

PRIMARY ANTIBIOTIC RESISTANCE OF *HELICOBACTER PYLORI* IN PEPTIC ULCER DISEASE PATIENTS

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ABSTRACT

Background: Antibiotic resistance is the main cause of failure in *Helicobacter pylori* (*H. pylori*) eradication. Updating the antibiotic resistance situation of *H. pylori* in each region is important for recommending appropriate treatment regimens for the population and optimizing the effectiveness of *H. pylori* eradication treatment for each region and country. **Objective:** To determine the rate of primary antibiotic resistance of *H. pylori* strains to Amoxicillin (AMX), Clarithromycin (CLA), Levofloxacin (LEV), Metronidazole (MET), and Tetracycline (TET). **Method:** A cross-sectional descriptive study was performed on 216 patients with peptic ulcer disease who underwent endoscopy and antibiotic culture by Epsilometer test (E-test) at the American International Hospital from October 2019 to September 2022. **Results:** The rate of primary resistance to Clarithromycin was the highest at 96.30%, while the rates of resistance to Levofloxacin, Metronidazole, and Amoxicillin were 58.8%, 8.80%, and 2.78%, respectively. In the study, there were no cases of primary antibiotic resistance to Tetracycline, with a resistance rate of 0%. There was no statistically significant difference in the rate of resistance to each antibiotic between the male and female groups ($p > 0.05$). The rate of dual resistance to two antibiotics was very high, with 161/216 cases (74.54%), and the highest rate of resistance was to CLA + LEV with 124 cases (57.41%). The

rates of *H. pylori* strains resistant to CLA + MET, MET + LEV, CLA + AMX, AMX + LEV, and AMX + MET were 7.41%, 3.7%, 2.78%, 1.39%, and 0.46%, respectively. There were 11 cases of *H. pylori* strains resistant to three types of antibiotics, a rate of 5.09%, and there were no cases resistant to four or more antibiotics. Only 1.39% remained sensitive to all five antibiotics in eradication regimens. **Conclusion:** The very high rate of resistance to Clarithromycin indicates that the standard triple regimen is no longer effective and should not be used in clinical practice. The regimen with Levofloxacin should be combined with Bismuth to enhance treatment effectiveness. The rates of resistance to Amoxicillin, Tetracycline, and Metronidazole were low, so a Bismuth quadruple or a combination of these three drugs may be very effective in eradicating *H. pylori*.

Key words: Primary antibiotic resistance, *Helicobacter pylori*, *H.pylori*, peptic ulcer disease.

I. INTRODUCTION

Helicobacter pylori (*H.pylori*) infection is one of the most common chronic bacterial infections in humans, affecting approximately half of the global population, around 4.4 billion people worldwide¹. It leads to various gastrointestinal issues, such as peptic ulcers and gastric cancer¹. In 2009, the International Agency for Research on Cancer classified *H.pylori* as a Group 1 carcinogen². Eradicating *H.pylori* through treatment is essential in resolving many cases of peptic ulcers and preventing the development of gastric cancer. However, the increasing antibiotic resistance of *Helicobacter pylori* is a significant factor

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affecting the effectiveness of current treatment regimens and a leading cause of treatment failure. A 2018 study by the World Health Organization revealed that the overall resistance rates for Clarithromycin, Metronidazole, and Levofloxacin were greater than 15%, while Amoxicillin and Tetracycline showed resistance rates of less than 10% ³. The antibiotic resistance situation of *H.pylori* tends to vary across different geographic regions and countries worldwide, including Vietnam. This presents a challenging obstacle for researchers and clinicians in the field of *H.pylori* eradication.

In Vietnam, a study conducted in 2019 by Vu Van Khiem and colleagues showed primary resistance rates of *H.pylori* to Amoxicillin, Clarithromycin, Levofloxacin, Metronidazole, and Tetracycline at 15%, 34.1%, 27.9%, 69.4%, and 17.9%, respectively ⁴. Since then, no other research has reported on the current primary antibiotic resistance status of *H.pylori* to these antibiotics in the southern region of Vietnam or the country as a whole. Therefore, updating the current antibiotic resistance patterns of *H.pylori* in each region is crucial for recommending appropriate treatment protocols tailored to specific populations and optimizing the effectiveness of *H.pylori* eradication strategies for different regions and countries. We aim to investigate whether the primary antibiotic resistance rates of *H.pylori* have trended upward and how they have changed compared to previous years.

II. METHOD:

The study will include all patients diagnosed with peptic ulcers in the gastrointestinal tract, infected with *H.pylori*, and with antibiotic resistance testing conducted at the American International

Hospital from October 2019 to September 2022.

Inclusion criteria:

Patients aged ≥ 18 years with gastrointestinal symptoms and endoscopy-diagnosed peptic ulcers.

Diagnosis of *H.pylori* infection with at least two positive tests:

Test 1: Rapid urease test (Pylori-test by Nam Khoa Company) positive in all patients.

Test 2: *H.pylori* culture.

H.pylori strains isolated from patients will be subjected to antibiotic susceptibility testing against Amoxicillin (AMX), Clarithromycin (CLA), Levofloxacin (LEV), Metronidazole (MET), and Tetracycline (TET) using the Epsilometer test (E-Test) method to determine minimum inhibitory concentrations (MICs). The *H.pylori* cultures will be grown on horse blood-enriched agar plates with antibiotics and incubated under microaerophilic conditions at 37 °C for 4 days.

H.pylori strains will be considered resistant when the MIC is ≥ 1 $\mu\text{g/ml}$ for AMX, CLA, LEV, ≥ 8 $\mu\text{g/ml}$ for MET, and ≥ 4 $\mu\text{g/ml}$ for TET.

Exclusion criteria:

Patients previously treated for *H.pylori* infection.

Patients with active gastrointestinal bleeding and Forrest IA, IB, IIA, IIB duodenal ulcers.

Patients with a history of gastric resection.

Research methods:

The study will employ a cross-sectional descriptive design. The sample size will be calculated using a specific formula.

$$N = Z^2_{(1-\alpha)/2} \times \frac{p \times (1-p)}{d^2}$$

The 2019 synthesis study by Vu Van Khiên and colleagues revealed the primary antibiotic resistance rates of *H.pylori* to AMX, CLA, MET, LEV, and TET were 15.0%, 34.1%, 69.4%, 27.9%, and 17.9%, respectively ⁴. The required sample size (n) for each corresponding antibiotic resistance rate was calculated to be 49, 87, 82, 78, and

57, respectively. Therefore, we opted for the largest sample size, which requires at least n=87 patients.

The research protocol has been approved by the Biomedical Research Ethics Committee of Pham Ngoc Thach University of Medicine, under reference number 537/TĐHYKPNT-HĐĐĐ

III. RESULTS:

We have selected 216 patients. The general characteristics of the study subjects are presented in Table 1

Table 6: The general characteristics of the study population

Total number of patient	N= 216	
Age	42,85 ± 11,76	
Gender	Male	107(50.5%)
	Female	109(49.5%)
BMI	23,68 ±3,69	
History	Gastrointestinal ulcers	21.3%
	Gastroesophageal reflux	9.26%
	Diabetes	6.02%
	Hypertension	11.11%
	Family history of <i>H.pylori</i> infection	5.56%
	Family history of gastric cancer	2.78%
	Smoking	2.78%

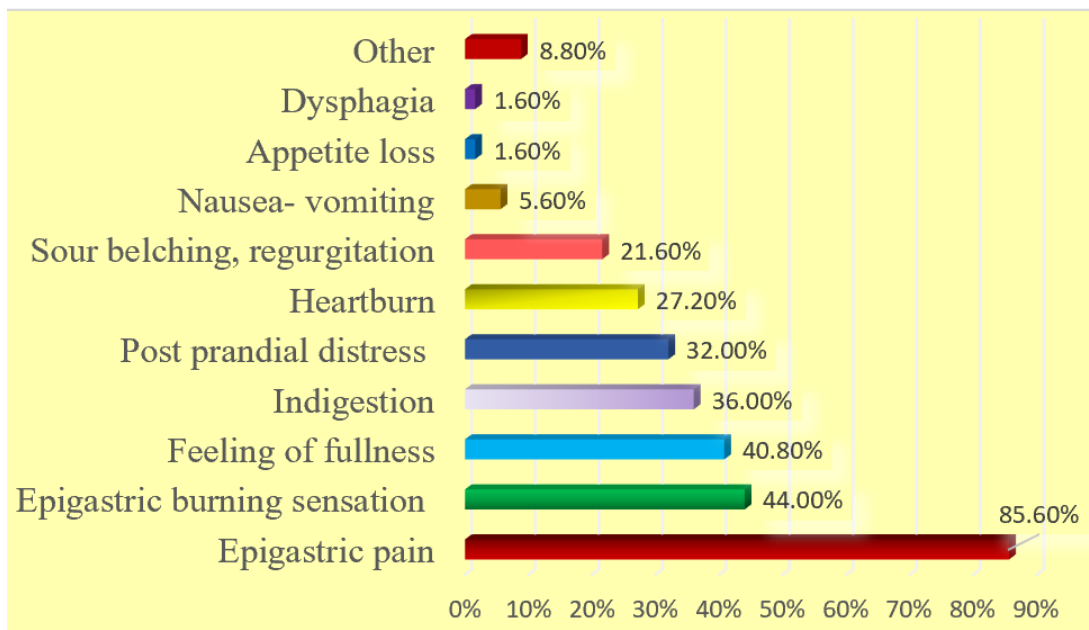


Figure 2: The frequency of clinical symptoms is as follows

The rate of primary resistance to each type of antibiotics in *H.pylori*

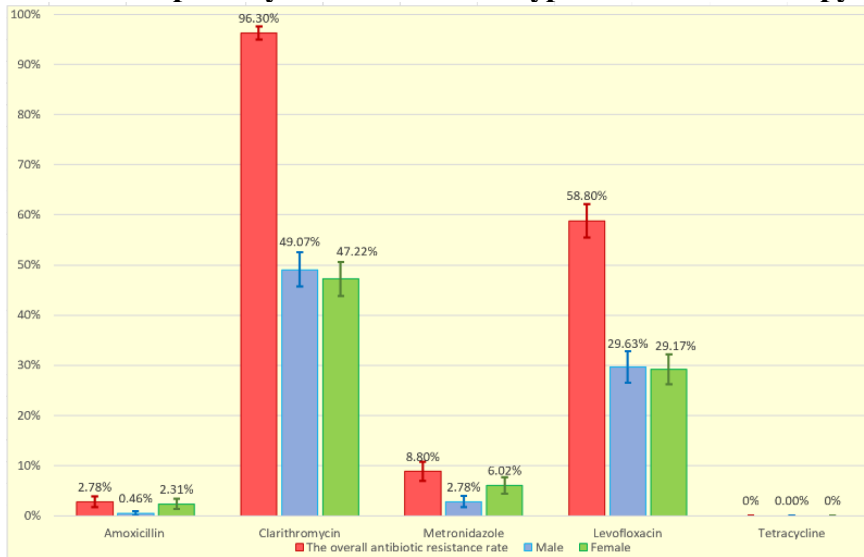


Figure 3: The rate of primary resistance to each type of antibiotics in *H.pylori* in the two groups of males and females

Comments: The rate of primary resistance to Clarithromycin is the highest at 96.30%, while there were no cases with primary resistance to Tetracycline (0%). The resistance rates to each type of antibiotic in both male and female groups showed no statistically significant difference, with $p > 0.05$

The rate of dual resistance of antibiotics

There were 161 cases of dual resistance of antibiotics, accounting for 74.54%

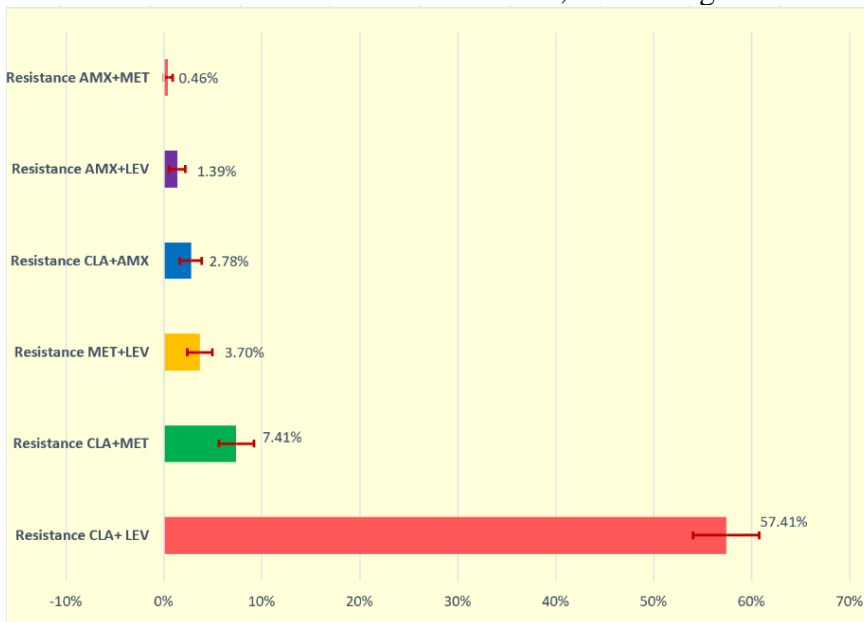


Figure 4: Resistance rate of *H.pylori* to 2 types of antibiotics

Comments: The rate of dual resistance of *H.pylori* to CLA+LEV is the highest, reaching 57.41%

The resistance rate to 3 types of antibiotics

Table 7: The primary resistance rate to 3 types of antibiotics of *H.pylori*

Triple drugs resistance		The number of drug-resistant strains	Percentage (%)	CI 95%
CLA+MET+LEV	N=216	7	3.24	1.41-6.84
AMX+CLA+MET		1	0.46	0.02-2.95
AMX+CLA+LEV		3	1.39	0.36-4.33
Total		11	5.09	2.7-9.17

Comments: There are 11 cases of *H.pylori* strains that are resistant to 3 types of antibiotics, accounting for 5.09% of the total. Among them, there are 07 cases resistant to CLA+MET+LEV, which represents the highest rate at 3.24%.

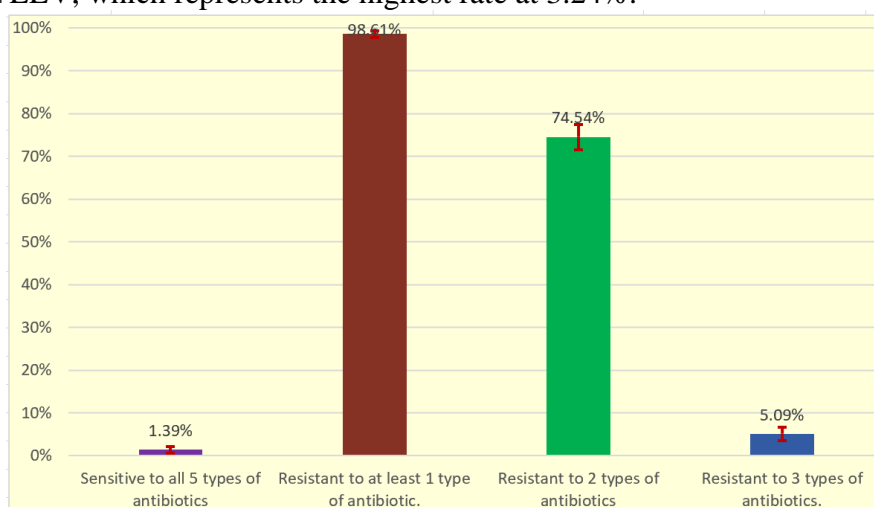


Figure 5: Chart of the distribution of antibiotic resistance rates

Comments: The primary resistance rate of *H.pylori* to at least 1 type of antibiotic accounts for 98.61% (213/216 cases). Resistance to 2 types of antibiotics represents 74.54%, while resistance to 3 types of antibiotics accounts for 5.09%. Only 1.39% (3 cases) remain sensitive to all 5 types of antibiotics in the eradication regimens. There are no cases showing primary resistance to 4 or more types of antibiotics, representing 0% of the cases

Characteristics of the distribution of MIC values with five types of antibiotics in the treatment of *H.pylori* eradication

Table 8: Characteristics of the MIC values of antibiotic-resistant *H.pylori* strains

Antibiotics	Median value	CI 95%
Amoxicillin	0,5	0.09-1
Clarithromycin	1.5	0.74 - 4
Metronidazole	2	0.30- 8
Levofloxacin	1	0.07-4
Tetracycline	0.5	0.14-2

Comments: The median MIC values of antibiotics AMX, CLA, MET, LEV, and TET are 0.5, 1.5, 2, 1, and 0.5, respectively. There is no statistically significant difference in the MIC values of each antibiotic between males and females ($p>0.05$)

IV. DISCUSSION:

General characteristics of the study population

The average age in our study was 42.85 ± 11.76, with the oldest participant being 74 years old and the youngest being 18 years old. There were 107 females, accounting for 49.5% of the participants, and 109 males, accounting for 50.5%. The male-to-female ratio was 1.02/1. Similarly to Tang's study (2022)⁵, in Ana Ferro's study (2019), it was found that males had a significantly higher rate of *H.pylori* infection compared to females, with an odds ratio (OR) of 1.33 (95% CI: 1.04-1.70) and a prevalence ratio (PR) of 1.05 (95% CI: 1.00-1.10)⁶. Therefore, in our study, the population consisted of *H.pylori* -infected patients who had not been previously treated, which resulted in a higher number of male patients.

The mean body mass index (BMI) in the study was 23.68 ± 3.69, with the highest being 35.30 and the lowest being 16.20. The rate of overweight and obesity was 55.1%. Several meta-analyses of various disease studies have found a positive correlation between *H.pylori* infection and the development of obesity. Therefore, *H.pylori* -positive patients were more likely to be obese, and obese individuals had a higher risk of *H.pylori* infection⁷.

Functional symptoms: In patients with gastric and duodenal ulcers, the most

common symptom is upper abdominal pain, accounting for 85.60% of cases. In Nguyen Thanh Liem's study, abdominal pain was also the most prevalent symptom, with a rate of 94.1%. Additionally, other functional symptoms such as heartburn, bloating, fast satiety, belching, and sour eructation accounted for the following rates: 44%, 40.8%, 36%, 32%, 27.2%, and 21.60%, respectively. Similar to Nguyen Thanh Liem's study, the prevalence of these symptoms ranged from approximately 20% to 40%⁸. These findings demonstrate that upper abdominal pain is the most commonly experienced symptom in patients with *H.pylori* -positive gastric and duodenal ulcers, and it is a significant reason why patients seek medical attention.

The research results showed that the prevalence of primary resistance to Clarithromycin was the highest, reaching 96.30%, while the resistance rates to Levofloxacin, Metronidazole, and Amoxicillin were 58.8%, 8.80%, and 2.78%, respectively. No cases of resistance to Tetracycline were found in the study, with a resistance rate of 0%. When comparing these findings with other studies on *H.pylori* antibiotic resistance conducted in different regions and countries over the years, our research revealed some differences, which are presented in the table.

Table 5: Prevalence of primary antibiotic resistance in various domestic and international studies.

Domesetic studies						
Author/n	Year/Region	Prevalence of primary antibiotic resistance%				
		AMX	CLA	MET	LEV	TET
Tran Thanh Binh (n=103) ⁹	2013 South/North	0	33	69.9	18.4	5.8
Phan Trung Nam (n=92) ¹⁰	2015/Central	0	30.2	67.4	39.5	-

Domesetic studies						
Author/n	Year/Region	Prevalence of primary antibiotic resistance%				
		AMX	CLA	MET	LEV	TET
	region					
Quek Camelia (n=57) ¹¹	2016/ South	5.3	87.7	47.4	36.8	24.6
Pham Hung Van (n=193)	2016/ South	1.9	85.5	35.2	27.9	24.4
Đang Ngoc Quy Hue ¹² (n=119)	2018/South	-	66.1	-	37.8	-
Vu Van Khien ⁴ (10 studies)	2019/ All	15	34.1	61.5	45.7	23.5
Our study /(n=216)	2022/ South	2.78	96.30	8.80	58.8	0
International studies						
Author/n	Year/ Nation	Prevalence of primary antibiotic resistance%				
		AMX	CLA	MET	LEV	TET
Shiota S ¹³ (n=135)	2015/US	0	16.4	20.3	31.3	0.8
Yu-Ting Kuo ¹⁴ (176 studies)	2016 Asia-Pacific region	3	17	44	18	4
Bachir M (n=151) ¹⁵	Algeria	0	22.8	61.1	0	-
Dan Wang (N=100) ¹⁶	2019/China	9	31	78	56	15
Palmitessa V (N=92) ¹⁷	2020/ Italy	1.6	37.7	16.4	26.2	0

The prevalence of primary Clarithromycin resistance in our study is quite high compared to national studies conducted between 2013-2019. However, we believe this is consistent with the current situation in Vietnam, where Clarithromycin, a widely used Macrolide antibiotic, is commonly prescribed by doctors and easily accessible to the public without a prescription for treating common infections such as upper respiratory tract infections, pharyngitis, etc. The high resistance rate of 96.3% indicates that the current standard triple therapy is no longer highly effective in eradicating *H.pylori*.

The prevalence of primary Levofloxacin resistance in our study is 58.8%, which is higher than other domestic studies. However, when considering the trend over time, it shows that the prevalence of Levofloxacin resistance is gradually increasing. In the years 2013, this rate was only about 18%, but it steadily increased over 5 years to

approximately 39% in 2018, as observed in Dang Ngoc Quy Hue's study. Continuing the trend, in our study conducted in 2022, the Levofloxacin resistance rate reached nearly 60%, surpassing the rates reported in other studies worldwide and in the region. According to Salvodi's meta-analysis study in 2018, the prevalence of primary Levofloxacin resistance in the Southeast Asia region was 30%³.

The prevalence of primary Metronidazole resistance in our study is only 8.8%, significantly lower than previous domestic studies. About 10 years ago, Tran Thanh Binh's study showed a Metronidazole resistance rate of nearly 70%. However, three years later, Pham Hung Van's study reported a decreased rate of approximately 35.2%. In our study, the prevalence was even lower at around 8.8%. In a long-term cohort study conducted in Spain by Ana Morilla over 13 years, the results indicated a decreasing trend

in Metronidazole resistance, from 45% in 2004 to 30% in 2015. This suggests that unlike the increasing trend observed with other antibiotics, Metronidazole resistance tends to decline over time.

Metronidazole is a type of antibiotic belonging to the Nitroimidazole group and is used to treat anaerobic bacterial infections. It is usually prescribed and used by specialized doctors. Strict adherence to the prescribed antibiotic regimen and proper treatment duration can contribute to limiting the development of *H.pylori* bacterial mutations and antibiotic resistance.

The prevalence of primary Amoxicillin resistance in our study is approximately 2.78%, which closely aligns with the findings of other studies. Yu-Ting Kuo reported a resistance rate of 3%, Quek Camelia found a rate of 5.3%, while Tran Thanh Binh and Phan Trung Nam's study did not identify any *H.pylori* strains resistant to Amoxicillin. Other studies conducted worldwide and in the region have also shown very low rates of Amoxicillin resistance. According to Salvodi's meta-analysis study in 2018, the prevalence of primary Amoxicillin resistance in the Southeast Asia region was 2%³, which is consistent with our findings. These results collectively suggest that Amoxicillin remains an effective antibiotic for treating *H.pylori* infections, and the prevalence of Amoxicillin resistance is relatively low in both local and global settings

In our study, no cases of primary Tetracycline resistance were detected. In Vietnam, Tran Thanh Binh's study in 2013 reported a similar rate of approximately 5.8%. However, in studies conducted by Quek Camelia and Pham Hung Van in 2016, the prevalence of primary Tetracycline

resistance showed an increasing trend, reaching nearly 25%.

The results of our study are consistent with the findings of Bachir¹⁵ and the meta-analysis conducted by Salvodi in 2018³, both of which reported a 0% prevalence of primary Tetracycline resistance in the Southeast Asia region and Italy¹⁷, respectively. Tetracycline remains a highly sensitive antibiotic against *H.pylori* in Vietnam, possibly due to its limited use and rarity in community treatments, leading to fewer occurrences of bacterial mutations. Additionally, our study found no statistically significant differences in resistance rates between male and female participants, which is in line with Tran Thanh Binh's study⁹.

The results reveal a very high dual resistance rate to two types of antibiotics, accounting for 161 out of 216 cases (74.54%). This rate is higher than the findings from Tran Thanh Binh's study in 2013⁹, where the dual resistance rate to two antibiotics was 57.28%, and Dan Wang's study¹⁶, which reported a rate of 23%. This is a concerning figure that highlights the alarming state of multi-drug resistance in *H.pylori*. Among the dual resistance cases, the highest rate was observed for CLA + LEV accounting for 124 cases (57.41%). This rate significantly increased and showed a statistically significant difference ($p < 0.001$) compared to Tran Thanh Binh's study (8.7%). Regarding the CLA+ MET dual resistance, the rate decreased from 24.3% in Tran Thanh Binh's study in 2013 to 7.41% in our study in 2022, which is a statistically significant reduction ($p = 0.006$). This improvement could be attributed to the decrease in the single resistance to MET, which dropped to 8.80% in our study, compared to 69.9% in Tran Thanh Binh's

study⁹. Additionally, our study did not identify any cases of dual resistance to MET+ TET which is an encouraging signal and aligns with the treatment recommendations for *H.pylori*, particularly the first-line quadruple therapy that includes Bismuth, Metronidazole, and Tetracycline as the main antibiotics¹⁸.

In our study, we observed 11 cases of triple resistance to three types of antibiotics, accounting for 5.09% of the cases. However, no cases were found to have resistance to four or more types of antibiotics. This triple resistance rate is lower than that reported in Tran Thanh Binh's study, where the triple resistance rate was 14.56%, and resistance to four types of antibiotics was found in 2 out of 103 cases (1.9%)⁹. Our study also revealed that only about 1.39% of *H.pylori* strains were susceptible to all five types of antibiotics tested, indicating that up to 98.61% of *H.pylori* strains were resistant to at least one type of antibiotic. This finding is similar to the study by Dan Wang, which reported a 1.9% rate of strains being susceptible to all five antibiotics¹⁶. The low rate of *H.pylori* strains remaining sensitive to all five antibiotics highlights the importance of using combination therapy in the eradication of *H.pylori* infections. Relying on a single antibiotic may not be effective due to the high prevalence of antibiotic resistance. In the future, it is hoped that clinical researchers will discover and develop new antibiotics to add to the treatment protocols for *H.pylori*, providing more effective options for eradicating the bacteria.

The Minimum Inhibitory Concentration (MIC) values for different antibiotics in our study showed the following characteristics: Amoxicillin: The MIC50 value was 0.5, and there were a few *H.pylori* strains with

unusually high MIC values ranging from 3 to 4 µg/ml. Clarithromycin: Nearly 97% of *H.pylori* strains exhibited an MIC50 value of 1 µg/ml. However, there were a few strains with unusually high MIC values around 12.5 µg/ml. Metronidazole: The median MIC value was around 2 µg/ml, and only 8.8% of *H.pylori* strains had high MIC values, all at the threshold of 8 µg/ml. There were no strains with abnormally high MIC values. Levofloxacin: The MIC50 value for Levofloxacin was 1, which is also the resistance threshold according to the E-test EUCAST method. Tetracycline: The MIC50 value was 0.5, and there were a few strains with unusually high MIC values around 3 µg/ml. However, no strain had an MIC value exceeding 4 µg/ml. Moreover, there were no statistically significant differences in MIC values between male and female *H.pylori* strains ($p>0.05$). Comparing our results with other studies, the MIC50 values reported by Yahav were 0.16 for AMX, 4 for CLA, 6 for MET, and 0.016 for Tetracycline¹⁹. In another study by Xueping Huang in 2021, the MIC50 values for AMX, CLA, MET, LEV, and TET were 0.125, 0.031, 8, 0.25, and 0.0625, respectively²⁰. In the study by Dang Ngoc Quy Hue, 79.3% of the MIC values for Clarithromycin-resistant *H.pylori* strains were within the range of (1-64 µg/ml)¹², while this percentage was 61.8% in Tran Thanh Binh's study⁹. The differences in MIC distribution of antibiotic-resistant *H.pylori* strains among various studies could be attributed to the variability in the resistance profiles of *H.pylori* strains and the usage of antibiotics in different regions, countries, and settings. Further in-depth research is needed to evaluate these factors more comprehensively.

V. CONCLUSION

Sensitivity testing to antibiotics is highly important in determining the appropriate eradication regimen for each patient with *Helicobacter pylori* infection. The high resistance rate to Clarithromycin indicates that the standard triple therapy is no longer effective and should not be used in clinical practice.

Regimens containing Levofloxacin should be combined with Bismuth to enhance treatment efficacy. On the other hand, the low resistance rates to Amoxicillin, Tetracycline, and Metronidazole suggest that the 4-drug regimen with Bismuth or the triple therapy combining these three antibiotics together is highly effective in eradicating *H.pylori*. Selecting the appropriate treatment regimen based on sensitivity testing results will improve treatment efficacy and prevent antibiotic resistance.

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