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

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Abstract

Objective: Antibiotic resistance has significantly impacted eradication rates for H. pylori infection and remains an 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, who 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 details of the questionnaire included information about the prevalence of H. pylori infection, facilities to perform H. pylori culture, molecular testing for antibiotic resistance and antibiotic resistance rates in their countries. Results: H. pylori infection remains common in ASEAN, ranging from 20% in Malaysia, 21-54% in Thailand, and 69% in Myanmar. Most 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 remains 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 be 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 depend on the local antibiotic resistance other than single recommendation.

Keywords: Antibiotic resistance- 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 declined and failed to recommend as first-line treatment (Chey and Wong, 2007; Mahachai et al., 2011, Vilaichone et al., 2017, Chotvitayatarakorn et al., 2017). Helicobacter pylori management in ASEAN: The Bangkok consensus report recommends 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 an 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 regimens. 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 on antibiotic resistance in ASEAN countries due to a 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.
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.

Discussion

This survey demonstrated that *H. pylori* infection is highly prevalent 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 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

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 \textit{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 (Malferttheiner 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 \textit{H. pylori} related gastrointestinal diseases (Vilaichone et al., 2006; Mahachai et al., 2016; Malferttheiner et al., 2017).

In summary, ASEAN countries should develop a standard protocol for regular susceptibility testing of \textit{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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