

## ORIGINAL PAPER

doi: 10.5455/medarch.2021.75.112-115

MED ARCH. 2021 APR; 75(2): 112-115

RECEIVED: MAR 23, 2021

ACCEPTED: APR 20, 2021

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# Antimicrobial Resistance and the Successful Eradication of *Helicobacter pylori*-Induced Gastroduodenal Ulcers in Vietnamese Children

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## ABSTRACT

**Background:** *Helicobacter pylori* infections induce chronic gastric mucosal inflammation and peptic ulcer disease, and eradication is recommended. **Objective:** To investigate antibiotic resistance and *H. pylori* eradication rates in children with gastroduodenal ulcers in Vietnam. **Methods:** We performed gastroduodenal endoscopies, *H. pylori* cultures, and antimicrobial susceptibility testing (clarithromycin, amoxicillin, metronidazole, tetracycline, and levofloxacin) in children with gastroduodenal ulcers at Children's Hospital 2 from November 1, 2019, to June 30, 2020. **Results:** A total of 76 participants were studied, with an average age of  $9.3 \pm 2.8$  years (range: 4–15 years), including 52.6% males and 47.4% females. The antibiotic resistance rates were clarithromycin, 92.1%; amoxicillin, 50%; levofloxacin, 31.6%; metronidazole, 14.5%; and tetracycline, 0%. The successful eradication rate was 44.7%. Bismuth increased the eradication rate by 3.69-fold that without bismuth ( $p = 0.030$ ). The eradication rate of levofloxacin was high (100%,  $p = 0.038$ ) compared with other antibiotics. The effectiveness of high-dose amoxicillin in cases with >50% *H. pylori* amoxicillin resistance was only 32.6% ( $p = 0.015$ ). **Conclusion:** Increased antibiotic resistance among *H. pylori* resulted in decreased eradication efficacy, which was 44.7% in this study. Drug combinations, such as levofloxacin and bismuth, can increase the *H. pylori* eradication efficacy in children.

**Keywords:** Children, resistance, eradication rate, *Helicobacter pylori*.

## 1. BACKGROUND

The discovery of *Helicobacter pylori* bacteria in the human stomach in 1982 by two Australian scientists, Marshall and Warren, earned them the Nobel Prize for Medicine (1). Typically, *H. pylori* infections are acquired during childhood, persist throughout life, and can induce chronic gastric mucosal inflammation, associated with the development of gastric cancer. The World Health Organization (WHO) determined that *H. pylori* eradication represented an essential strategy for preventing stomach cancer (2).

Various treatments, including the use of proton pump inhibitors (PPIs), antibiotics, bismuth, and probiotics, have been proposed to eradicate *H. pylori*. However, the therapeutic efficacies of these regimens have been very low, with lower than expected results reported in a previous study (<80%), especially among children (3).

The successful eradication of *H. pylori* depends on many factors, including bacterial contamination, bacterial virulence, the CYP2C19 phenotype, antibiotic resistance, and patient compliance. The increasing antibiotic resistance of *H. pylori* is thought to be a leading cause of treatment failure (4). Among Asian adults, the antibiotic resistance rates of *H. pylori* against metronidazole, clarithromycin, levofloxacin, amoxicillin, and tetracycline were reported to be 46.57%, 27.45%, 25.28%, 23.61%, and 7.38%, respectively (5). Among children, many global studies have also reported the increased incidence of primary antibiotic-resistant *H. pylori* strains (6).

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## 2. OBJECTIVE

In this study, we aimed to investigate the *H. pylori* antibiotic resistance rate among pediatric patients in Vietnam, to evaluate the eradication rates in response to tailored regimens that were designed according to the results of antibiotic susceptibility tests, and to examine the factors that influence eradication efficacy.

## 3. MATERIAL AND METHODS

**Study subjects:** All children diagnosed with a peptic ulcer at Children's Hospital 2 from November 1, 2019, to June 30, 2020, who had positive *H. pylori* cultures, antibiotic susceptibility testing results, and no prior history of eradication treatment.

**Inclusion criteria:** The following inclusion criteria were applied: patients indicated and received gastroduodenoscopy; endoscopic and histopathological findings suggested inflammatory lesions or peptic ulcers, according to the Sydney 1996 classification; bacteria were cultured and antibiotic susceptibility testing was performed; and patients complied with antibiotic regimens for 14 days and PPI regimens for eight weeks.

**Exclusion criteria:** The following exclusion criteria were applied: patients did not comply with the treatment, and no test was performed to assess the outcomes after treatment (stool antigens).

***H. pylori* diagnosis:** The criteria for positive *H. pylori* infection diagnosis was based on the 2016 guidelines established by the European Society for Paediatric Gastroenterology Hepatology and Nutrition/North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN/NASPGHAN) (7), and included either (1) an *H. pylori*-positive culture or (2) *H. pylori*-positive histopathology, combined with at least one other positive biopsy-based test, such as a rapid urease test (RUT) or polymerase chain reaction (PCR).

**Criteria for successful eradication:** Successful eradication was defined as a negative antigen/stool test following regimen therapy. Stool tests were performed at least four weeks following antibiotic discontinuation and two weeks after PPI discontinuation.

**Eradication regimen for *H. pylori*:** Regimens and dosages were determined according to the 2016 ESPGHAN/NASPGHAN guidelines (7).

**Data processing and statistical analysis:** All data analysis was performed using Excel 2010 and SPSS 20.0 software. Descriptive statistics are expressed as the mean  $\pm$  standard deviation or as frequency and percentage (%). We used the Chi-square test to analyze the associations among independent qualitative variables. We used Fisher's exact test if the expected value was lower than 5. Logistic regression was used to examine the odds ratios and 95% confidence intervals. A p-value  $< 0.05$  was considered significant.

**Ethical issues:** This study was approved by the Medical Ethics Committee of Children's Hospital 2.

## 4. RESULTS

### Characteristics of the study population and antibiotic resistance rate

This study enrolled 76 eligible cases. The mean age of participants was  $9.3 \pm 2.8$  years, ranging from 4 to 15 years. The percentages of females and males were 47.4% and 52.6%, respectively.

Among the tested *H. pylori* cultures, clarithromycin resistance was observed at the highest rate, at 92.1%, followed by amoxicillin at 50%. The rate of *H. pylori* resistance to the combination of clarithromycin and amoxicillin was 44.7% (Table 1).

### Characteristics of treatment and eradication results

The successful eradication rate among all included patients was 44.7% (Table 2).

#### Factors associated with eradication results

The inclusion of levofloxacin, high-dose amoxicillin, and bismuth in treatment regimens was significantly associated with improved *H. pylori* eradication efficacy ( $p < 0.05$ ) (Table 3).

Using multivariate logistic regression, the eradication success rate for regimens that included bismuth was

Antimicrobial resistance rate	Frequency (n)	Percentage (%)
Resistance to 1 antibiotic		
CLA	70	92.1
MET	11	14.5
AMO	38	50.0
LEV	24	31.6
TET	0	0.0
Resistance to 2 antibiotics		
CLA-MET	10	13.2
CLA-AMO	34	44.7
MET-AMO	8	10.5
Resistance to 3 antibiotics		
CLA- MET- AMO	7	9.2
Resistance to 4 antibiotics		
CLA- MET- AMO- LEV	3	3.9

**Table 1. Antibiotic resistance rate. AMO, amoxicillin; AMOH, high-dose amoxicillin; CLA, clarithromycin; MET, metronidazole; TET, tetracycline; LEV, levofloxacin; PPI, proton pump inhibitor.**

Eradication results according to regimen	Eradication results				Rate of regimen use	
	Failure		Success		n	Percentage (%)
	n	Percentage (%)	n	Percentage (%)		
EAC	0	0.0	1	100.0	1	1.3
EAM	13	50.0	13	50.0	26	34.2
EAhM	27	65.9	14	34.1	41	54.0
Based on antimicrobial susceptibility	2	25.0	6	75.0	8	10.5
Overall eradication rate	42	55.3	34	44.7	76	100.0

**Table 2. Treatment regimens and outcomes. E, esomeprazole; A, amoxicillin; Ah, high-dose amoxicillin; M, metronidazole; C, clarithromycin.**

Eradication efficacy based on related factors	Eradication results				OR 95% CI	P	
	Failure		Success				
		n	Percentage (%)	n	Percentage (%)		
LEV	No	42	58.3	30	41.7	12.25 (1-236.1)	0.038**
	Yes	0	0.0	4	100.0		
Ah	No	13	39.4	20	60.6	0.31 (0.12-0.81)	0.015*
	Yes	29	67.4	14	32.6		
Bismuth	No	36	63.2	21	36.8	3.71 (1.22-11.23)	0.016*
	Yes	6	31.6	13	68.4		

**Table 3. Factors associated with eradication results. \* Chi-squared test, \*\* Fisher's exact test. OR, odds ratio; 95% CI, 95% confidence interval, P, p-value; LEV, levofloxacin; Ah, high-dose amoxicillin.**

Dependent factor	Independent factors	OR	P	95% CI
Eradication efficacy of <i>H. pylori</i>	LEV	1	NA	
	AMOh	0.36	0.054	0.13-1.01
	Bismuth	3.69	0.030	1.13-11.98

**Table 4. Multivariate logistic regression. OR, odds ratio; P, p-value; 95% CI, 95% confidence interval; LEV, levofloxacin**

found to be 3.69-fold that for regimens without bismuth ( $p < 0.05$ ) (Table 4).

### 5. DISCUSSION

Our study examined 76 children with gastroduodenal ulcers caused by *H. pylori*, with a mean age of  $9.3 \pm 2.8$  years, ranging from 4 to 15 years, which is similar to the ages reported by other studies. In the 2015 study by Esmaeili-Dooki *et al.* in Iran, the mean age of pediatric patients with gastroduodenal ulcers treated with an omeprazole, amoxicillin, and clarithromycin (OAC) regimen was  $9.1 \pm 3.6$  years (8). Our study included 40 males (52.6%) and 36 females (47.4%), whereas the 2019 study by Galal *et al.* in Egypt reported nearly equal proportions of males and females, at 51.6% and 48.4%, respectively (9).

Our study found that the *H. pylori* resistance was the highest against clarithromycin, at 92.1%, followed by amoxicillin (50%), levofloxacin (31.6%), and metronidazole (14.5%). All children infected with *H. pylori* in our study were susceptible to tetracycline. However, tetracycline causes side effects in children's organs, including the teeth, liver, and bones, particularly among those younger than eight years, and is not widely recommended. Recently, the rate of *H. pylori* antibiotic resistance has been increasing, especially in developing countries such as Vietnam. In 2015, a meta-analysis by Ghotaslou *et al.* reported the following antibiotic resistance rates for *H. pylori* worldwide (5).

For clarithromycin, in Asia, the resistance rate increased from 15.28% in 2009 to 32.46% in 2014.

For amoxicillin, in Asia, a fairly high resistance rate was identified in India, at 72.5%, whereas in South Africa, the resistance rate was reported as high as 97.5%.

For metronidazole, the overall global resistance rate was reported at 47.22%. The resistance rates, in ascending order, for North America, Europe, Asia, South America, and Africa were 30.5%, 31.19%, 46.57%, 52.85%, and 75.02%.

For levofloxacin, in Asia, the respective figures in Japan, South Korea, Iran, and Malaysia were reported at 57%, 24.55%, 5.3%, and 2.6%.

Among the five popular antibiotics used to treat *H. pylori*, tetracycline had the lowest resistance rate, with a global resistance rate of 11.7%; however, tetracycline resistance also varied widely across countries and regions.

Our study examining 76 children resulted in a successful *H. pylori* eradication rate of 44.7% (95% confidence interval: 34.1%–55.9%). This rate is lower than that reported by other recent studies. From 2013 to 2017, Silva *et al.* reported an eradication rate of 97.8% at a northern Portuguese pediatric center (10), and Dehghani's study in Iran reported an eradication rate of 82.5% (11). However, our result was similar to other studies performed in Asia, such as Zhang *et al.*'s study in China, which reported an eradication rate of 64.5% (12). Our study results included 4 cases that achieved 100% eradication using levofloxacin, and we identified a significant difference in the eradication rate associated with levofloxacin ( $p = 0.038$ ) compared with other antibiotic treatments. However, levofloxacin is expensive compared with other treatments and is not commonly prescribed for children. Thus, additional research remains necessary to examine the efficacy of this antibiotic for the eradication of *H. pylori* in children.

The first-line regimen recommended by the 2016 ESPGHAN/NASPGHAN guidelines (7) is amoxicillin, regardless of whether resistance is detected. In our study, the successful eradication efficacy among children who were treated with high-dose amoxicillin when *H. pylori* cultures revealed resistance to both clarithromycin and metronidazole was 32.6%, which was significantly lower than the efficacy of standard-dose amoxicillin (60.6%,  $p = 0.015$ ). This result indicated that high-dose amoxicillin was not effective for the treatment of multiantibiotic-resistant *H. pylori*, likely due to the high resistance against amoxicillin (>50%) in Vietnam. Additional studies using larger sample sizes remain necessary to explore the most effective treatment method when bacteria are already amoxicillin-resistant, as a different antibiotic conversion regimen may be more suitable for these patients.

The eradication rate in response to the bismuth-based regimen in our study was 68.4%, which was significantly higher than the rate for regimens without this active ingredient (36.8%,  $p = 0.016$ ). In 2015, according to a report by the European Pediatric Treatment Registry, bismuth-containing regimens had a success rate of 77% compared with 64% for bismuth-free regimens, which represented a significant increase in efficacy ( $p = 0.02$ ) (13). According to another retrospective study per-

formed in Korea from 2004 to 2012, which compared the eradication efficacy between a 7-day bismuth-containing quadruple regimen (OAMB: omeprazole, amoxicillin, metronidazole, and bismuth) and a 14-day triple therapy regimen (OCA: omeprazole, clarithromycin, and amoxicillin), the eradication success rates were 83.9% and 67.7%, respectively, which represented a significant difference ( $p = 0.041$ ) (14).

Some authors have concluded that bismuth-based regimens increased the *H. pylori* eradication efficacy. Therefore, the ESPGHAN/NASPGHAN 2016 guidelines recommended that bismuth should be included in first-line regimens when *H. pylori* is determined to be resistant to clarithromycin or metronidazole (13).

Although tetracycline had a resistance rate of 0%, it was rarely prescribed for children older than eight years, which was a limitation of this study. However, all 4 cases prescribed levofloxacin resulted in successful eradication. The eradication efficacy of *H. pylori* in pediatric patients requires additional studies using larger samples and multiple centers, especially with regards to the efficacy of tetracycline and levofloxacin.

## 6. CONCLUSION

The rate of antibiotic resistance among *H. pylori* has been increasing at an alarming level. The clarithromycin and amoxicillin resistance rates for *H. pylori* were very high in this study, at 92.1% and 50.0%, respectively. The successful eradication rate for *H. pylori* in this study was 44.7%. Factors associated with increased *H. pylori* eradication efficacy included the use of bismuth-based regimens and high-dose levofloxacin or amoxicillin regimens. Multivariate regression analysis showed that the eradication rate for the bismuth-containing regimens was 3.69-fold higher than that for regimens without bismuth.

- **Ethical approval:** This study was approved by the Medical Ethics Committee of Children's Hospital 2.
- **Author's contribution:** Ha Van Thieu and Nguyen Minh Duc contributed equally to this article as co-first authors. Ha Van Thieu and Nguyen Minh Duc gave a substantial contribution in acquisition, analysis, and data interpretation. Each author had a part in preparing article for drafting and revising it critically for important intellectual content. Each author gave the final approval of the version to be published and agreed to be accountable for all aspects of the work, ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.
- **Conflicts of interest:** There are no conflicts of interest to declare.

- **Financial support and sponsorship:** Nil.

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