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

Vu Van Khien¹, Duong Minh Thang¹, Tran Manh Hai²,³, Nguyen Quang Duat⁴, Pham Hong Khanh⁴, Dang Thuy Ha⁵, Tran Thanh Binh⁶, Ho Dang Quy Dung⁶, Tran Thi Huyen Trang⁶, and Yoshio Yamaoka⁷

Departments of GI Endoscopy and Molecular Biology, 108 Central Hospital, University of Science and Technology of Hanoi, Department of Gastroenterology, 103 Hospital, Department of Gastroenterology, National Children Hospital, Hanoi, Department of Endoscopy, Cho Ray Hospital, Ho Chi Minh City, Vietnam, and Department of Environmental and Preventive Medicine, Oita University Faculty of Medicine, Oita, Japan

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; Clarithromycin; 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.²⁻³ 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.⁴⁻⁵ Globally, *H. pylori* has been classified as a class I carcinogen and the major cause of gastric cancer.⁶⁻¹⁰

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⁻⁲¹ In addition, diseases related to *H. pylori* such as MALT lymphoma, gastric atrophy and intestinal dysplasia are also recoverable after antibiotic
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. 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. 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.

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. 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.

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. on 284 children at 6 months and 15

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. 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. 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. 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.

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years, through serological test showed that the rate of \( \text{H. pylori} \) infection in children was 34.0%. Study examined the relationship between \( \text{H. pylori} \) 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 \( \text{H. pylori} \) infection.

Besides the serological test, urine tests are conducted to investigate the rate of \( \text{H. pylori} \) infection in community, as well as applied for people with gastric diseases. Nguyen et al.\(^{43}\) found that Rapinrun 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 \( \text{H. pylori} \) in 200 patients by Rapinrun 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 \( \text{H. pylori} \) infection rate in community.

Recently, there have been some epidemiological investigation of \( \text{H. pylori} \) infection rates in ethnic, including adults and children.\(^{41-44}\) In 2014, Binh et al.,\(^{41}\) investigated \( \text{H. pylori} \) 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 \( \text{H. pylori} \) infection among ethnic minorities (adults) was 188 out of 494 (38.1%). There were significant differences in rates of \( \text{H. pylori} \) infection in Daklak and Lao Cai (51.0% vs 29.3%, p<0.001). There are many factors may contribute to \( \text{H. pylori} \) infection such as geographical location, ethnicities, dietary habit, etc. The results showed that subjects living in Daklak had a significantly higher risk of \( \text{H. pylori} \) 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 significantly higher risk, whereas Tay (crude OR, 0.3099%; 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 \( \text{H. pylori} \) acquisition.

Nguyen et al.\(^{45}\) was studied the epidemiology of \( \text{H. pylori} \) infection in Khmer children in Mekong Delta (South Vietnam). Research results showed that the prevalence of \( \text{H. pylori} \) infection among children of Khmer ethnicity is 32.1%. \( \text{H. pylori} \) infection in mothers, in first sibling and in two first siblings in particular were found as high-risk factors for \( \text{H. pylori} \) 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.\(^{45}\) showed that epidemiology of \( \text{H. pylori} \) infection in Tay children (Lang Son province-North Vietnam). Study concluded that intra-familial \( \text{H. pylori} \) transmission are factors associated with \( \text{H. pylori} \) infection. In 2017, Nguyen et al.\(^{44}\) also investigated the epidemiology of \( \text{H. pylori} \) infection in Muong people. Muong is the thirst 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 \( \text{H. pylori} \) infection.

Limitations of the study in Vietnam focused on the region and the number of volunteers has less.\(^{14-16}\) However, the above studies show that family, race, geography, life-style and age are related to \( \text{H. pylori} \) 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 \( \text{H. pylori} \) infection in the community. However, to demonstrate this matter, should have investigated the epidemiology of \( \text{H. pylori} \) infection nationwide.

In Korea, Lim et al.\(^{45}\) has evaluated the time trend of seropositivity of \( \text{H. pylori} \) over the period of 13 years in an asymptomatic Korean population, and investigate associated risk factors. The overall seroprevalence of \( \text{H. pylori} \) 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 \( \text{H. pylori} \) infection.

### PREVALENCE \( \text{H. pylori} \) INFECTION IN GASTRIC DISEASES IN VIETNAM

#### 1. Prevalence \( \text{H. pylori} \) infection in patients with chronic gastritis

Chronic gastritis is rather popular among the gastric diseases. But the studies of the rate of \( \text{H. pylori} \) 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 \( \text{H. pylori} \) 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 \( \text{H. pylori} \) infection on the tests: urease test, histopathology and serological test was 44.5%; 57.6% and 88.1%, respectively.

Thang\(^{47}\) found that the rate of \( \text{H. pylori} \) infection in patients with chronic gastritis (n=235) was 75.9% (determined by histopathology and CLO test). Thinh\(^{48}\) using four various methods: urease test, polymerase chain reaction (PCR), histopathology and culture showed that the rates of \( \text{H. pylori} \) infection were 58.1%, 58.1%, 56.3% and 57.0%, respectively. Dung\(^{49}\) also obtained similar results, with the rate of 59.9%. Thus, these study results proved that the rate \( \text{H. pylori} \) infection in patients with chronic gastritis in Kinh group is rather high.

Recently, studies of the frequency of \( \text{H. pylori} \) infection in the ethnic groups of Vietnam have been conducted. Binh et al.\(^{41}\) conducted a study of the rate of \( \text{H. pylori} \) 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 gastro-duodenal 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 Long et al. on 300 patients with gastroduodenal ulcer pointed out that the rate of *H. pylori* infection was 91.7%. A study of Huong 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. 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), gastrointestinal 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. 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 Tho studied on 205 patients with gastric cancer and the rate of *H. pylori* infection was 136 out of 250 (66.3%). Long et al. 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. 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 cancer). Further studies of virulence factor of *H. pylori* (cagA and vacA) indicated close relation between *H. pylori* infection and the gastric diseases in Vietnam. 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:

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 µm 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).

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.

One study 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),6-62 Central Vietnam (two studies)63,64 and South Vietnam (three studies).65,66,67 Results showed the rate of *H. pylori* eradication in North Vietnam (67.9% to 91.0%) 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%60 and minimum efficiency of *H. pylori* eradication in 2011 was 62.8%.67

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 200265 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.55,56 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, Ngôi61 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 2000 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 Gastroenterology65 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 recommend after the first treatment is unsuccessful.58,60 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.75 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

Vinh72 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 | *H. pylori* Eradication rate |
|--------|-------|------|----------|------------|-----------|--------|-----------------------------|
| Mao et al.64 | North | 2000 | OAC | 54 | 10 | PyloriTek test & histology | 91.0 |
| Hai65 | North | 2002 | EAC | 53 | 10 | CLO test & histology | 98.1 |
| Vinh et al.66 | North | 2003 | OAC | 59 | 7 | PyloriTek test & histology | 91.7 |
| Duat et al.67 | North | 2007 | PAC | 106 | 7 | CLO test | 95.8 |
| Tiep et al.68 | North | 2008 | RAC | 36 | 7 | CLO test & histology | 91.6 |
| Thang69 | North | 2010 | EAC | 30 | 7 | CLO test | 90.0 |
| Vinh70 | North | 2014 | EAC | 162 | 10 | HpFast test & histology | 67.9 |
| Huong and Thang71 | Central | 2007 | EAC | 77 | 7 | CLO test & histology | 90.0 |
| Nho et al.72 | Central | 2011 | EAC | 72 | 14 | CLO test & histology | 84.7 |
| Ngôi73 | South | 2009 | OAC | 35 | 14 | CLO test & histology | 68.5 |
| Trung et al.74 | South | 2009 | EAC | 43 | 7 | CLO test & UBT | 68.3 |
| Hoang75 | South | 2011 | PAC | 80 | 10 | CLO test & histology | 70.2 |

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.

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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.\textsuperscript{72} found that the efficacy of eradication of \textit{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 \textit{H. pylori} eradication of over 80%.\textsuperscript{73,74} These results indicate that the therapeutic effect of levofloxacin in the rescue regimen is low and is associated with \textit{H. pylori} resistance.

These results show that primary and secondary antibiotic resistance of \textit{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 \textit{H. pylori}. Therefore, there should be many more studies, in many different centers and longer duration.

### Table 2. Results of \textit{Helicobacter pylori} Eradication by the Second Treatment Regimen in Vietnam

| Author            | Local   | Year | Regimens | Patient (n) | Time (day) | Methods                                      | H. pylori eradication rate |
|-------------------|---------|------|----------|-------------|------------|----------------------------------------------|----------------------------|
| Trung et al.\textsuperscript{70} | South   | 2008 | EAL      | 19          | 10         | Clo test & UBT                               | 58.8                       |
|                   |         |      | EBMT     | 26          | 14         | Clo test & UBT                               | 95.7                       |
| Vinh\textsuperscript{71}    | North   | 2011 | EAC      | 31          | 10         | PyloriTek test & histology                  | 80.7                       |
|                   |         |      | EBMT     | 45          | 14         | PyloriTek test & histology                  | 86.7                       |
| Hue et al.\textsuperscript{72} | South   | 2016 | EBMT     | 166         | 10         | E-test & histology                           | 89.3                       |
| Di and Thang\textsuperscript{73} | Central | 2012 | EAL      | 101         | 10         | Clo test & histology                           | 83.2                       |
| Thang and Anh\textsuperscript{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 \textit{Helicobacter pylori} in Vietnam (2001–2016)

| Author/strains (n) | Year/local | Method     | A | C | M | L | Te | Multidrug resistance* |
|--------------------|------------|------------|---|---|---|---|----|-----------------------|
| Hoan\textsuperscript{75} (n=152) | 2001/North | ADM        | 0 | 0 | 38.1 | 5.8 |                |
| Vinh\textsuperscript{76} (n=178) | 2003/North | E-test & ADM | 18.1 | 21.6 | 54.3 |         |
| Nhan and Mai\textsuperscript{77} (n=69) | 2006/South | ADM        | 0 | 38.5 | 50.8 | 9.2  |                     |
| Thinh et al.\textsuperscript{78} (n=73) | 2009/North | DDM        | 33.9 | 21.4 | 94.6 | 21.4 |                     |
| Nguyet and Hanh\textsuperscript{79} (n=98) | 2010/North | DDM        | 35.5 | 26.7 | 95.5 | 17.8 |                     |
| Toan et al.\textsuperscript{80} (n=172) | 2012/North | DDM        | 43.6 | 36.6 | 94.2 | 20.9 | 56.4                 |
| Binh et al.\textsuperscript{81} (n=103) | 2013\textsuperscript{1} | E-test | 0 | 33.0 | 69.9 | 18.4 | 5.8 | 24.3 |
| Dung et al.\textsuperscript{82} (n=220) | 2015\textsuperscript{2} | ADM | 7.7 | 43.6 | 83.6 | 33.2 | 10.9 | 58.2 |
| Phan et al.\textsuperscript{83} (n=73) | 2015/Central | E-test | 0 | 34.2 | 75.3 | 35.6 | 50.7 |
| Quck et al.\textsuperscript{84} (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-test\textsuperscript{15} (AB Biodisk, Solna, Sweden), E-test\textsuperscript{16} (bioMerieux, Marcy l’Etoile, France), E-test\textsuperscript{17} (bioMerieux).

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

### ANTIBIOTIC RESISTANCE OF \textit{H. pylori} IN VIETNAM

#### 1. Prevalence of primary antibiotic resistance of \textit{H. pylori} from 2001 to 2016

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

There are two methods for detecting \textit{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 \textit{H. pylori} genotype resistance has only been applied in recent years.

Table 3 presents the rate of primary antibiotic resistance to \textit{H. pylori}.
Helicobacter pylori in Vietnam from 2001 to 2016 period (16 years). \(^{10,13,35,75-80}\) 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 English).\(^{13}\) 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 Hoang\(^{81} \) 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. Hue\(^ {82} \) 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.\(^ {83} \) 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.\(^ {84} \)

Recently, Kuo et al.\(^ {85} \) 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

![Average rate of primary resistance with Helicobacter pylori in Vietnam from 2001 to 2016.](image)

**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 et al.\(^ {31} \) (n=102) | 2014/South | ADM    | 13.7 | 56.9 | 44.1 | 25.5 | 23.5 | - |
| Phan et al.\(^ {83} \) (n=19) | 2015/South | 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, Epsilometer 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).\textsuperscript{65}

In Korea, Lee et al.\textsuperscript{65} 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=0.05), 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.\textsuperscript{65}

### 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.\textsuperscript{66,67} In European regions,\textsuperscript{68,69} 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.\textsuperscript{70}

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.\textsuperscript{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.\textsuperscript{70} In the North Vietnam, clarithromycin resistance had tended to further increase from 18.5% in 2013 to 42.1% in 2015 (Table 5).\textsuperscript{16}

The patients with the primary clarithromycin resistance will 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%.\textsuperscript{81} 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%.\textsuperscript{30}

In Vietnam, in 2003, Vinh\textsuperscript{76} found that the rate of clarithromycin resistance was 21.6% before treatment and 78.9% after treatment. Minh and Hoang\textsuperscript{81} 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.\textsuperscript{76} 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 Maastrict III guidelines on *H. pylori* infection management recommend substituting metronidazole for clarithromycin when resistance to this antibiotic exceeds 15% to 20%.\textsuperscript{30}

### 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.\textsuperscript{81} In Asia, mean overall prevalence of resistance to amoxicillin was 3% (95% CI, 21% to 34%).\textsuperscript{64}

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).\textsuperscript{16,33,77,80} The rate of the primary amoxicillin resistance in the North Vietnam has tended to further increase (18.1% to 43.6%)\textsuperscript{76,78,80} than in the South Vietnam (0% to 10.4%) (Table 3).\textsuperscript{16,33,77,78}

Vinh\textsuperscript{76} found that the rate of the secondary resistance of amoxicillin was 36.8%. Minh and Hoang\textsuperscript{81} 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, 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.\textsuperscript{48} 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

| Local                  | Antibiotic  | Binh et al. (2013)\textsuperscript{13} | Dung et al. (2015)\textsuperscript{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.
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% to 95.5%. The rate of the primary metronidazole resistance in the North Vietnam increased (38.1% to 95.5%) higher than that in the South Vietnam (37.8% to 50.8%) (Table 3). 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).

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. 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.

### 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. In Asia and Africa, tetracycline and bismuth are used more than in Europe and the America. 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 in South Korea (0.01%). In contrast, increased values were found 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 varies in almost parts of the world except for Africa. The comparison of data showed that tetracycline resistance was decreasing in the world, 26.85% in 2009 to 6.11% in 2014.

In Vietnam (see Table 5), the primary tetracycline resistance ranges 5.8% to 21.4% (Table 3). Minh and Hoang 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. 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. The European recommendation only uses levofloxacin in the rescue regimen, when the results of antibiotic therapy are available. When first-line therapy fails, the Maastricht IV Consensus Report recommends that bismuth-containing quadruple therapy can be a choice for second-line therapy. Many studies have investigated levofloxacin based regimens as second-line treatments, including meta analyses.

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 (24.5%), Iran (5.3%), and Malaysia (2.6%).

In Vietnam, a majority of the studies focused in the South Vietnam 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. The rates of the secondary levofloxacin resistance after 1, 2 and 3 treatments were 25.7%, 23.3%, and 33.3% respectively (Table 4). Phan et al. 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.
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.\(^\text{16}\) 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.\(^\text{98}\) 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, Hue\(^\text{34}\) studied the relationship between risk factors and *H. pylori* resistance. Research 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.\(^\text{17}\) 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.\(^\text{98-102}\) There are a total of five studies of gene mutation of *H. pylori* bacteria related to antibiotic resistance (one study in the North Vietnam, two studies in the Central Vietnam,\(^\text{98-102}\) and two studies in the South Vietnam\(^\text{98-100}\)).

Toan et al.\(^\text{98}\) 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.\(^\text{34}\) 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.\(^\text{101}\) also showed the mutation rate of A2143G was very high: 40 out of 41 (97.6%).

Trung et al.\(^\text{100}\) 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.\(^\text{100}\) 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       | OR (95% CI)     | p-value         |
|-----------------|-----------------|-----------------|-----------------|
| Clarithromycin  | Age ≥30 yr      | 3.2 (1.3–7.7)   | 0.011           |
| Cl (n=153)      | Previous eradication | 7.7 (1.7–34.7) | 0.008           |
| Levofoxacin     | Age ≥40 yr      | 1.9 (0.9–3.7)   | 0.057           |
| Cl (n=154)      | Previous eradication | 1.4 (0.6–3.1)  | 0.386           |

OR, odds ratio; CI, confidence interval.
Table 7. Helicobacter pylori Eradication Regimens in Vietnam\textsuperscript{66}

| 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.

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)\textsuperscript{6} 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).\textsuperscript{6} The followings are some main contents related to H. pylori eradication: (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 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%).\textsuperscript{66}

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%).\textsuperscript{66}

However, recent data indicate that primary and secondary resistance of H. pylori to clarithromycin, metronidazole and levofloxacin is increasing.\textsuperscript{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%.\textsuperscript{66} 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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