-90.4)	0.736
	2011	21/32	65.6 (48.2-83.0)	
	2012	13/20	65.0 (42.1-87.9)	
	2013	15/20	75.0 (54.2-95.8)	
	2014	29/41	70.7 (57.9-85.3)	
Levofloxacin	2010	9/24	37.5 (16.6-58.4)	0.391
	2011	11/32	34.4 (17.0-51.8)	
	2012	6/20	30.0 (8.0-52.0)	
	2013	7/20	35.0 (12.1-57.9)	
	2014	11/41	26.8 (7.9-41.0)	
Metronidazole	2010	9/24	37.5 (16.6-58.4)	0.312
	2011	8/32	25.0 (9.1-40.9)	
	2012	6/20	30.0 (8.0-52.0)	
	2013	6/20	30.0 (8.0-52.0)	
	2014	18/41	43.9 (23.3-59.8)	
Tetracycline	2010	0/24	0 (-)	0.556
	2011	0/32	0 (-)	
	2012	2/20	10.0 (0-24.4)	
	2013	0/20	0 (-)	
	2014	1/41	2.4 (0-7.4)	

been exposed to any antibiotics according to our hospital's chart recoding were excluded.

Culture and antimicrobial susceptibility testing

One biopsy specimen from the antrum and one from the corpus were obtained for *H. pylori* isolation using previously described culture methods[10,11]. The biopsy specimens were cultured on plates that contained Brucella chocolate agar with 7% sheep blood and were incubated for 4-5 d under micro-aerobic conditions. The minimal inhibitory concentration (MIC) was determined by the agar dilution test. The *H. pylori* strains were tested for susceptibility to amoxicillin (AMX), CAM, levofloxacin (LEV), metronidazole (MET) and tetracycline (TET) using the E-test method (AB BIODISK, Solna, Sweden). *H. pylori* strains had MIC values of $\geqslant$ 0.5, $\geqslant$ 1, $\geqslant$ 1, $\geqslant$ 4 and $\geqslant$ 8 mg/L, which were considered to be the resistance breakpoints for AMX, CAM, LEV, TET and MET, respectively.

Statistical analysis

A χ^2 test for linear trends was used to assess the trend of antibiotic resistance over time from 2010-2014. A *P* value < 0.05 was considered statistically significant.

RESULTS

All isolates from 137 *H. pylori*-infected patients who failed first-line therapy were cultured for *H. pylori* and demonstrated a positive result. The resistance rates

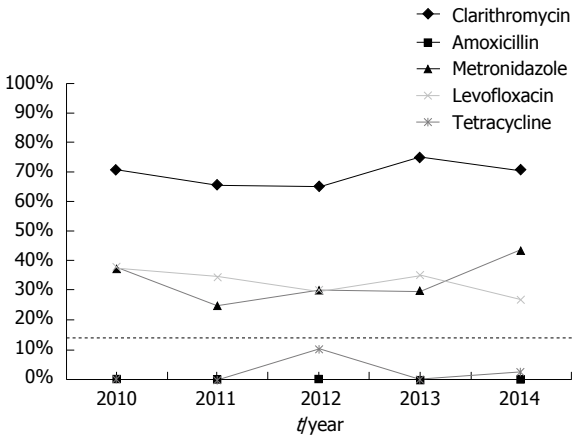

Figure 1 The trend of annual antibiotic resistance rates in the treatment of *Helicobacter pylori*. Values located above 15% (horizontal line) indicated the intention-to-treat cure rate categories below C (fair, 85%-89%)[39].

to AMX, CAM, LEV, TET and MET were 0%, 70.8%, 37.5%, 0% and 37.5%, respectively, in 2010, 25%, 65.8%, 0%, 34.4%, and 0%, respectively, in 2011 and 30%, 65%, 10%, 30%, and 0%, respectively, in 2012. The resistance rates to AMX, CAM, LEV, TET and MET were 30%, 75%, 0%, 35% and 0%, respectively, in 2013 and 0%, 70.7%, 26.8%, 2.4% and 43.9%, respectively, in 2014 (Table 1 and Figure 1). However, none of the isolates showed a statistically significant upward or downward trend in terms of resistance rates when they were analyzed by χ^2 test for linear trends (Table 1).

DISCUSSION

In our study, the annual changes in the antibiotic resistance rates of *H. pylori* after failure of standard first-line treatment in southern Taiwan from 2010 to 2014 revealed a high resistance to CAM (up to 70%) and MET (43.9%) and a low resistance to both AMX (0%) and TET (0%-10%). The resistance to LEV was as high as 37.5% in 2010 but was only 26.5% in 2014.

The cause of CAM resistance may be point mutations, which occur at A2143G, A2142G and A2142C, in the 23S rRNA component of ribosomes[12]. The second-line resistance rate to CAM was as high as 65%-75%. Therefore, CAM should no longer be used as a second-line regimen for eradication therapy because high CAM resistance decreased the efficacy of CAM-based therapy by 66%-77% according to previous studies[13]. The high rate of resistance to CAM in Taiwan was one of the major reasons for the failure of first-line standard triple therapy[14]. In fact, the eradication rate after first-line therapy in Taiwan dropped from 95% in 2005 to 79.3% in 2014[7,8]. This result indicated that the standard first-line therapy may need to be substituted with alternative combination treatments such as non-bismuth quadruple (concomitant, sequential or hybrid therapy)

therapy in Taiwan.

MET resistance in cases of *H. pylori* infection is complex and is primarily associated with mutational inactivation of several redox-related genes (*frxA*, *rdxA*)[15]. Fortunately, in contrast to CAM resistance, MET resistance had less impact on the eradication rate and could be overcome *via* an increase in the dose[16,17]. Therefore, MET continues to be a widely used drug for eradication therapy, despite a relatively high resistance rate. Some studies have shown that MET resistance is not a major determinant of the failure rate because MET-resistant *H. pylori* isolates reduce the efficacy of MET-containing regimens but do not render them completely ineffective[18,19]. This discrepancy between *in vitro* MET resistance and treatment outcomes may be partially explained by changes in the oxygen pressure in the gastric environment, as MET-resistant *H. pylori* isolates can become susceptible to MET under low oxygen conditions *in vitro*. These combined results suggested that treatment with MET could overcome MET resistance to some degree[20]. However, MET, which is an important antibiotic that is used in quadruple therapy, demonstrated a high, continuous level of resistance (25%-43.9%). This is similar to what has been observed in other Asian countries such as Malaysia and South Korea[21,22].

Nevertheless, it is still recommended that bismuth-based quadruple therapy or levofloxacin-containing triple therapy be used as a second-line therapy[3,23]. However, bismuth is not available in many countries. Alternatively, the Maastricht IV Consensus Report has also recommended LEV-based therapy as a second-line rescue treatment after failure of first-line therapy. Unfortunately, the growing resistance to LEV has become a global problem[9]. Quinolone resistance is determined in *H. pylori* (N87 and D91) in the quinolone resistance-determining region of the *gyrA* gene of *H. pylori*[24]. In the current study, the prevalence of LEV resistance was 37.5% in 2010, and fortunately, it has not increased since then. This might be because the bureau of our hospital, *via* an electronic audit program, issued a reimbursement regulation that restricts the use of any antibiotics in patients throughout the hospital. Another reason might be due to the practice of tailored therapy for patients with documented LEV-susceptibility strains whenever *H. pylori* culture was available[25]. However, additional follow-up reports on LEV resistance are needed in the next couple of years. Although the current 5-year report showed no statistically significant upward or downward trend, the resistance rate reported in the current study was still much higher than the 11.8% that was reported in 2007 and the 26.5% in 2014[26].

Furthermore, the impact of the increase in levofloxacin resistance might be crucial in the eradication of *H. pylori*. Perna *et al*[27] reported that the eradication rate was lower in patients with LEV-resistant strains compared with those with susceptible strains (33.3% *vs* 75%). In addition, Tai *et al*[25] noted that the eradication rate dropped from 92.8% to 14.3% in patients with levofloxacin-resistance strains who received 10-d LEV triple therapy. These results imply that treatment with levofloxacin-based therapy for *H. pylori* should be limited to patients with susceptible strains in order to avoid a potential resistance problem.

Importantly, the global increase in the prescription of quinolones is responsible for the rapid rise in the resistance of *H. pylori,* but it has also impacted other types of bacteria[28]. For example, *Mycobacterium tuberculosis* is highly prevalent in Taiwan. One study reported that patients who were recently exposed to quinolone for 5 d or more were less likely to be smear-positive (OR = 0.27, 95%CI: 0.11-0.63) and were more likely to experience a delay in the receipt of proper treatment for tuberculosis (time ratio 2.02, 95%CI: 1.19-3.44)[29]. Moreover, quinolone exposure for > 10 d that occurred > 60 d before a diagnosis of tuberculosis was associated with the highest risk of quinolone resistance (OR = 17.0, 95%CI: 5.1-56.8) compared with no exposure[30]. Importantly, the current report reminds us of the potential impact of the empiric use of LEV as a second-line eradication therapy, which is recommended by the Maastricht IV Consensus Report, and that the use of this antibiotic should be carefully monitored.

Our study showed that *H. pylori* isolates were highly susceptible to AMX and TET (0% throughout the 5-year period except for 10% in TET strains that were resistant in 2012). This is similar to what was found in previous reports by Hung *et al*[26] and Mégraud[31]. AMX resistance is associated with alterations in penicillin-binding proteins. For time-dependent antibiotics such as AMX, it is more important to prolong the time so that the plasma concentration is higher than the minimal inhibitory concentration (MIC) to achieve higher plasma levels of the drug[32]. On the contrary, the bactericidal activity of TET is a result of the drug' s ability to prevent the synthesis of nascent peptide chains by binding to the 30S ribosomal subunit as well as by blocking the binding of aminoacyl-tRNA[33]. The low resistance rates to both AMX and TET imply that they might be good candidate antibiotics for use as second-line therapies for *H. pylori* eradication when given in combination because the prevention of antibiotic resistance is a key factor for success. Unfortunately, the reported success rates when these two antibiotics were given in combination were unacceptable in two previous publications from Taiwan (62%-75% in an intention-to-treat analysis and 64%-80% in a per-protocol analysis)[34,35]. The reason for the disappointing *in vivo H. pylori* eradication rates might be related to a drug-drug interaction between amoxicillin and tetracycline, both of which exhibit low antibiotic resistance *in vitro*. Sorice *et al*[36] proposed that bacteriostatic drugs such as tetracycline might interfere with the bactericidal action of penicillin. The bactericidal action of penicillin involves the inhibition

of cell wall formation, which is dependent on how fast the bacteria multiply. Bacteriostatic antibiotics such as TET may reduce the effectiveness of penicillin *via* the inhibition of the cellular protein synthesis that is required for cell division[37].

The current study has some limitations. First, this was a single-center report, and multicenter data would be more convincing with respect to this issue. Second, it is a retrospective study with a relatively small sample size, and thus, bias may exist. Third, we were unable to provide any further genetic data for these resistant strains. As is already known, antibiotic resistance is conferred by point mutations in *H. pylori* DNA[38]. Resistance is currently detected by culture-based and molecular methods. Molecular techniques could predict the antibiotic resistance by the detection of point mutations. In reality, these techniques are not always feasible and are still difficult to apply in clinical practice due to the high costs that are associated with routine use[9].

In conclusion, antibiotic resistance of *H. pylori* remains a hindrance to the effective eradication of *H. pylori* infections in Taiwan. High CAM resistance indicates that it should not be prescribed as a second-line therapy for *H. pylori* eradication. Levofloxacin-based second-line therapy should be used cautiously, and the local resistance rates should be carefully monitored.

COMMENTS

Background

The prevalence of antibiotic resistance of *Helicobacter pylori* (*H. pylori*) varies among countries and may be partly determined by geographical factors. *H. pylori* infects approximately 50% of the global population; its prevalence is approximately 70% in developing nations and approximately 20%-30% in industrialized nations. Antibiotic resistance of *H. pylori* is one of the major causes of failure of eradication therapy.

Research frontiers

The growing primary resistance to levofloxacin has been reported worldwide, including in the studies from Taiwan that were conducted between 1998 and 2007. Due to the rapid development of quinolone resistance, the issue of empirical second-line quinolone-based therapy should be further examined. Clearly, antibiotic resistance determines the success of eradication therapies. We investigated the 5-year sequential change in the antibiotic susceptibility of *H. pylori* among patients who failed first-line therapy in southern Taiwan.

Innovations and breakthroughs

The result of the present study showed high resistance rates to clarithromycin (65%-75%) and metronidazole (30%-40%) among patients who failed first-line standard therapy. The resistance to amoxicillin and tetracycline remained very low, but the resistance to levofloxacin was as high as 37.5% in 2010; however, this value did not increase during the past 5 years. The resistance rates to these antibiotics did not show a statistically significant upward or downward trend.

Applications

Antibiotic resistance of *H. pylori* has remained a problem in the effective eradication of *H. pylori* infection in Taiwan. High clarithromycin resistance indicated that this antibiotic should not be prescribed as a second-line therapy for *H. pylori* eradication. A levofloxacin-based second-line therapy should be used cautiously, and the local resistance rates should be carefully monitored.

Terminology

The *H. pylori* strains were tested for susceptibility to amoxicillin (AMX), CAM, levofloxacin (LEV), metronidazole (MET) and tetracycline (TET) using the E-test method (AB BIODISK, Solna, Sweden). *H. pylori* strains had minimal inhibitory concentration values $\geqslant 0.5$, $\geqslant 1$, $\geqslant 1$, $\geqslant 4$ and $\geqslant 8$ mg/L, which were considered to be the resistance breakpoints for AMX, CAM, LEV, TET and MET, respectively.

Peer-review

The study is well written and organized. The issue is very interesting.

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