RESEARCH ARTICLE

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Prevalence and Pattern of Antibiotic Resistant Strains of *Helicobacter Pylori* Infection in ASEAN

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Abstract

Objective: Antibiotic resistance has significantly impact on eradication rates for *H. pylori* infection and remains important cause of treatment failure worldwide including ASEAN countries. The aim of this study was to survey the prevalence and antibiotic resistant pattern of *H. pylori* infection in ASEAN. **Methods:** This study was a survey among 26 experts from 9 ASEAN countries including Thailand, Cambodia, Indonesia, Laos, Malaysia, Myanmar, Philippines, Singapore and Vietnam whom attended a meeting to develop the ASEAN consensus on *H. pylori* management in Bangkok in November 2015. A questionnaire was sent to each member of the consensus meeting. The detail of the questionnaire included information about prevalence of *H. pylori* infection, facilities to perform *H. pylori* culture, molecular testing for antibiotic resistance and antibiotic resistance rate in their countries. **Results:** *H. pylori* infection remain common in ASEAN ranging from 20% in Malaysia, 21-54% in Thailand and 69% in Myanmar. Most of ASEAN countries can perform *H. pylori* cultures and antibiotic susceptibility tests except Laos and Cambodia. In ASEAN countries, metronidazole resistant *H pylori* is quite common whereas amoxicillin resistance remain rare. Clarithromycin resistance results in a significant decrease in *H. pylori* eradication rate with clarithromycin-containing regimens. The prevalence of clarithromycin resistance varies in ASEAN countries being high in Vietnam (30%) and Cambodia (43%), moderate to high in Singapore (17%) and low in Malaysia (6.8%), Philippine (2%) and Myanmar (0%). In Thailand, clarithromycin resistance tends to higher in large cities (14%) than in rural areas (~3.7%). **Conclusion:** ASEAN countries should develop a standard protocol for regular susceptibility testing of *H. pylori* so that clinicians would be better able to choose reliably effective empiric therapies. The wide range of antibiotic resistance in ASEAN countries suggests that the preferred first line regimen should be depend on the local antibiotic resistance other than single recommendation.

Keywords: Antibiotic resistant- *Helicobacter pylori*- ASEAN

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Introduction

Helicobacter pylori (*H. pylori*) infection is the major cause of chronic gastritis, peptic ulcer, precancerous lesions to gastric cancer and mucosa associated lymphoid tissue lymphoma (Vilaichone and Mahachai, 2001; Vilaichone et al., 2006; Ford et al., 2014; Mahachai et al, 2018). Currently, the eradication rate of standard triple regimen for *H. pylori* infection in several countries has been declining and failed to recommend as first line treatment (Chey and Wong, 2007; Mahachai et al., 2011, Vilaichone et al., 2017, Chotivitayatarakorn et al., 2017). *Helicobacter pylori* management in ASEAN: The Bangkok consensus report recommend that first line therapy should be varied regionally, geographically and per individual patient depending upon the pattern of antibiotic resistance in each ASEAN country (Mahachai et al., 2018). Antibiotic resistance is the important cause of eradication failures. After failure of second-line treatment, antibiotic susceptibility testing (Epsilometer test [E-test] or molecular genetic test) should be performed for appropriate regimen. The major indication for antibiotic susceptibility testing is identifying the proper management for each patient and to prepare population-based recommendations. However, there is limited information of antibiotic resistance in ASEAN countries due to lack of available culture laboratories in many countries.

We conducted this study to survey the prevalence of *H. pylori* infection and antibiotic resistant pattern of *H. pylori* infection in ASEAN countries. The results of this study could be guided clinicians in ASEAN countries

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for treatment of this particular infection associated with various clinical outcomes.

Materials and Methods

This study was a survey among 26 experts from 9 ASEAN countries including Thailand, Cambodia, Indonesia, Laos, Malaysia, Myanmar, Philippines, Singapore and Vietnam whom attended a meeting to develop the ASEAN consensus on *H. pylori* management in Bangkok in November 2015. A questionnaire was sent to each member of the consensus meeting. The detail of the questionnaire included information about prevalence of *H. pylori* infection, facilities to perform *H. pylori* culture, molecular testing for antibiotic resistance and antibiotic resistance rate in their countries.

Results

At the meeting, the prevalence of *H. pylori* infection and pattern of antibiotic resistance from each country were presented and extensive discussed by all members. All information were then submitted and finalized to all experts. *H. pylori* infection remain common in ASEAN ranging from 20% in Malaysia, 21-54%% in Thailand, 31% in Singapore, 50-70% in Vietnam and 69% in Myanmar. The prevalence of *H. pylori* infection was summarized in table 1. Most of ASEAN countries have standard laboratories and can perform *H. pylori* cultures and antibiotic susceptibility tests (Epsilometer test) except Laos and Cambodia. Some of ASEAN countries have their own antibiotic resistant pattern. However, susceptibility data regarding clarithromycin resistance is not widely available in most countries. In ASEAN countries, metronidazole resistant H pylori remain a major common antibiotic resistance, highest in Indonesia (100%) and lowest in Philippine (30%), whereas amoxicillin and tetracycline resistance remain rare. Clarithromycin resistance results in a significant decrease in *H. pylori* eradication rate with clarithromycin-containing regimens. The prevalence of clarithromycin resistance varies in ASEAN countries being high in Vietnam (30%), Indonesia (28%) and Cambodia (43%), moderate to high in Singapore (17%) and low in Malaysia (6.8%), Philippine (2%) and Myanmar (0%). In Thailand, clarithromycin resistance tends to higher in large cities (14%) than in rural areas where it remains low (~3.7%). Ciprofloxacin and levofloxacin resistance is a growing problem ranging from 1.4% in Indonesia up to 18% in Vietnam. The pattern of antibiotic resistance in ASEAN was summarized in Table 2.

Table 1. Prevalence of *H. pylori* Infection in ASEAN

Country	Prevalence
Thailand*	21%(S), 30% (C, E), 46% (N), 54%(NE)
Cambodia	30-50%
Laos	68.7%
Myanmar	69%
Vietnam	50-70%
Indonesia	22.1%
Malaysia	20%
Singapore	31%
Philippine	34%

*S, South; C, Central; E, East; N, North; NE, Northeast

Discussion

This survey demonstrated that *H. pylori* infection is highly prevalence in ASEAN and also has great impact in quality of life of people in this important region. Antibiotic resistance pattern is the key for developing effective therapeutic regimen. *H. pylori* infection is also a global problem and a major cause of malignant diseases especially gastric cancer. Successful eradication of this particular bacteria is the important first step to cure these diseases. At the present time, *H. pylori* eradication with standard triple therapy was reported to be ineffective (<70% eradication rate) in several countries worldwide, including ASEAN (Vilaichone et al., 2006; Graham, 2009).

Recent *Helicobacter pylori* management in ASEAN: The Bangkok consensus report suggested to use local antibiotic resistant pattern for developing appropriate first line regimen for their own countries. For second-line therapy, the regimen should contain antibiotics which never used prior e.g. amoxicillin, bismuth compound and tetracycline, or available drugs that resistance is uncommon. Furthermore, proper second-line regimen should also be based upon local antibiotic susceptibility tests. In cases with more than 2 treatment failures, antibiotic susceptibility testing such as E-Test or molecular test is mandatory prior to start an appropriate choice of rescue therapy based on antibiotic resistance pattern. (Mahachai et al., 2018). This study had some limitations. First, the prevalence of *H. pylori* infection and the pattern of antibiotic resistance in different region of ASEAN might be different from each other. Second, specific patterns of *H. pylori* antibiotic resistance, such as dual

Table 2. Pattern of *H. pylori* Antibiotic Resistance in ASEAN

Antibiotics	Thailand	Cambodia	Laos	Myanmar	Vietnam	Indonesia	Malaysia	Singapore	Philippine
Amoxicillin	5.2%	-	-	0%	5%	19.4%	0%	4%	-
Clarithromycin	14%	43%	12.6%	0%	30%	28%	6.8%	17%	2%
Metronidazole	36%	73%	-	36.5%	70%	100%	32.3%	48%	30%
Tetracycline	1.7%	-	-	0%	-	-	-	-	-
Ciprofloxacin	7.7%	-	13.4%	5.8%	18%	1.4%	6.8%	14%	-
Levofloxacin	7.2%	-	13.4%	5.8%	18%	1.4%	6.8%	14%	-

resistance and multiple resistance, were not addressed due to format of the survey. This survey, however, is an importantly preliminary overview for future collaborative and provide better treatment for *H. pylori* infection among ASEAN countries.

In ASEAN, clarithromycin and metronidazole resistance remain the major problem. In area with high prevalence of clarithromycin resistance (>15%), standard triple therapy could not be used as first line treatment and quadruple therapy might be a better choice (Malfertheiner et al., 2017). Unlike clarithromycin, metronidazole might be overcome the resistance by using longer duration or combination with other antibiotics (Vilaichone et al., 2006; Vilaichone et al., 2015; Mahachai et al., 2016). However, amoxicillin and tetracycline resistance have low prevalence in this region and could be consider as important drugs for first line therapy. Moreover, amoxicillin, tetracycline and bismuth compound could be reused after multiple treatment failures (Vilaichone et al., 2006). Confirming eradication by reliable methods such as urea breath test or stool antigen test should be performed in all cases prevent recurrence of *H. pylori* related gastrointestinal diseases (Vilaichone et al., 2006; Mahachai et al., 2016; Malfertheiner et al., 2017).

In summary, ASEAN countries should develop a standard protocol for regular susceptibility testing of *H. pylori* so that clinicians would be better able to choose reliably effective empiric therapies. The wide range of prevalence of antibiotic resistance in ASEAN countries suggests that the preferred first line regimen should be depend on the local antibiotic resistance other than single recommendation.

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