

Management of Antibiotic-Resistant *Helicobacter pylori* Infection: Perspectives from Vietnam

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Antibiotic resistance is the most important factor leading to the failure of eradication regimens. This review focuses on the prevalence of *Helicobacter pylori* primary and secondary resistance to clarithromycin, metronidazole, amoxicillin, levofloxacin, tetracycline, and multidrug in Vietnam. We searched the PubMed, EMBASE, Vietnamese National Knowledge Infrastructure, and Vietnamese Biomedical databases from January 2000 to December 2016. The search terms included the following: *H. pylori* infection, antibiotic (including clarithromycin, metronidazole, amoxicillin, levofloxacin, tetracycline, and multidrug) resistance in Vietnam. The data were summarized in an extraction table and analyzed manually. Finally, Excel 2007 software was used to create charts. Ten studies (three studies in English and seven in Vietnamese) were included in this review. A total of 308, 412, 523, 408, 399, and 268 *H. pylori* strains were included in this review to evaluate the prevalence of *H. pylori* primary resistance to amoxicillin, clarithromycin, metronidazole, levofloxacin, tetracycline, and multidrug resistance, respectively. Overall, the primary resistance rates of amoxicillin, clarithromycin, metronidazole, levofloxacin, tetracycline, and multidrug resistance were 15.0%, 34.1%, 69.4%, 27.9%, 17.9% and 48.8%, respectively. Secondary resistance rates of amoxicillin, clarithromycin, metronidazole, levofloxacin, tetracycline, and multidrug resistance were 9.5%, 74.9%, 61.5%, 45.7%, 23.5% and 62.3%, respectively. In Vietnam, primary and secondary resistance to *H. pylori* is increasing over time and affects the effectiveness of *H. pylori* eradication. (**Gut Liver 2019;13:483-497**)

Key Words: *Helicobacter pylori*; Amoxicillin; Bismuth; Clar-

ithromycin; Metronidazole

INTRODUCTION

In 1983, Marshall and Warren¹ discovered *Helicobacter pylori*—a gram-negative bacillus that infects the human stomach mucosa. Further studies confirmed that *H. pylori* is the main cause of chronic gastritis, peptic ulcer disease, gastric marginal zone/mucosa-associated lymphoid tissue (MALT) lymphoma and gastric carcinoma.²⁻⁷ Recently, it has been suggested that *H. pylori* may be associated with extraintestinal diseases, including immune thrombocytopenic purpura, refractory iron deficiency anemia and vitamin B₁₂ deficiency.^{8,9} Globally *H. pylori* has been classified as a class I carcinogen and the major cause of gastric cancer.¹⁰

In Vietnam, frequency of *H. pylori* infection is rather popular and similar to that in the other developing countries. A large-scale study showed that frequency of *H. pylori* infection made up over 70% in adults and lightly reduced in children.¹¹⁻¹⁴ An investigation study in a hospital indicated that frequency of *H. pylori* infection was 59.9% to 69.9% for chronic gastritis; 77.8% for gastric ulcer; 85% to 95% for duodenal ulcer and 85.3% to 93.6% for gastroduodenal ulcer.¹⁴⁻¹⁶

Generally, *H. pylori* eradication is indicated in cases of peptic ulcer including active, non-active and complicated, gastric MALT lymphoma, and to some extent, chronic gastritis and functional dyspepsia. Eradication of *H. pylori* not only heals peptic ulcers, but also prevents their recurrence and reduces the risk of development of gastric cancer.¹⁷⁻²¹ In addition, diseases related to *H. pylori* such as MALT lymphoma, gastric atrophy and intestinal dysplasia are also recoverable after antibiotic

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treatment.^{22,23}

Triple therapy regimens including one proton pump inhibitor (PPI) and two antimicrobial agents such as amoxicillin (A), clarithromycin (C), metronidazole (M), levofloxacin (L), and tetracycline (Te) have been widely used to eradicate this bacterium. Although rate of successful eradication treatment depends on many factors such as smoking and patients' compliance, antibiotic resistance is an important factor reducing treatment efficiency.^{24,25} Rate of the antibiotic resistance is higher in the developing countries than in the developed countries.^{26,27} In addition, the rate of antibiotic resistance often correlates with the amount of antibiotics consumed in the population.^{3,28-30} In Vietnam, based on International Consensus, regimens of using two antibiotic drugs: clarithromycin and amoxicillin, or clarithromycin and metronidazole, are standard regimen to eradicate *H. pylori*.^{20,31,32} In Vietnam, in early 1990s, rate of *H. pylori* eradication exceeded 90%. However, recent statistics indicate that *H. pylori* eradication rate has decreased to 60%–70%. The most important cause for the reduced success of standard triple therapy is the increasing rate of *H. pylori* clarithromycin/metronidazole/levofloxacin resistance.³³⁻³⁵ In this review, we provide the following information: (1) frequency of *H. pylori* infection in Vietnam; (2) rate of *H. pylori* infection in chronic gastritis, gastric ulcer and gastric cancer in Vietnam; (3) efficiency of *H. pylori* eradication regimen in Vietnam; (4) antibiotic resistance rate of *H. pylori* in Vietnam; (5) the cause of *H. pylori* resistance in Vietnam; or (6) perspectives from Vietnam.

The data was summarized in extraction table and analyzed manually. Finally, Excel 2007 software (Microsoft, Redmond, WA, USA) was used to draw charts.

1. Prevalence and risk factors of *H. pylori* infection in Vietnam

There is a difference in rate of *H. pylori* infection among the Asian countries and even in a country.³⁶ The rate of *H. pylori* infection depends on socio-economic and environmental conditions. Frequency of *H. pylori* infection in the developing countries is often higher than that in the developed countries. In developing countries such as India and Saudi Arabia and African countries, the infection rate is high and approximately 80% of the population infected with *H. pylori* by 20 years old.³⁷ In contrast, the infection rate is reported to be as low as 10% to 20% in developed countries, and the infection rate increases at a rate of approximately 1% per year.³⁸ In Japan, the rate of *H. pylori* infection in children under the age of 10 is very low (approximately 5%) and the rate of *H. pylori* infection gradually increases by ages.³⁹

Vietnam is in the center of Southeast Asia Region and in the East of the Indochinese Peninsula and borders Chinese to the North, Laos and Cambodia to the West and the South China Sea and Pacific Sea to the Southeast. Vietnam has its population of about 94 million people and 54 ethnic groups, including over 80% of Kinh group. Vietnam divided into three different areas:

Northern Vietnam (25 provinces), Central Vietnam (19 provinces), and Southern Vietnam (19 provinces). There are three main cities: Hanoi, Hue, and Ho Chi Minh City. Fig. 1 shows the map of Vietnam, with three different regions (north, central, and south), with three major cities in Vietnam (Hanoi, Hue, and Ho Chi Minh City).

Vietnam does not have a national survey of *H. pylori* infection epidemiology. The study only focused on some areas in major cities, or delta. These studies also focus only on Kinh people. Before 2010, there was no study on the epidemiology of *H. pylori* in the ethnic group

In 2005, Hoang *et al.*¹¹ conducted epidemiologic investigation of *H. pylori* infection rate in the community, including children and adults, through serological test, in urban (Hanoi) and rural Vietnam (Hatay province). Study results indicated that the rate of *H. pylori* infection in community was 74.6%. The rate of *H. pylori* infection in Hanoi (78.8%) was higher than that in Hatay (69.2%). This difference was significant ($p=0.0007$). These study results showed that the rate of *H. pylori* infection in the community in Vietnam is very high, especially in the urban areas (Hanoi). They proved that the frequency of *H. pylori* infection has gradually increased by ages, particularly at the age of 30 and above. The rate of *H. pylori* infection at the age of 30, 52, 59 and 83 is 33.3%, 49.2%, 69.2%, and 78.3%, respectively.¹¹ The study shows that the prevalence of *H. pylori* infection is high in Vietnam and especially high in large urban, such as the city of Hanoi.

Prevalence of *H. pylori* infection is also high in children. A study of Nguyen *et al.*¹² on 284 children at 6 months and 15



Fig. 1. Map of Vietnam with three different regions: North, Central, and South. Note: North Vietnam includes northwestern, northeast and Red River Delta areas. Central Vietnam includes north central coast, south central coast and central highlands. South Vietnam includes southeastern and Mekong River Delta areas. Reprinted with the permission of Nations Online Project.

years, through serological test showed that the rate of *H. pylori* infection in children was 34.0%. Study examined the relationship between *H. pylori* infection and a number of factors, including: sociodemographic characteristics, health status, environmental status, health status, and so on. Study concluded that person-to-person transmission and sociodemographic factors are factors associated with *H. pylori* infection

Besides the serological test, urine tests are conducted to investigate the rate of *H. pylori* infection in community, as well as applied for people with gastric diseases. Nguyen *et al.*¹⁵ found that Rapirun test had sensitivity, specificity and accuracy rate of 79.5%, 90.7%, and 84.5%, respectively. These results were similar to those of Quach *et al.*⁴⁰ upon testing and finding *H. pylori* in 200 patients by Rapirun Stick test to obtain sensitivity, specificity and accuracy rate of 84.7%, 89.9%, and 87%, respectively. However, these urine tests only helped investigation of *H. pylori* infection rate in community.

Recently, there have been some epidemiological investigation of *H. pylori* infection rates in ethnic, including adults and children.⁴¹⁻⁴⁴ In 2014, Binh *et al.*,⁴¹ investigated *H. pylori* infection rates (five different methods) on 494 volunteers. Research subjects are ethnic in two different areas: Lao Cai province (North Vietnam), Daklak Province (Central Vietnam). Results of the study indicate that the prevalence of *H. pylori* infection among ethnic minorities (adults) was 188 out of 494 (38.1%). There were significant differences in rates of *H. pylori* infection in Daklak and Lao Cai (51.0% vs 29.3%, $p < 0.001$). There are many factors may contribute to *H. pylori* infection such as geographical location, ethnicities, dietary habit, etc. The results showed that subjects living in Daklak had a significantly higher risk of *H. pylori* infection than those in Lao Cai (crude odds ratio [OR], 2.52; 95% confidence interval [CI], 1.73 to 3.65). With respect to minor ethnic groups, E De (crude OR, 2.44; 95% CI, 1.64 to 3.62) was at significantly higher risk, whereas Tay (crude OR, 0.3095%; CI, 0.16 to 0.56) and Dao (crude OR, 0.37; 95% CI, 0.17 to 0.73) were at significantly lower risk of *H. pylori* acquisition.

Nguyen *et al.*⁴² was studied the epidemiology of *H. pylori* infection in Khmer children in Mekong Delta (South Vietnam). Research results showed that the prevalence of *H. pylori* infection among children of Khmer ethnicity is 32.1%. *H. pylori* infection in mothers, in first sibling and in two first siblings in particular were found as high-risk factors for *H. pylori* infection in children (OR, 1.98; 95% CI, 1.12 to 3.18; OR, 2.12; 95% CI, 1.2 to 4.12; OR, 4.39; 95% CI, 2.81 to 6.94; respectively).

According to the statistics of the Government of Vietnam (2009), the Tay is the second largest ethnic group in Vietnam after the majority Kinh ethnic. Tay people live mainly in the mountains of northern Vietnam. Nguyen *et al.*⁴³ showed that epidemiology of *H. pylori* infection in Tay children (Lang Son province-North Vietnam). Study concluded that intra-familial *H. pylori* transmission are factors associated with *H. pylori* infection. In 2017, Nguyen *et al.*⁴⁴ also investigated the epidemiol-

ogy of *H. pylori* infection in Muong people. Muong is the thirteenth largest ethnic group in Vietnam after the majority Kinh and Tay ethnic group. The findings showed a familial clustering in these multi-generation familial structures and supported the hypothesis of person-to-person transmission in *H. pylori* infection.

Limitations of the study in Vietnam focused on the region and the number of volunteers has less.⁴¹⁻⁴⁴ However, the above studies show that family, race, geography, life-style and age are related to *H. pylori* infection in Vietnam.

Today, the economic conditions of Vietnam are going up, improve public sanitation, improve health care, could also be a factor in reducing the rate of *H. pylori* infection in the community. However, to demonstrate this matter, should have investigated the epidemiology of *H. pylori* infection nationwide.

In Korea, Lim *et al.*⁴⁵ has evaluated the time trend of seropositivity of *H. pylori* over the period of 13 years in an asymptomatic Korean population, and investigate associated risk factors. The overall seroprevalence of *H. pylori* infection was 54.4% (95% CI, 53.5% to 55.4%) in 2011 which is significantly decreased from 66.9% (95% CI, 65.4% to 68.6%) in 1998, and 59.6% (95% CI, 58.5 to 60.7%) in 2005 ($p < 0.001$). Factors including elderly, male gender, low income, residence in a rural area and high cholesterol (≥ 240 mg/dL) (OR, 1.33; 95% CI, 1.14 to 1.54) are related to *H. pylori* infection.

PREVALENCE *H. PYLORI* INFECTION IN GASTRIC DISEASES IN VIETNAM

1. Prevalence *H. pylori* infection in patients with chronic gastritis

Chronic gastritis is rather popular among the gastric diseases. But the studies of the rate of *H. pylori* infection in patients with chronic gastritis focused on Kinh group. In 2003, Long *et al.*⁴⁶ collaborated with Fukui University (Japan) to determine the rate of *H. pylori* infection by three methods: urease test, histopathology and serological test (ELISA) in 104 patients with gastric cancer and 104 patients with chronic gastritis. Study results indicated that the rate of positive *H. pylori* infection on the tests: urease test, histopathology and serological test was 44.5%; 57.6% and 88.1%, respectively.

Thang⁴⁷ found that the rate of *H. pylori* infection in patients with chronic gastritis ($n=235$) was 75.9% (determined by histopathology and CLO test). Thin⁴⁸ using four various methods: urease test, polymerase chain reaction (PCR), histopathology and culture showed that the rates of *H. pylori* infection were 58.1%, 58.1%, 56.3% and 57.0%, respectively. Dung⁴⁹ also obtained similar results, with the rate of 59.9%. Thus, these study results proved that the rate *H. pylori* infection in patients with chronic gastritis in Kinh group is rather high.

Recently, studies of the frequency of *H. pylori* infection in the ethnic groups of Vietnam have been conducted. Binh *et al.*⁴¹ conducted a study of the rate of *H. pylori* infection in the eth-

nic groups in Daklak (Central Highlands–Vietnam) and Lao Cai (North Vietnam). The author used four combined methods; including culture, histopathology-immunohistochemical, test urease and serological test. Study results pointed out that the rate of *H. pylori* infection was 188 out of 494 (38.1%), in which the rate of *H. pylori* infection in Lao Cai province (51.0%) significantly increased (crude OR, 2.52; 95% CI, 1.73 to 3.65) higher than that in Daklak province (29.3%).

2. Prevalence of *H. pylori* infection in patients with gastroduodenal ulcer in Vietnam

There are two main causes of gastric duodenal ulcer: using nonsteroidal anti-inflammatory drugs and *H. pylori* infection. Many studies of the rate of *H. pylori* infection in patients with gastric duodenal ulcer have been conducted.

A study of Long⁵⁰ on 300 patients with gastroduodenal ulcer pointed out that the rate of *H. pylori* infection was 91.7%. A study of Huong⁵¹ on patients with gastroduodenal ulcer in Hue National Hospital for 2 years (1998 to 1999), the rate of *H. pylori* infection was 72.6%, while the rate of *H. pylori* infection in patients with duodenal ulcer was 79.1%.

Nguyen *et al.*¹⁴ combined five different methods (urease test, histopathology, culture, serological test, and immunohistochemical) to determine that rate of *H. pylori* infection on 270 patients, including gastric ulcer (n=38), chronic gastritis (n=245), gastroesophageal reflux disease (n=9), and normal (n=25). Study results showed that the rate of *H. pylori* infection was 177 out of 270 (65.6%). There is no significant difference in the rate of *H. pylori* infection between male and female patients (66.0% and 65.0%) as well as between Hanoi and Ho Chi Minh City (66.4% and 64.7%).

3. Prevalence of *H. pylori* infection in patients with gastric cancer

Globally *H. pylori* has been classified as a class I carcinogen and the major cause of gastric cancer.¹⁰ Many studies focused on the relation between the gastric cancer and the rate of *H. pylori* infection, virulence factors of *H. pylori* (*cagA*, *vacA*, etc.). Hop and Tho⁵² studied on 205 patients with gastric cancer and the rate of *H. pylori* infection was 136 out of 250 (66.3%). Long *et al.*⁴⁶ found that the rate of positive *H. pylori* infection in patients with gastric cancer on the tests (n=104): Urease test, histopathology and serological test (ELISA) was 55.1%, 71.1%, and 90.6%, respectively. Binh *et al.*⁴¹ found that the rate of positive *H. pylori* infection by four methods (culture, histopathology, urease test, and serological test) on 282 in patients with gastric cancer was 224 out of 282 (79.4%). There is no difference in the rate of *H. pylori* infection in patients with gastric cancer between in Hanoi (77.3%) and in Ho Chi Minh City (80.5%).

These results showed that the frequency of *H. pylori* infection increased not only in community but also in gastric diseases (chronic gastritis, gastric ulcer, duodenal ulcer, and gastric can-

cer). Further studies of virulence factor of *H. pylori* (*cagA* and *vacA*) indicated close relation between *H. pylori* infection and the gastric diseases in Vietnam.^{14,15,53} Therefore, *H. pylori* eradication is necessary, especially in patients with chronic gastritis and gastric duodenal ulcer.

EFFICIENCY OF *H. PYLORI* ERADICATION REGIMEN IN VIETNAM

1. Efficiency of *H. pylori* eradication by first-line therapy

Triple therapy has been early and widely used in three regions of Vietnam (North, Central, and South Vietnam). In the decade: 1990 to 2000, when there had not been the antibiotic resistance, the triple therapy had been widely applied in clinical treatment in Vietnam. The triple therapy includes a proton pump inhibitors (PPI) and two antibiotics. PPIs having been used in Vietnam consist of omeprazole, lansoprazole, pantoprazole, rabeprazole and esomeprazole. There are three antibiotics commonly used in legacy triple therapies including clarithromycin (CLR), amoxicillin (AMX), metronidazole (MNZ).

The appropriate regimen is to achieve the following criteria:⁵⁴ (1) Efficacy of eradication of *H. pylori* should be >90% as per protocol (PP) and >80% according to the intent to treat (ITT); (2) Low side effects, patients' easy to accept and reasonable prices, etc.

Underlying methods in the published papers and analyzed data from different hospitals in Vietnam were selected for this review. All most patients were undergone upper gastrointestinal endoscopy and tested for *H. pylori* (before and after treatment for 30 days).

Diagnosis of *H. pylori* infection by histopathology: two gastric biopsy specimens, one from the antrum and one from the corpus, were fixed in 10% formalin in separate containers and were sent to the pathology laboratory. Samples were embedded in paraffin wax, cut at 5 μ m thickness, and stained with modified Giemsa and hematoxylin and eosin. Histological evaluation of the samples for *H. pylori* was performed according to the modified Sydney system.

Rapid urease test (RUT) is the most useful invasive test for the diagnosis of *H. pylori* infection because it is inexpensive, rapid, easy to perform and shows high sensitivity. Several commercial urease tests including gel-based tests (CLO test, HpFast), paper-based tests (PyloriTek, ProntoDry) and liquid-based tests (UFT300, EndoscHp) are available now.

Recently, we also use the breath test to detect *H. pylori*. However, we only use the ¹⁴C-urease breath test (¹⁴C-UBT).⁵⁵

Before 2010, techniques for the detection of *H. pylori* infection as UBT, cultures are not applied much (due to lack of equipment and lack of funds). Thus, most studies use RUT and / or histopathology to evaluate the efficacy of *H. pylori* eradication. Two studies have used RUT to detect *H. pylori* infection.^{56,57} One study⁵⁵ used a ¹⁴C-UBT.

Table 1 presents efficiency of triple therapy in treatment for patients with gastroduodenal ulcer due to *H. pylori* infection. The studies are divided into three regions: North Vietnam (seven studies),⁵⁶⁻⁶² Central Vietnam (two studies)^{63,64} and South Vietnam (three studies).^{55,65,66} Results showed the rate of *H. pylori* eradication in North Vietnam (67.9% to 98.1%) and in Central Vietnam (84.7% to 90.0%), higher than that in South Vietnam (62.8% to 88.2%). Maximum efficiency of *H. pylori* eradication in 2002 was 98.1%⁵⁹ and minimum efficiency of *H. pylori* eradication in 2011 was 62.8%.⁵⁷

A common feature for three regions indicated that the rate of *H. pylori* eradication has trended to decrease by time, especially in the South Vietnam: 88.2% in 2009⁶⁵ and 62.8% in 2011.⁶⁶ Similarly, the rate of *H. pylori* eradication in the North Vietnam was very high 98.1% in 2002⁵⁹ but reduced: 67.9% in 2014.⁶²

In the South (Vietnam), due to increased drug resistance, a number of studies have used levofloxacin in first-line regimens (triple therapy) to treat *H. pylori* eradication.^{55,65} However, the results were opposite. Trung *et al.*⁵⁵ found that no difference in the efficacy of *H. pylori* eradication in EAL regimen (70.2%) versus EAC regimen (68.3%). On contrary, Ngoi⁶⁵ showed efficiency of *H. pylori* eradication in OAL therapy (88.2%), significantly higher than that in OAC therapy (68.5%). Vinh⁶² indicated that the rate of *H. pylori* eradication was only 68%; the rate of clarithromycin resistance was 71 out of 175 (40.6%) and the rate of amoxicillin resistance was 43 out of 175 (24.6%).

In Vietnam, for 11 years (2000 to 2011), the rate of *H. pylori*

eradication by first line therapy (triple therapy) was significantly reduced: 91.0% in 2000⁵⁸ to 62.8% in 2011.⁶⁶ Hence, it is required to change treatment strategy using sequential therapy, or concomitant therapy, or bismuth-containing quadruple therapy, or rescue therapy. Based on the world's recommendations and statistic figures of the antibiotic resistance to *H. pylori*, on June 2012, in Ho Chi Minh City, Vietnam Association of Gastroenterology⁶⁷ concluded a consensus of diagnosis and treatment of *H. pylori* infection.

2. Eradication of *H. pylori* by second-line regimen

The second indication of *H. pylori* eradication is recommended after the first treatment is unsuccessful.^{68,69} Results of the second *H. pylori* eradication treatment often depends on many factors, in which the antibiotic resistance to *H. pylori* has been increasing, especially clarithromycin/metronidazole/levofloxacin resistance. The Maastricht IV consensus recommended bismuth containing quadruple therapy or levofloxacin containing triple therapy as second-line treatment options.⁸

In Vietnam, from 2009 to 2016, five studies⁷⁰⁻⁷⁴ used second-line therapy for *H. pylori* eradication (Table 2). Trung *et al.*⁷⁰ found that *H. pylori* eradication of the quadruple therapy (EBMT) (95.7%) was more efficient than the triple therapy (EAL) with levofloxacin (58.8%) (p=0.013). This study recommends that levofloxacin should not be used in rescue regimens in Southern Vietnam.⁷⁰

Vinh⁷¹ found that the rate of *H. pylori* eradication was higher

Table 1. Results of *Helicobacter pylori* Eradication in Triple First-Line Therapy in Vietnam

Author	Local	Year	Regimens	Patient (n)	Time (day)	Method	<i>H. pylori</i> eradication rate
Mao <i>et al.</i> ⁵⁸	North	2000	OAC	54	10	PyloriTek test & histology	91.0
			R*AC	45	10	PyloriTek test & histology	96.0
Hai ⁵⁹	North	2002	EAC	53	10	CLO test & histology	98.1
Vinh <i>et al.</i> ⁶⁰	North	2003	OAC	59	7	PyloriTek test & histology	91.7
			OAM	57	7	PyloriTek test & histology	73.9
			OMC	58	7	PyloriTek test & histology	82.2
Duat <i>et al.</i> ⁵⁶	North	2007	PAC	106	7	CLO test	95.8
Tiep <i>et al.</i> ⁶¹	North	2008	RAC	36	7	CLO test & histology	91.6
Thang ⁵⁷	North	2010	EAC	30	7	CLO test	90.0
			EAC	30	7	CLO test	93.3
Vinh ⁶²	North	2014	EAC	162	10	HpFast test & histology	67.9
Huong and Thang ⁶³	Central	2007	EAC	77	7	CLO test & histology	90.0
Nho <i>et al.</i> ⁶⁴	Central	2011	EAC	72	14	CLO test & histology	84.7
Ngoi ⁶⁵	South	2009	OAC	35	14	CLO test & histology	68.5
			OAL	35	14	CLO test & histology	88.2
Trung <i>et al.</i> ⁵⁵	South	2009	EAC	43	7	CLO test & UBT	68.3
			EAL	38	10	CLO test & UBT	70.2
Hoang ⁶⁶	South	2011	PAC	80	10	CLO test & histology	62.8

A, amoxicillin; C, clarithromycin; E, esomeprazole; M, metronidazole; L, levofloxacin; R, rabeprazole; P, pantoprazole; O, omeprazole; R*, ranitidine bismuth citrate; CLO test, campylobacter-like organism test; UBT, urease breath test.

Table 2. Results of *Helicobacter pylori* Eradication by the Second Treatment Regimen in Vietnam

Author	Local	Year	Regimens	Patient (n)	Time (day)	Methods	<i>H. pylori</i> eradication rate
Trung <i>et al.</i> ⁷⁰	South	2008	EAL	19	10	CLO test & UBT	58.8
			EBMT	26	14	CLO test & UBT	95.7
Vinh ⁷¹	North	2011	EAC	31	10	PyloriTek test & histology	80.7
			EBMT	45	14	PyloriTek test & histology	86.7
Hue <i>et al.</i> ⁷²	South	2016	EBMT	166	10	E-test & histology	89.3
Di and Thang ⁷³	Central	2012	EAL	101	10	CLO test & histology	83.2
Thang and Anh ⁷⁴	Central	2015	RLTi	59	7	CLO test & histology	86.3

A, amoxicillin; B, bismuth; C, clarithromycin; E, esomeprazole; M, metronidazole; L, levofloxacin; R, rabeprazole; T, tetracycline; Ti, tinidazole; UBT, urea breath test; CLO test, campylobacter-like organism test.

Table 3. Rate of Primary Antibiotic Resistance of *Helicobacter pylori* in Vietnam (2001–2016)

Author/strains (n)	Year/local	Method	Primary antibiotics resistance (%)					
			A	C	M	L	Te	Multidrug resistance*
Hoan ⁷⁵ (n=152)	2001/North	ADM	0	0	38.1		5.8	
Vinh ⁷⁶ (n=178)	2003/North	E-test & ADM	18.1	21.6	54.3			
Nhan and Mai ⁷⁷ (n=69)	2006/South	ADM	0	38.5	50.8		9.2	
Thinh <i>et al.</i> ⁷⁸ (n=73)	2009/North	DDM	33.9	21.4	94.6		21.4	
Nguyet and Hanh ⁷⁹ (n=98)	2010/North	DDM	35.5	26.7	95.5		17.8	
Toan <i>et al.</i> ⁸⁰ (n=172)	2012/North	DDM	43.6	36.6	94.2		20.9	56.4
Binh <i>et al.</i> ³³ (n=103)	2013 [†]	E-test	0	33.0	69.9	18.4	5.8	24.3
Dung <i>et al.</i> ¹⁶ (n=220)	2015 [‡]	ADM	7.7	43.6	83.6	33.2	10.9	58.2
Phan <i>et al.</i> ³⁴ (n=73)	2015/Central	E-test	0	34.2	75.3	35.6		50.7
Quek <i>et al.</i> ³⁵ (n=193)	2016/South	E-test	10.4	85.5	37.8	24.4		
Mean			14.9	34.1	69.4	27.9	17.9	47.4

A, amoxicillin; C, clarithromycin; M, metronidazole; L, levofloxacin; Te, tetracycline; ADM, agar dilution method; E-test, Epsilometer test; DDM, disk diffusion method. E-test³³ (AB Biodisk, Solna, Sweden), E-test³⁴ (bioMerieux, Marcy l'Etoile, France), E-test³⁵ (bioMerieux).

*Multidrug resistance: includes resistance to at least two antibiotics; [†]North Vietnam + South Vietnam; [‡]North Vietnam + Central Vietnam + South Vietnam.

with EBMT (96.7%) than with EAC (80.7%) ($p < 0.05$). However, EBMT therapy had more side-effects (46.7%) than EAC therapy (12.3%). Hue *et al.*⁷² found that the efficacy of eradication of *H. pylori* by EBMT was 89.3%. However, in this study, the number of patients with moderate, severe and severe adverse events was 19.88%, 0.60% and 1.81%, respectively. Other two studies using the triple therapy with levofloxacin had the rate of *H. pylori* eradication of over 80%.^{73,74} These results indicate that the therapeutic effect of levofloxacin in the rescue regimen is low and is associated with *H. pylori* resistance.

These results show that primary and secondary antibiotic resistance of *H. pylori* in Vietnam has increased over time, especially for clarithromycin and metronidazole. However, limitations in our study that the number of studies is small, intermittent and use classic methods (RUT, endoscopy and histology) to detect *H. pylori*. Therefore, there should be many more studies, in many different centers and longer duration.

ANTIBIOTIC RESISTANCE OF *H. PYLORI* IN VIETNAM

1. Prevalence of primary antibiotic resistance of *H. pylori* from 2001 to 2016

There are many factors that affect efficiency of *H. pylori* eradication therapies such as patient's compliance, doses, quality of drugs, combined diseases, etc. Among those factors, the emergence of antibiotic-resistant *H. pylori* strains have been implicated as highest risk of treatment failure. The antibiotic resistance to *H. pylori* is divided into two types: primary antibiotic resistance and secondary antibiotic resistance.

There are two methods for detecting *H. pylori* resistance, including resistance to phenotypic resistance and genotype resistance. Phenotypic methods are applied in Vietnam since 2000. The methods include agar dilution method, disk dilution method and Epsilometer test. Method of detecting *H. pylori* genotype resistance has only been applied in recent years.

Table 3 presents the rate of primary antibiotic resistance to *H.*

pylori in Vietnam from 2001 to 2016 period (16 years).^{16,33-35,75-80} Ten studies (three papers in English and seven papers in Vietnamese) were included in this review. A total of 308, 412, 523, 408, 399, and 268 *H. pylori* strains were included in this review to evaluate the prevalence of *H. pylori* primary resistance to amoxicillin, clarithromycin, metronidazole, levofloxacin, tetracycline, and multidrug resistance, respectively. Overall, the primary resistance rates of amoxicillin, clarithromycin, metronidazole, levofloxacin, tetracycline, and multidrug resistance were 15.0%, 34.1%, 69.4%, 27.9%, 17.9%, and 48.8%, respectively. Here, we also analyze in detail the rate of *H. pylori* resistance to the most commonly used antibiotics in *H. pylori* treatment in Vietnam. Fig. 2. shows the average rate of primary resistance of *H. pylori* with amoxicillin, clarithromycin, metronidazole, levofloxacin, and tetracycline in Vietnam during 16 years (from 2001 to 2016).

2. Prevalence of secondary antibiotic resistance of *H. pylori* from 2001 to 2016

Studies on secondary resistance of *H. pylori* in Vietnam have been less published. From 2014 to 2016, three studies have been published (two papers in Vietnamese and one paper in Eng-

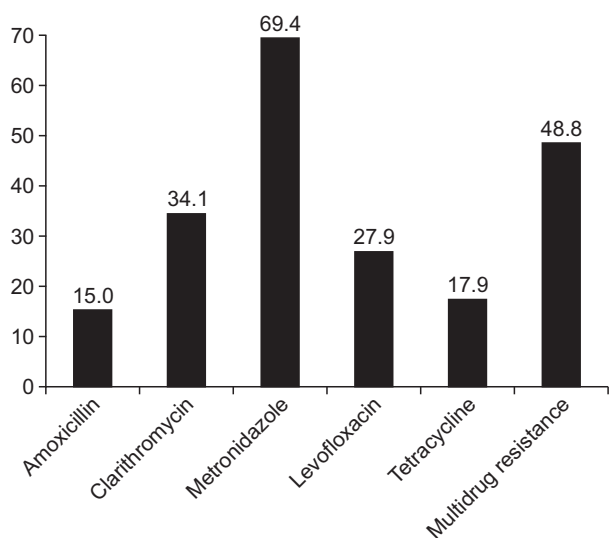


Fig. 2. Average rate of primary resistance with *Helicobacter pylori* in Vietnam from 2001 to 2016.

lish).^{34,81,82} These studies only in central and Southern Vietnam—where the rate of primary drug resistance tends to increase. Table 4 presents the rate of secondary antibiotic resistance to *H. pylori* in Vietnam trends in clarithromycin, levofloxacin and multiple drug resistance in Southern Vietnam are likely to increase over time. Minh and Hoang⁸¹ studied the rate of secondary resistance to *H. pylori* in 102 patients who failed treatment (at least one time). Research results showed that the secondary resistance rates of amoxicillin, clarithromycin, metronidazole, levofloxacin and tetracycline were 13.7%, 56.9%, 44.1%, 25.5%, and 23.5%, respectively. Hue⁸² showed that secondary rates of resistance to clarithromycin, levofloxacin and multidrug were 94.3%, 48.6%, and 45.7%, respectively.

In Central Vietnam, the secondary resistance rates of clarithromycin and levofloxacin are also likely to increase. Phan *et al.*³⁴ showed that secondary rates of resistance to amoxicillin, clarithromycin, metronidazole, levofloxacin and multidrug were 5.3%, 73.7%, 78.9%, 63.2%, and 78.9%, respectively.

Overall, the secondary resistance rates of amoxicillin, clarithromycin, metronidazole, levofloxacin, tetracycline, and multidrug resistance were 9.5%, 74.9%, 61.5%, 45.7%, 23.5%, and 62.3%, respectively.

Today, antibiotic resistance of *H. pylori* has become more serious and affect the outcome of treatment. The prevalence of bacterial resistance varies in different geographic areas and appears to be increasing with time in many countries. The European multicenter study group included 2,204 patients from 2008 to 2009, spanning 18 European countries and demonstrated *H. pylori* resistance rates to clarithromycin, metronidazole and levofloxacin at 17.5%, 34.9%, and 14.1% respectively.⁸³

Recently, Kuo *et al.*⁸⁴ have reviewed the system and meta-analysis of primary antibiotic resistance to *H. pylori* and the efficacy of first-line regimens in the Asia-Pacific region. The overall mean prevalence of primary *H. pylori* resistance were 17% (95% CI, 15% to 18%) for clarithromycin, 44% (95% CI, 39% to 48%) for metronidazole, 18% (95% CI, 15% to 22%) for levofloxacin, 3% (95% CI, 2% to 5%) for amoxicillin, and 4% (95% CI, 2% to 5%) for tetracycline. Prevalence of resistance to clarithromycin and levofloxacin rose significantly over time during the period investigated, whereas resistance to other antibiotics remained stable. In Vietnam, the prevalence of primary

Table 4. Rate of Secondary Antibiotic Resistance of *Helicobacter pylori* in Vietnam (2014–2016)

Author/strains (n)	Year/local	Method	Primary antibiotics resistance (%)					
			A	C	M	L	Te	Multidrug resistance*
Minh <i>et al.</i> ⁸¹ (n=102)	2014/South	ADM	13.7	56.9	44.1	25.5	23.5	-
Phan <i>et al.</i> ³⁴ (n=19)	2015/Central	E-test	5.3	73.7	78.9	63.2	-	78.9
Hue ⁸² (n=35)	2016/South	E-test	-	94.3	-	48.6	-	45.7 [†]
Mean			9.5	74.9	61.5	45.7	23.5	62.3

A, amoxicillin; C, clarithromycin; M, metronidazole; L, levofloxacin; Te, tetracycline; ADM, agar dilution method; E-test, Epsilonometer test.

*Multidrug resistance: includes resistance to at least two antibiotics; [†]Clarithromycin+levofloxacin.

resistance of *H. pylori* with clarithromycin and metronidazole was 34.0% and 72.0%, respectively, and it was ranked second (after Pakistan).⁸⁵

In Korea, Lee *et al.*⁸⁵ studied the prevalence of primary and secondary resistance of *H. pylori* in 347 patients during 2003 to 2012. The study results showed that the prevalence of primary resistance of *H. pylori* increases for amoxicillin (6.3% to 14.9%, $p=0.051$), clarithromycin (17.2% to 23.7%, $p=0.323$) and both of levofloxacin and moxifloxacin (4.7% to 28.1%, $p=0.002$). Secondary resistance rate significantly increased in metronidazole, levofloxacin and moxifloxacin.⁸⁵

3. Primary and secondary clarithromycin resistance of *H. pylori* in Vietnam

Because clarithromycin is the most potent antibiotic involved in the management of *H. pylori* infections, resistance to clarithromycin is important.^{86,87} In European regions,⁸⁸ the lowest clarithromycin resistance was reported from Norway (5.9%), whilst the highest in Spain (32.01%) and Portugal (42.35%). European studies performed at the past 6 years intervals reported that *H. pylori* resistance decreased from 36.65% in 2009 to 24.38% in 2014. In Asian, mean overall prevalence of resistance to clarithromycin was 17% (95% CI, 15% to 18%), ranging from 0% in Bhutan and Myanmar to 34% in Vietnam and 37% in Pakistan.⁸⁴

In Vietnam, clarithromycin is the first line antibiotic selected in the triple therapy for *H. pylori* eradication treatment. Table 3 shows the proportion of primary resistance clarithromycin according to various studies.^{16,33-35,75-80} Rate of primary resistance to clarithromycin ranged from 21.4% to 85.5%. Therefore, clarithromycin resistance has increased, especially in the studies in the South Vietnam.³⁵ In the North Vietnam, clarithromycin resistance had trended to further increase from 18.5% in 2013 to 42.1% in 2015 (Table 5).¹⁶

The patients with the primary clarithromycin resistance will

Table 5. Rate of Antibiotic Resistance of *Helicobacter pylori* in Hanoi and Ho Chi Minh City-Vietnam

Local	Antibiotic	Binh <i>et al.</i> (2013) ³³	Dung <i>et al.</i> (2015) ¹⁶
Hanoi	Amoxicillin (A)	0	3.9
	Clarithromycin (C)	18.5	42.1
	Metronidazole (M)	70.3	89.5
	Levofloxacin (L)	18.5	21.1
	Tetracycline (Te)	7.4	11.8
Ho Chi Minh City	Amoxicillin (A)	0	6.9
	Clarithromycin (C)	49.0	39.2
	Metronidazole (M)	69.3	81.4
	Levofloxacin (L)	18.3	41.2
	Tetracycline (Te)	4.0	12.7

Data are presented as percentage.

have risk of the secondary resistance. For the 2006 to 2008 period, a study in the South of Poland found that the primary clarithromycin resistance was 21% and the secondary resistance was 80%.⁸⁹ In Thailand, in 2009, there was a report on rate of the primary resistance after treatment of 78.7%, compared to the secondary resistance of 10.6%.⁹⁰

In Vietnam, in 2003, Vinh⁷⁶ found that the rate of clarithromycin resistance was 21.6% before treatment and 78.9% after treatment. Minh and Hoang⁸¹ found that the rate of clarithromycin resistance after 1, 2 and 3 treatments was incremental and 44.0%; 66.7% and 83.6%, respectively (Table 4). Phan *et al.*³⁴ indicated very high rate of the primary and secondary clarithromycin resistance: 34.2% and 73.7%, respectively ($p<0.05$). The rate of primary and secondary resistance of *H. pylori* to clarithromycin has increased, affecting the therapeutic effect. The Maastricht III guidelines on *H. pylori* infection management recommend substituting metronidazole for clarithromycin when resistance to this antibiotic exceeds 15% to 20%.²⁰

4. Primary and secondary amoxicillin resistance of *H. pylori* in Vietnam

Resistance to amoxicillin has been shown to be negligible (0 to <2%) in European countries, such as Germany and the Netherlands.⁹¹ In Asia, mean overall prevalence of resistance to amoxicillin was 3% (95% CI, 21% to 34%).⁸⁴

In Vietnam, amoxicillin is used in the triple therapy or the quadruple therapy for *H. pylori* eradication. The rate of the primary amoxicillin resistance varies in different times and studies: from 0% to 43.6% (Table 3).^{33,77,80} The rate of the primary amoxicillin resistance in the North Vietnam has trended to further increase (18.1% to 43.6%)^{76,78-80} than in the South Vietnam (0% to 10.4%) (Table 3).^{16,33-35,77}

Vinh⁷⁶ found that the rate of the secondary resistance of amoxicillin was 36.8%. Minh and Hoang⁸¹ found that the rate of the secondary amoxicillin resistance after 1, 2 and 3 treatments was 13.6%, 16.7%, and 0% (Table 4). Secondary resistance rates of amoxicillin in Southern Vietnam are lower than in the North Vietnam. Because of amoxicillin resistance rate is not high, so amoxicillin still used for *H. pylori* eradication in Vietnam.

5. Primary and secondary metronidazole resistance of *H. pylori* in Vietnam

Metronidazole in order to eradicate this bacterium, has been widely used in combination therapies such as metronidazole-based triple therapy, concomitant therapy and bismuth-containing quadruple therapy. Metronidazole resistance is the most common antibiotic resistance in *H. pylori* and overall metronidazole resistance found in 47.22% in descending order in Africa 75.02%, South America 52.85%, Asia 46.57%, Europe 31.19%, to 30.5% in North America.⁸⁸ In Asia, mean overall prevalence of resistance to metronidazole was 44% (95% CI, 39% to 48%) ranging from 10% in Japan to 84% in Bangladesh and 88% in

Nepan.⁸⁴

In the 1990s, metronidazole was early used in *H. pylori* eradication regimen and used in the North Vietnam more than in the South Vietnam. Primary resistance rate of metronidazole from: 37.8%³⁵ to 95.5%.⁷⁷ The rate of the primary metronidazole resistance in the North Vietnam increased (38.1% to 95.5%)^{75,79} higher than that in the South Vietnam (37.8% to 50.8%) (Table 3).^{35,77} The rate of the primary metronidazole resistance has increased by time. In Hanoi, the rate of the primary metronidazole resistance increased from 70.3% in 2013 to 89.5% in 2015 (Table 5). In Ho Chi Minh City, the rate of the primary metronidazole resistance increased from 69.3% in 2013 to 81.4% in 2015 (Table 5).^{16,33}

Metronidazole is used frequently to treat not only *H. pylori* infection but also other infections such as intestinal parasites, periodontal, and gynecological diseases, which are common in developing countries, including Vietnam.²⁶ Because the drug has many side-effects, causing tiredness for the patients and high rate of resistance, metronidazole has not been used in the regimen of *H. pylori* eradication in Vietnam.⁶⁷

6. Primary and secondary tetracycline resistance of *H. pylori* in Vietnam

In the world, the rate of tetracycline resistance is low, especially in the developed countries.⁹⁰ In Asia and Africa, tetracycline and bismuth are used more than in Europe and the America.^{84,88} The total rate of tetracycline resistance did not vary in South America and North America (the resistance was absent), whilst it was relatively high in Africa (50%). In Asia, the resistance was absent in Thailand, and very low in China (0.6%) and South Korea (0.01%). In contrast, increased values were found in India (53.8%), and Iran (11.7%). The prevalence of tetracycline resistance stays very low (less than 7.4%) in almost parts of the world except for Africa.⁸⁸ The comparison of data showed that tetracycline resistance was decreasing in the world, 26.85% in 2009 to 6.11% in 2014.⁸⁸

In Vietnam (see Table 5), the primary tetracycline resistance ranges 5.8% to 21.4% (Table 3). Minh and Hoang⁸¹ found that the rate of the secondary tetracycline resistance after 1, 2, and 3 treatments (Table 4) was 19.7%, 30.0%, and 33.3%, respectively. So far, the research and use of tetracycline for the eradication of *H. pylori* in Vietnam is very limited.

7. Primary and secondary levofloxacin resistance of *H. pylori* in Vietnam

Many studies have examined levofloxacin-PPI as a first-line therapy for eradication of *H. pylori* infection.^{92,93} However, the eradication rates achieved with first-line levofloxacin-based treatments are not uniform. Some reports show the improved efficacy with levofloxacin-based regimens in comparison to standard first-line therapy, whereas others have found equivalent or poorer responses.^{94,95} The European recommendation only

uses levofloxacin in the rescue regimen, when the results of antibiotic therapy are available.²⁰ When first-line therapy fails, the Maastricht IV Consensus Report recommends that bismuth-containing quadruple therapy can be a choice for second-line therapy.⁸ Many studies have investigated levofloxacin based regimens as second-line treatments, including meta analyses.⁹⁶

Generally, resistance to levofloxacin is low (<19%) worldwide. The rate of the primary levofloxacin resistance varies in the world's regions and increases in Asian (25.28%) and South America (21.23%) higher than that in Africa and Europe (<15%). In Asia, the rate of levofloxacin resistance also varies in different countries: Japan (57%), Korea (24.55%), Iran (5.3%), and Malaysia (2.6%).⁸⁸

In Vietnam, a majority of the studies focused in the South Vietnam^{16,33-35} and their results indicated that the rate of the primary levofloxacin resistance ranged from 18.4% to 35.6% (Table 3). The rate of the primary levofloxacin resistance increased from 18.3% in 2013 to 41.2% in 2015 in Ho Chi Minh City (Table 5).^{16,33} The rates of the secondary levofloxacin resistance after 1, 2 and 3 treatments were 25.7%, 23.3%, and 33.3% respectively (Table 4).⁸¹ Phan *et al.*³⁴ found that the rates of the primary and secondary levofloxacin resistance were very high and 35.6% and 63.2%, respectively ($p < 0.05$). Other fluoroquinolones such as nalidixic acid, ciprofloxacin and ofloxacin, which are commonly used in Vietnam, may lead to cross resistance with levofloxacin. Because the rate of levofloxacin resistance increased, so levofloxacin is not used much in *H. pylori* eradication in Vietnam.

8. Multidrug resistance patterns of *H. pylori* in Vietnam

Multidrug resistance has recently appeared as a serious challenge in the fight against infections in over the world. *H. pylori* strains harboring triple or quadruple resistance can hinder the choice and success of the eradication regimen. Binh *et al.*³³

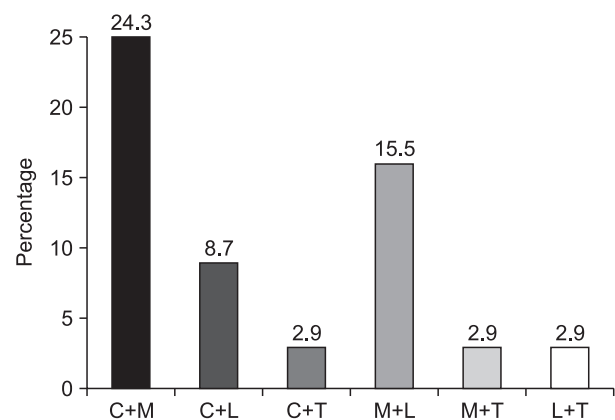


Fig. 3. Multidrug resistance patterns of *Helicobacter pylori* in Vietnam. C+M, clarithromycin+metronidazole; C+L, clarithromycin+levofloxacin; C+T, clarithromycin+tetracycline; M+L, metronidazole+levofloxacin; M+T, metronidazole+tetracycline; L+T, levofloxacin+tetracycline.

showed that 33% (34 strains) of the isolates were the resistant to at least two antibiotics. Resistance to clarithromycin and metronidazole was most commonly observed (24.3%), and this may be the main reason for failure of treatment in Vietnam. Fig. 3 presents the multidrug resistance of *H. pylori* in Vietnam.

CAUSES OF ANTIBIOTIC RESISTANCE IN VIETNAM

1. Contributory factors

The contributory factors to treatment failure are multidimensional and complex. Host genetic factors, *H. pylori* virulent factors, antibiotic-resistant *H. pylori* strains, smoking habits, compliance to therapy and duration of therapy affect totally treatment outcome. In Vietnam, Dung *et al.*¹⁶ found that some causes as follows: wide use of antibiotics, incorrect dosage, quality of antibiotic, noncompliance of treatment protocol, bad habits (alcohol and tobacco consumption), mutation of *H. pylori*.

In fact, arbitrary use antibiotics (without a prescription, increase dose arbitrarily) is a common problem in Vietnam and might leading to the development of new antibiotic-resistant *H. pylori* strains. In addition, bad habits such as alcohol, beer, smoking can also affect the effectiveness of *H. pylori* eradication.

Several studies have examined the relationship between risk factors and the frequency of primary and secondary resistance of *H. pylori*. Risk factors should be analyzed include: age, gender, history of previous eradication treatment, smoking, occupation, type of residence, etc. Lee *et al.*⁸⁵ showed that “previous eradication” was an independent risk factor for the development of clarithromycin ($p < 0.001$), azithromycin ($p < 0.001$), levofloxacin ($p = 0.003$) and moxifloxacin ($p = 0.006$) resistance. District: “rural area” was an independent risk factor for the development of azithromycin ($p = 0.049$) resistance. Job: “no occupation” was an independent risk factor for the development of azithromycin ($p = 0.034$) resistance. However, other risk factors (gender, disease, alcohol, smoking, and socioeconomic) was not related to antimicrobial resistance of *H. pylori*.

In Vietnam, there are very few studies on the risk factors associated with *H. pylori* resistance. Recently, Hue⁸² studied the relationship between risk factors and *H. pylori* resistance. Re-

search results showed that “age ≥ 30 ” and “previous eradication” was an independent risk factor for the development of clarithromycin. However, no correlation was found with levofloxacin (Table 6).

2. Gene mutation of *H. pylori* related to antibiotic resistance

Two techniques applied clinically to define the antibiotic resistance to *H. pylori* comprise *H. pylori* culture and resistance regimen.⁹⁷ However, culturing *H. pylori* bacteria is very difficult, obtains low positive rate and requires long time; and not establishments can do it. To add these methods, at present, gene mutation of *H. pylori* bacteria with different antibiotics is defined. In Vietnam, initial studies of gene mutation of *H. pylori* bacteria related to antibiotic resistance (clarithromycin and levofloxacin) have been conducted.⁹⁸⁻¹⁰² There are a total of five studies of gene mutation of *H. pylori* bacteria related to antibiotic resistance (one study in the North Vietnam,⁹⁸ two studies in the Central Vietnam,^{77,78,102} and two studies in the South Vietnam^{35,100}).

Toan *et al.*⁹⁸ showed two types of gene mutation in two positions detected: A2143G (26.7%), A2143T (6.7%), and T2182C (80.0%). Two types of gene mutation combined on a patient were A2143G+T2182C and A2143T+T2182 at the respective rates of 13.3% and 6.7%.

Phan *et al.*³⁴ studied gene mutation of *H. pylori* bacteria with clarithromycin and levofloxacin in Hue (Central Vietnam). Study results pointed that the mutation rate of A2143G was 85.7% (30/35) in the strain of bacteria resisted to clarithromycin. Similarly, the study of Doanh *et al.*¹⁰² also showed the mutation rate of A2143G was very high: 40 out of 41 (97.6%).

Trung *et al.*¹⁰⁰ studied gene mutation on 30 strains of *H. pylori* bacteria resisted to clarithromycin and 31 strains of *H. pylori* bacteria resisted to levofloxacin. Study results indicated 96.7% strains of *H. pylori* bacteria mutated with clarithromycin and 54.8% strains of *H. pylori* bacteria mutated with. The mutation rate with clarithromycin and levofloxacin was 56.7%.

However, gene mutation of *H. pylori* bacteria with clarithromycin in Vietnam is a controversy.¹⁰² While continuously studying situation and causes of the antibiotic resistance to *H. pylori*, applying the latest consensus (Maastricht V/Toronto) is extremely necessary. Selection of the regimens, combination of

Table 6. Multivariate Analysis of Predictors for *Helicobacter pylori* Resistance

Antibiotic	Parameter	Multivariate analysis	
		OR (95% CI)	p-value
Clarithromycin (n=153)	Age ≥ 30 yr	3.2 (1.3–7.7)	0.011
	Previous eradication	7.7 (1.7–34.7)	0.008
Levofloxacin (n=154)	Age ≥ 40 yr	1.9 (0.9–3.7)	0.057
	Previous eradication	1.4 (0.6–3.1)	0.386

OR, odds ratio; CI, confidence interval.

Table 7. *Helicobacter pylori* Eradication Regimens in Vietnam⁴⁵

	Regimen	Duration of therapy
Triple therapy	PPI+A+C	7 Days
Sequential therapy	First 5 days: PPI+A	5 Days
	Next 5 days: PPI+C+Ti	5 Days
Concomitant therapy	PPI+A+C+M/Ti	10 Days
Bismuth quadruple therapy	PPI+M+Te+B	14 Days

PPI, proton pump inhibitor; A, amoxicillin; C, clarithromycin; Ti, tinidazole; M, metronidazole; Te, tetracycline; B, bismuth.

PPI doses and time, and *H. pylori* tests (culture, PCR and study of gene mutation of *H. pylori*) plays an importance role for efficiency of *H. pylori* eradication.

PERSPECTIVES FROM VIETNAM ASSOCIATION OF GASTROENTEROLOGY FOR DIAGNOSIS AND TREATMENT OF *H. PYLORI* INFECTION

In Vietnam, from 1990 to 2010, triple therapy (PPI + combination of two antibiotics) was used clinically for eradication with *H. pylori*. However, after more than two decades, the antibiotic resistance to *H. pylori* has increased by time. Based on International Consensus (Maastricht IV)⁸ and based on the increasing resistance of *H. pylori* to antibiotics in Vietnam, Vietnam Association of Gastroenterology has established a consensus on *H. pylori* eradication (June 2012 in Ho Chi Minh City).⁶⁷ The followings are some main contents related to *H. pylori* eradication:⁶⁷ (1) treatment regimens and duration (Table 7); (2) provide treatment recommendations for areas with increased rates of resistance.

Recommendation 25: First-line therapy for *H. pylori* eradication: Because the rate of antibiotic resistance in the North Vietnam and the Central Vietnam is lower than that in the South Vietnam, the triple therapy (PPI+A+C for 10 to 14 days) is recommended to be applied in this region (grade of recommendation B; agreement: 76%). In the South Vietnam, due to high rate of antibiotic resistance, sequential therapy regime or quadruple therapy (with/without bismuth) for *H. pylori* eradication (grade of recommendation B; agreement: 83%).⁶⁷

Recommendation 26: Second-line therapy for *H. pylori* eradication: (1) Use Bismuth quadruple therapy if it has not yet been used before (grade of recommendation A; agreement: 97%). (2) Use PPI+A+L triple therapy if Bismuth quadruple therapy was used but unsuccessful (grade of recommendation A; agreement: 93%).⁶⁷

However, recent data indicate that primary and secondary resistance of *H. pylori* to clarithromycin, metronidazole and levofloxacin is increasing.³³⁻³⁵ This is of concern and suggests two important principles when prescribing a therapy in Vietnam: (1) clarithromycin-based or metronidazole-based triple therapy

might not be useful as first-line therapies; (2) levofloxacin-based triple therapy should not be used as an alternative treatment. Therefore, first-line strategies such as bismuth-based quadruple or non-bismuth-based quadruple therapy should be recommended for Vietnamese infected patients.

In addition, it is necessary to apply techniques such as bacterial culture, antimicrobial susceptibility, gene mutation study of *H. pylori* is very necessary. The Maastricht V Consensus showed that treatment regimens for areas with clarithromycin resistance >15% and <15%.⁶⁹ Based on this, Vietnam Association of Gastroenterology needs to have a new consensus, to improve the effectiveness of *H. pylori* eradication in the future.

CONCLUSIONS

Vietnam has high rate of *H. pylori* infection in community as well as in gastric duodenal diseases (chronic gastritis, gastric ulcer, duodenal ulcer, and gastric cancer). In Vietnam, in early 1990s, rate of *H. pylori* eradication exceeded 90%. But, recent statistics indicated that rate of *H. pylori* eradication has reduced to 60%–70% and related to antibiotic resistance of *H. pylori*. The rate of metronidazole, clarithromycin and levofloxacin resistance has been increasing. Application of the recommendations from the International Consensus (Maastricht V/Toronto) is extremely necessary to improve efficiency of *H. pylori* eradication.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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