



# Evaluation of the Antibiotic Resistance Rate of *Helicobacter pylori* in Peptic Ulcer Patients in Tien Giang Central General Hospital, Tien Giang Province, Vietnam

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## Abstract

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**BACKGROUND:** Peptic ulcer (PU), trauma on the lining of the stomach and/or small intestine, is among the top five reasons for hospitalization in Tien Giang, a province in the South of Vietnam. Since *Helicobacter pylori* (HP) is one of the main causes of PU, its features, especially the antibiotic-resistant status, have critical significance in PU treatment.

**AIM:** This study evaluates the HP infection prevalence, HP antibiotic resistance rate, and its associations with the patients' sociodemographic characteristics.

**MATERIALS AND METHODS:** A cross-sectional study was conducted on PU patients in Tien Giang province, Vietnam, from June 2020 to June 2021. The volunteers were tested for HP infection and antibiotic resistance using three methods, where appropriate, including Gram staining, CLO (urease) test, and bacterial culture method.

**RESULTS:** Among 368 samples, 31.5% had infected with antibiotic-resistant HP. The resistance rates to five antibiotics commonly used in HP treatment, including metronidazole, clarithromycin, tetracycline, levofloxacin, and amoxicillin, were 96.6%, 94.8%, 70.7%, 61.2%, and 53.4%, respectively. The rates of tetracycline and clarithromycin resistance were related to alcohol consumption (t-test,  $p < 0.05$ ). The HP treatment history was significantly associated with the levofloxacin resistance (t-test,  $p < 0.05$ ).

**CONCLUSIONS:** The emergence of antibiotic-resistant HP is a major public health concern in Tien Giang, Vietnam. This issue should be tackled at the national level to avoid the further spread of these multi-drug resistant HP strains.

## Introduction

*Helicobacter pylori* (HP), Gram-negative spiral bacteria that infects over 50% of the world population, is the main cause of peptic ulcer (PU) and gastric cancer [1], [2]. Among infected patients, about 1–3% progress to gastric cancer, 10% develop PU, and <0.1% advance to mucosa-associated lymphoid tissue lymphoma [3]. HP suppression treats not only PU but also avoids the disease recurrence and decreases the risk of gastric cancer [4]. Regarding the prevalence rate, Vietnam is one country with a high prevalence of HP infection in the community, at 70.3% [5]. Although in Tien Giang, a province in the South of Vietnam, PU is one of the five most common causes of patients coming to the hospitals for examination and treatment [6], [7], HP infection prevalence in PU patients in this province has not yet been reported.

To treat HP, triple therapy regimens comprise a proton pump inhibitor and two antibiotics, such as

clarithromycin, amoxicillin, levofloxacin, metronidazole, and tetracycline, which are considered. However, the success rates of these regimens are varied and dependent on many factors, including patient compliance, smoking, and antibiotic resistance [8], [9], [10]. Antibiotic resistance, one of the biggest risks to global health that is mainly due to the misuse of antibiotics in animals and humans, has been found in increasingly many types of bacteria [11], [12]. The World Health Organization (WHO) has confirmed that HP is one of 16 types of antibiotic-resistant bacteria that pose the greatest threat to human health [13]. High antibiotic resistance causes a decrease in the HP treatment eradication rate and probably an increased risk of complications such as PU and gastric cancer [14]. Despite this severity, no national guidelines are available for antibiotic-resistant-HP treatment in Vietnam [4]. The HP treatment regimens in Vietnam are commonly selected based on an empirical approach (i.e., physician experience), without an antimicrobial susceptibility test. These issues might further increase the HP antibiotic resistance rate

in Vietnam. Conclusively, it is crucial to determine the HP prevalence, HP antibiotic resistance rate, and its associations with the patients' sociodemographic characteristics in Vietnam.

To this end, the present research focused on the determination of the antibiotic resistance rate of HP in PU patients and its associated factors in Tien Giang province, Vietnam. A cross-sectional study was conducted and the volunteers have tested HP infection and antibiotic resistance using three methods, where appropriate, including Gram staining, CLO (urease) test, and bacterial culture method. This work could yield valuable data on the antibiotic resistance of HP in a province with a high PU rate in Vietnam.

## Materials and Methods

### Study designs

A cross-sectional study was conducted on PU patients, diagnosed by endoscopic observation, who came to Tien Giang Central General Hospital for examination and treatment, between June 2020 and June 2021. Patients were determined HP infection when their gastric mucosa – duodenum specimen demonstrates positive results with at least two, out of three, tests, including CLO (urease) test, Gram staining (Gram-negative spiral bacteria), or bacterial culture method. Exclusion criteria included patients with contraindications to gastroduodenoscopy (i.e., gastrointestinal hemorrhage, history of gastrotomy, heart failure, pregnancy, and low platelets) and the patient who was taking at least one of the five antibiotics used in the study (amoxicillin, clarithromycin, metronidazole, levofloxacin, and tetracycline) and/or bismuth therapy within 4 weeks before the study.

The sample size was calculated based on the Cochran formula, where  $n$  is the sample size, and the confidence coefficient was set at 0.95, which has the corresponding value  $Z_{1-\alpha/2} = 1.96$ . The allowed error in the study was 5%, thus,  $d = 0.05$ . Based on a high prevalence of HP infection in PU patients from our preliminary study,  $p$  was set at 0.6. Therefore, the required sample size was 368 patients.

$$n = Z_{1-\alpha/2}^2 \times \frac{p(1-p)}{d^2} \quad (1)$$

### Instruments

The patients' information was collected from the medical records and laboratory test results. Variables used in the study are set up based on the research objectives and are divided into three groups, namely, sociodemographic characteristics of the patients (age, sex, smoking status, and alcohol consumption);

antibiotic resistance rate of HP (susceptibility/resistant) on five commonly used antibiotics for HP treatment, including amoxicillin, clarithromycin, metronidazole, levofloxacin, and tetracycline [15]; and factors related to HP antibiotic resistance.

To detect the HP, the bacterial culture method was utilized. Briefly, the patient gastric mucosa-duodenum samples were diluted in normal saline (NaCl 0.9%), inoculated onto Mueller-Hinton Agar medium + 7% defibrinated horse blood, and incubated for a maximum of 10 days at 37°C under microaerophilic conditions (5% CO<sub>2</sub>, 10% O<sub>2</sub>, and 85% N<sub>2</sub>). HP was identified when the culture shows positive results with at least two, out of three, tests, including CLO (urease) test, Gram staining (Gram-negative spiral bacteria), or colony morphology [16].

To determine the HP antibiotic resistance status, the Epsilometer test (E-test) was used. For this, the HP culture suspension (turbidity equal to McFarland opacity standard of 3.0) was inoculated onto the plates containing Mueller-Hinton II Agar medium + 10% defibrinated horse blood. Then, the E-test strip containing the respective antibiotic (amoxicillin, clarithromycin, metronidazole, levofloxacin, and tetracycline) was inserted on the plate, followed by incubation for 3 days at 37°C under microaerophilic conditions. The minimum inhibitory concentrations (MIC) of these five antibiotics were then determined. The HP strain was considered antibiotic-resistant when the MIC was >1 µg/mL, ≥1 µg/mL, ≥8 µg/mL, ≥1 µg/mL, and ≥4 µg/mL for amoxicillin, clarithromycin, metronidazole, levofloxacin, and tetracycline, respectively [16].

### Statistical analysis

All analytical tests were conducted in triplicate to confirm the results. The SPSS software, version 20.0, was used to analyze the data. The Chi-squared test was utilized to investigate differences between categorical variables, with  $p$ -value of <0.05 for statistical significance.

### Ethical considerations

All patients were informed of the aims and objectives of the study. Informed consent was obtained from all participants, and the protocol was approved by the Medical Ethics Council of Can Tho University of Medicine and Pharmacy, Can Tho, Vietnam (No 11/HDDD-PCT, 15 February 2019).

## Results

Among a total of 368 PU patients, 116 (31.5%) possessed HP, in which high antibiotic resistance rates

of >50% in all tested antibiotics were observed. The resistance rates of HP to each type of antibiotic are presented in Figure 1.

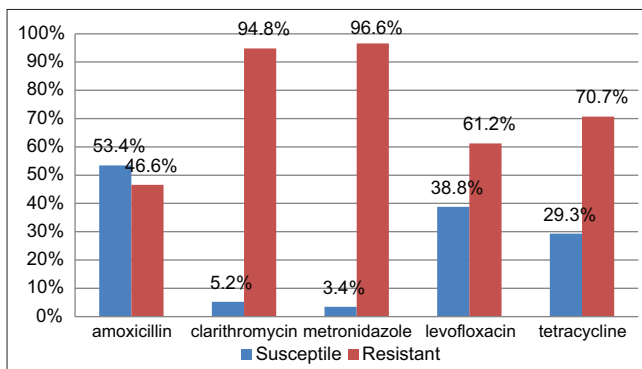


Figure 1: Antibiotic resistance rate of *Helicobacter pylori* in peptic ulcer patients (n = 116)

Sociodemographically, in terms of age groups, the patients who aged <30, 31–40, 41–50, 51–60, and >60 years old accounted for 12.9%, 20.7%, 25.0%, 22.4%, and 19.0%, respectively. Regarding gender, the majority of patients were female (53.4%). In addition, 20.7% of the participants had a history of smoking, and 38.8% of them consumed alcohol.

For the associations between the antibiotic resistances status of HP on five commonly used antibiotics (amoxicillin, clarithromycin, metronidazole, levofloxacin, and tetracycline) and the patient sociodemographic factors (Table 1), patients who consume alcohol had a higher rate of HP resistance to tetracycline (95% CI 1.30–8.50, p < 0.05) and clarithromycin (95% CI 0.85–0.98, p < 0.05) than those who do not drink alcohol. Moreover, patients with a history of HP treatment had a higher rate of levofloxacin resistance than the others (95% CI 1.20–5.59, p < 0.05).

## Discussions

The HP infection prevalence in PU patients significantly varies between different countries and even different provinces in the same country. For instance, in some African countries, as well as in India, this prevalence is as high as 80% of the investigated population [17]. In Japan and the U.S.A., the HP infection rate was commonly <20% [18], [19]. Interestingly, in the same country such as Vietnam, the HP prevalence differs among different areas. In Hanoi, the capital city, this rate was approximately 70% in 2005 [6]. However, in Tien Giang, a province in the South of Vietnam, our result shows that this rate was only 31.5%. As HP infection is mainly due to the state of environmental and food hygiene, these differences might be because of the difference in cuisine style of the North and the South of Vietnam. Since the previous study was conducted in

Table 1: Difference in antibiotic resistance between the patient sociodemographic groups

Antibiotic	Variable	Susceptible n (%)	Resistant n (%)	95% CI	p-value
Tetracycline	Gender				
	Male	16 (25.8)	46 (74.2)	0.64–3.20	>0.05
	Female	18 (33.3)	36 (66.7)		
	Smoking status				
	Yes	6 (25.0)	18 (75.0)	0.47–3.65	>0.05
	No	28 (30.4)	64 (69.6)		
	Alcohol consumption				
	Yes	7 (15.6)	38 (84.4)	1.30–8.50	<0.05*
	No	27 (38.0)	44 (62.0)		
	Treatment history				
Untreated	19 (55.9)	15 (44.1)	0.79–4.00	>0.05	
Treated	15 (44.1)	48 (58.5)			
Metronidazole	Gender				
	Male	2 (3.2)	60 (96.8)	0.15–8.45	>0.05
	Female	2 (3.7)	52 (96.3%)		
	Smoking status				
	Yes	0 (0)	24 (100.0)	0.91–0.99	>0.05
	No	4 (4.3)	88 (95.7)		
	Alcohol consumption				
	Yes	0 (0)	45 (100.0)	0.89–0.99	>0.05
	No	4 (5.6)	67 (94.4)		
	Treatment history				
Untreated	1 (25.0)	3 (75.0)	0.03–3.81	>0.05	
Treated	52 (46.4)	60 (53.6)			
Clarithromycin	Gender				
	Male	4 (6.5)	58 (93.5)	0.09–3.17	>0.05
	Female	2 (3.7)	52 (96.3%)		
	Smoking status				
	Yes	2 (8.3)	22 (91.7)	0.08–2.90	>0.05
	No	4 (4.3)	88 (95.7)		
	Alcohol consumption				
	Yes	0 (0)	45 (100.0)	0.85–0.98	<0.05*
	No	6 (8.5)	65 (91.5)		
	Treatment history				
Untreated	4 (66.7)	2 (33.3)	0.43–14.16	>0.05	
Treated	49 (44.5)	61 (55.5)			
Levofloxacin	Gender				
	Male	23 (37.1)	39 (62.9%)	0.55–2.46	>0.05
	Female	22 (40.7)	32 (59.3)		
	Smoking status				
	Yes	9 (37.5)	15 (62.5)	0.42–2.70	>0.05
	No	36 (39.1)	56 (60.9)		
	Alcohol consumption				
	Yes	16 (35.6)	29 (64.4)	0.57–2.70	>0.05
	No	29 (40.8)	42 (59.2)		
	Treatment history				
Untreated	27 (60.0)	26 (36.6%)	1.20–5.59	<0.05*	
Treated	18 (40.0)	45 (63.4)			
Amoxicillin	Gender				
	Male	24 (38.7)	38 (61.3)	0.94–4.15	>0.05
	Female	30 (55.6)	24 (44.4)		
	Smoking status				
	Yes	8 (33.3)	16 (66.7)	0.78–5.13	>0.05
	No	46 (50.0)	46 (50.0)		
	Alcohol consumption				
	Yes	20 (44.4)	25 (55.6)	0.45–2.43	>0.05
	No	34 (47.9)	37 (52.1)		
	Treatment history				
Untreated	25 (46.3)	28 (45.2)	0.48–14.16	>0.05	
Treated	29 (53.7)	34 (54.8)			

\*significant difference (Chi-squared test).

2005, the decrease in HP infection rate could indicate the effectiveness of the government educational campaigns in enhancing the public awareness of these diseases, and Vietnam’s public health system.

Regarding the rate of antibiotic-resistant HP, high resistance rates of HP (>50%) to all commonly used antibiotics were observed (Figure 1). Our results were significantly higher than that of another work conducted in Ho Chi Minh city, the largest economic center in the South of Vietnam, which stated that the HP resistance rates were 0% for amoxicillin (53.4% in our result), 33% for clarithromycin (94.8% in our result), 69.9% for metronidazole (96.6% in our result), 18.4% for levofloxacin (61.2% in our result), and 5.8% for tetracycline (70.7% in our result) [4]. This alarming fact states that although the rates of HP infection are

decreasing, the prevalence of antibiotic-resistant HP in PU patients is rocketing in recent year, especially in areas with high numbers of PU patients (due to eating habits) such as Tien Giang. Seriously, nearly 100% of the HP strains in tested samples resisted metronidazole and clarithromycin. The reason behind the extremely high rates of resistance to these two drugs in Vietnam could be their widespread over-the-counter utilization. Metronidazole and clarithromycin are easily purchased in any pharmacy or drug store in Vietnam, without prescriptions, and they are not only used to treat HP but also other infections [11], [12]. More importantly, metronidazole and clarithromycin are considered the first-line therapies for HP infection in Asian countries [20]. Thus, Vietnamese policy-makers should reconsider these medications to improve the effectiveness of HP eradication.

In case of first-line therapy failure, levofloxacin has been used as a rescue drug [21], [22]. Nevertheless, the incidence of levofloxacin resistance is increasing statistically in the world [23], [24] and Vietnam. The prevalence of levofloxacin-resistant HP increased from 18.4% in 2013 [4] to 61.2% in 2021 (our study). Although levofloxacin is not commonly purchased as an over-the-counter drug, other fluoro-quinolones, namely, ciprofloxacin, are generally used for various infections in Vietnam. This could lead to HP cross-resistance with levofloxacin. On the other hand, amoxicillin, although being extensively used in other common bacterial infections in the nose, throat, and open wounds, HP resistance to amoxicillin was the lowest in our study. This contradiction might be due to the HP mechanisms of developing resistance to amoxicillin, which through the genomic mutation in the *pbp1A* gene, and this phenotype is death when being frozen [25], [26].

Regarding the associations between HP antibiotic resistance and patient sociodemographic characteristics, patient gender and smoking status did not possess any correlation. On the other hand, participants who consumed alcohol had higher rates of HP resistance to tetracycline and clarithromycin than those who did not drink alcohol. Although the risk of HP infection in alcohol drinkers was lower than that of non-drinkers [27], the risk of HP developing resistance to antibiotics is higher in alcohol drinkers. This fact might be due to the effect of alcohol in accelerating the HP genetic mutations. Further research is necessary to elucidate this phenomenon. Interestingly, patients who have previously been treated with levofloxacin for HP eradication were at a higher risk of developing HP resistance to this antibiotic than the untreated group. Notably, other antibiotics did not demonstrate a similar issue. This indicates that HP could develop resistance to levofloxacin much easier than other antibiotics. These data also reconfirm that HP's resistance to levofloxacin in Vietnam increased more than 3-fold within 10 years, even though this drug is not commonly used for other diseases.

## Conclusion

This study investigated the HP infection and HP antibiotic resistance rates, and their associations between participants' sociodemographic factors, in PU patients, in a high PU rate province in Vietnam. Although the rate of HP infection decreased significantly compared to the previous studies, the HP resistance rates were rocketing and become alarmingly high (>50%), for all five antibiotics commonly used in HP treatment (metronidazole, clarithromycin, tetracycline, levofloxacin, and amoxicillin). Furthermore, significant links were noted between the alcohol consumption and clarithromycin/tetracycline resistance; and between the previous uses of levofloxacin and its resistance. Alcohol consumption might play an important role in developing antibiotic-resistant HP, thus, further research is necessary to elucidate this phenomenon. Conclusively, urgent needs are required for continuous antibiotic resistance surveillance to timely monitor the changes in microbes' antibiotic resistance, especially HP, to inform policy-makers on appropriate decision-making and action.

## Compliance with Ethics Requirements

The authors declare no conflict of interest regarding this article. The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008 [5], as well as the national law. Informed consent was obtained from all the patients included in the study.

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