Risk factor, diagnosis, and current treatment of *H. pylori* Infection in Indonesia: A Literature Review

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ABSTRAK

Infeksi Helicobacter pylori (H. pylori) di Indonesia merupakan suatu masalah yang telah berkembang, meskipun prevalensi di Indonesia dilaporkan lebih rendah dibanding negara ASEAN dan Asia lainnya. Dominasi jenis bakteri H. pylori dengan virulensi genotipe yang lebih lemah di Indonesia diduga menjadi penyebab rendahnya prevalensi infeksi tersebut serta kanker gaster sebagai komplikasinya. Walaupun pemeriksaan endoskopi masih menjadi alat utama untuk mengevaluasi status mukosa gaster pada pasien yang terinfeksi H. pylori, infeksi H. pylori sendiri dapat secara sederhana didiagnosis menggunakan strategi test-and-treat, terutama pada daerah dengan sumber daya terbatas. Beberapa temuan menunjukkan angka resistensi terhadap berbagai antibiotik yang tinggi di banyak daerah dan etnik Indonesia, di mana hal tersebut mengindikasikan bahwa pengobatan menggunakan triple therapy regimen tidak dapat diaplikasikan terhadap semua populasi secara keseluruhan. Pengobatan infeksi H. pylori sebaiknya didasarkan terhadap pola resistensi pada area tersebut, dan regimen menggunakan antibiotik jenis baru seperti furazolidone, rifabutin, dan sitafloxacin dapat dipertibangkan sebagai terapi potensial untuk mengeradikasi infeksi tersebut. Untuk menentukan pendekatan yang paling adekuat, studi multisenter menggunakan sampel yang lebih besar penting untuk dilakukan.

Kata kunci: *faktor risiko, diagnosis, penatalaksanaan terkini, infeksi, Helicobacter pylori.*

ABSTRACT

Helicobacter pylori (H. pylori) infection has become an emerging problem in Indonesia despite its relatively low prevalence as opposed to other Southeast Asian and Asian countries. Strains containing less virulent genotypes predominantly found in Indonesia is suggested to be the rationale for why the disease prevalence, as well as its gastric cancer complication, remain inferior in respect of neighboring counterparts. Although endoscopic evaluation is still necessary to determine the gastric mucosal status of those infected with H. pylori, the infection itself can be easily diagnosed with test-and-treat strategy especially in areas with limited resources. Several findings revealed high rates of antibiotic resistance varying among Indonesian regions and ethnicities, suggesting that triple therapy regimen may not be suitable for all populations. Whereas treatment should be based on the pattern of resistance in respective regions, novel regimens involving furazolidone, rifabutin, and sitafloxacin are proposed as potential drugs of choice to eradicate H. pylori infection. In order to determine the adequate approach for H. pylori infection in Indonesia, further multicenter studies involving larger sample size should be conducted.

Keywords: *risk factor, diagnosis, current treatment, infection, Helicobacter pylori.*

INTRODUCTION

Indonesia is one of the most populous countries in the world. Indonesia is unique in that its land mass is formed of an archipelago consisting of more than 1,000 ethnicities and even more sub-ethnic groups. *Helicobacter pylori* (*H. pylori*) infection has been an emerging problem in Indonesia with a prevalence of 22.1% reported by Syam et al.[1] Globally, 4.4 billion people are infected with *H. pylori*.[2] The prevalence of *H. pylori* infection in Indonesia is relatively low compared with that of other countries in Southeast Asia and Asia. In developing countries, the prevalence of *H. pylori* infection ranges from 85% to 90%; however, this figure is significantly lower in developed countries, ranging between 30% and 50%.[3,4] For instance, the United Arab Emirates has an overall prevalence of 41%.[5] In Southern Asia, Pakistan and India have the highest *H. pylori* infection prevalence—81% and 63.5%, respectively. In line with the low prevalence of *H. pylori* infection, Indonesia has only the fifth highest incidence of gastric cancer among Southeast Asian countries, reported as 3,014 cases per year according to GLOBOCAN 2018.[6] In contrast to neighboring countries, Vietnam ranks first, with 17,527 new cases of gastric cancer per year.[6] China leads Asia in term of gastric cancer incidence, with 456,124 cases per year. Southeast Asia in general has a gastric cancer incidence of 8.2 per 100,000 and 4.1 per 100,000 per year for men and women, respectively. These relatively high numbers are only less than a third of those in East Asia (the highest in the world).[7] These data spark the question: *"Is the low prevalence of gastric cancer in Indonesia due to the low prevalence of H. pylori infection?"*.

ETIOPATHOGENESIS AND RISK FACTORS

The low prevalence of *H. pylori* infection remains a point of curiosity. Initially, the prevalence of *H. pylori* in Indonesia was expected to be as high as in other developing Asian countries, as sanitation infrastructures are not yet well constructed. Several studies have assessed the risk factors of *H. pylori* infection in Indonesia. A study by Goto et al. showed that the risk factors significantly associated with *H. pylori* infection are infrequent hand washing before meals (OR 4.10; 95% CI: 1.15-14.6), cucumber intake more than once a week (OR 6.61; 95% CI: 1.87-23.3), chicken intake more than once a week (OR 1.40; 95% CI: 0.43-4.56), and former and current alcohol drinking (OR 61.9; 95% CI: 1.67-2300.8).[8] On the other hand, drinking soy milk more than once a week decreased the risk with marginal significance (OR 0.10; 95% CI: 0.01-0.97). The Buginese and Batak ethnicities were shown to have a higher risk of *H. pylori* infection than the Javanese, as Buginese and Bataknese eat using their fingers more frequently.[8] Drinking tap water instead of mineral water is also a risk factor for *H. pylori* infection.[9] The same risk factors are also seen in the United Arab Emirates.[5]

With regard to ethnicity, a study conducted by Syam et al. assessing the prevalence of *H. pylori* on the five largest islands of Indonesia revealed much interesting data. They found differences in the prevalence of *H. pylori* infection between ethnicities, hence establishing ethnicity as an independent risk factor for *H. pylori* infection. The Papuan, Batak, and Buginese ethnicities had a higher risk of developing *H. pylori* infection than the Javanese, Dayak, and Chinese ethnicities.[10] Ethnicity is also a risk factor for *H. pylori* infection in the United Arab Emirates ($p < 0.001$). Khoder et al. showed that people of African descent have a significantly higher prevalence than those of Asian or Arab ethnicity. Among Asians, Indians have the highest prevalence of *H. pylori* infection, followed by the people of Pakistan and the Philippines.[5]

There is an ongoing debate over whether or not psychological stress is a risk factor for *H. pylori* infection. The idea is that psychological stress provokes gastric acid secretion, increasing the level of aggressive factors and inhibiting protective factor of the gastric mucosa. These conditions facilitate infection of the stomach by *H. pylori*. A study by Darwin et al. in Padang showed that psychological stress appears to have no correlation with the expression of IL-6 in the gastric mucous of patients with functional dyspepsia. However, there is evidence of increasing activity of *H. pylori* in patients with increased psychological stress.[11]

H. pylori can manifest as a broad spectrum of clinical symptoms and diseases ranging from peptic ulcer to gastric cancer and from bloating to dyspepsia. A cross-sectional study in Medan conducted by Siregar et al. involving 80 patients with gastritis showed that serum TNF-α and VEGF levels were significantly increased in the *H. pylori*-infected group, but there were no significant differences in serum levels of IL-8 between *H. pylori*-positive and negative groups. High levels of TNF-α were associated with a severe degree of chronic inflammation, high levels of IL-8 were associated with severe degree of chronic inflammation and neutrophil infiltration, and high levels of VEGF were associated with a severe degree of premalignant gastric lesion.[12]

One of the clinical manifestations of *H. pylori* infection is Gastroesophageal Reflux Disease (GERD). It was suggested that there is a parallel association of increasing GERD incidence with decreasing *H. pylori* infection prevalence in Asia. Miftahussurur et al. conducted a study involving 104 dyspeptic patients evaluated by endoscopy in Indonesia. This study found a high prevalence of GERD in areas with a low *H. pylori* prevalence, although the association could not be measured due to an insufficient number of cases.[12]

Peptic ulcer disease is still a significant health burden, despite decreasing rates of *H. pylori* infection due to eradication therapy. In Indonesia the prevalence of *H. pylori* infection in peptic ulcer disease is 90%-100%. Peptic ulcer disease itself can be differentiated into duodenal and gastric ulcer disease. *H. pylori* plays a role in those two ulcer locations. The location of *H. pylori* infection determines whether gastric acid secretion will be up- or downregulated, based on the inflammatory zone. Untreated *H. pylori* infection may lead to gastric cancer, as *H. pylori* is classified as a Class 1 carcinogen in humans. However, the risk of malignancy depends on the virulence factor of *H. pylori*.[13]

An interesting point concerning the prevalence of gastric cancer in Indonesia is that it is relatively low compared with other Asian countries. A multicenter study conducted by Miftahussurur et al. in Java, Papua, Sulawesi, Borneo, and Sumatera showed that virulence factors of genotypes presenting in *H. pylori* strains were suggested to contribute to the low rate of gastric cancer in Indonesia. Their study revealed the genetic profile of *H. pylori* in Indonesia. Of the strains examined, 97.7% possessed the cagA gene, 60.5% of which were East-Asian-type cagA, while 20.9% were Western-type-cagA. In all, 18.6% were of the novel ABB type, most of which were obtained from Papuan subjects. Patients infected with East-Asian-type-cagA strains possessing a 6-bp deletion showed significantly lower inflammation and atrophy scores in the corpus area than those with strains expressing the Western-type cagA. These findings suggest that the low incidence of gastric cancer in Indonesia may also be due to less virulent genotypes in the predominant strains.[10] Variations in *H. pylori* strains affect the prevalence of gastric cancer within a country. hspEAsia isolates among Chinese people appear linked to a higher incidence than hpAsia2 or hpEurope strains, found among Indians and Malays.[7]

H. pylori vacA and cagA genes are associated with higher virulence, whereas Vascular Endothelial Growth Factor (VEGF) is one important marker for neo-angiogenesis. Siregar et al. conducted a study in Medan and concluded that an increased level of VEGF is correlated with *H. pylori* infection and its virulence status. There was a significant rise in serum levels of VEGF in *H. pylori*-infected patients compared with those without infection. Moreover, cagA-positive strains of *H. pylori* also showed significantly higher VEGF levels than cag-A negative strains.[14]

DIAGNOSIS OF *H. PYLORI* INFECTION

Several studies were performed in Indonesia to identify other diagnostic tools and biomarkers and to compare them with the urea breath test (UBT) and endoscopic evaluation, for the diagnosis of *H. pylori* infection in the Indonesian population.

Budyono et al.[15] conducted a cross-sectional study from November 2016 to March 2017 to analyze the association between the severity of dyspepsia, measured with a modified Glasgow Dyspepsia Severity Score (GDSS) questionnaire,

and *H. pylori* infection, measured with 14C UBT Examination. There was a significant difference in GDSS scores between *H. pylori*-negative and positive patients. However, clinical assessment failed to show a significant difference in severity between the two groups (GDSS of 3.06 in positive and GDSS of 1.67 negative, out of 10). Therefore, it is difficult to recommend modified GDSS as a substitute for the current examination method, as it has a sensitivity of 41.6% and specificity of 85.5%, taking UBT as the gold standard. *H. pylori* eradication should be considered in patients with a modified GDSS score of 4 and above if there is no better examination available.

Nurdin et al.[16] conducted a study to investigate *H. pylori* detection in gastric biopsy. They compared immunohistochemistry and Giemsa staining for the detection of *H. pylori* in active chronic gastritis. The Giemsa sensitivity test performed upon immunohistochemistry showed a sensitivity value of 65% and a specificity value of 100%. Immunohistochemistry staining in active chronic gastritis was more sensitive than Giemsa, particularly in detecting coccoid-shaped bacteria.

As for the use of serology in *H. pylori* infection, Miftahussurur et al. found than an ELISA test for *H. pylori* infection had sensitivity of 66.7% and specificity of 97.2%, compared with immunohistochemistry as the gold standard. This showed the low accuracy of the ELISA kit when used in an Indonesia population.[17]

Other studies attempted to generate markers that could be used to evaluate gastric mucosal status in patients with *H. pylori* infection. Miftahussurur et al. studied the use of serum pepsinogen (PGs) as a non-invasive method to determine gastric mucosal status, in order to favor areas in Indonesia in which gastrointestinal endoscopy is unavailable. PG levels were determined using the PG ELISA kit. The samples were then classified according to the ABC method as follows: *H. pylori*-negative/ PG-negative (group A), *H. pylori*-positive/ PG-negative (group B), *H. pylori*-positive/ PG-positive (group C), and *H. pylori*-negative/ PG-positive (group D). *H. pylori* (+) patients had significantly higher PG II levels and lower PG I/PG II ratios than *H. pylori* (-) patients. The prevalence of chronic and atrophic gastritis was also significantly higher in *H. pylori* (+) patients. PG levels can be useful to determine chronic gastritis but have modest sensitivity for atrophic gastritis in Indonesia.[17]

A cross-sectional study conducted by Dairi et al. aimed to determine serum malondialdehyde (MDA) levels in patients with *H. pylori* (+) gastritis. *H. pylori* infection produces reactive oxygen species (ROS), whereas ROS itself are an important factor for the development of gastritis. *H. pylori* infection also causes recruitment of neutrophils and macrophages, which in turn increase free radicals. This oxidative stress causes tissue damage that can be measured by MDA, the product of lipid peroxidase. The mean MDA level in *H. pylori* (+) patients was 1.58, whereas in *H. pylori* (-) it was 1.19, with $p = 0.013$ for the difference. There is still no normal value of MDA that can be used as standard, as it can be affected by age, enzyme activities, antioxidant supplements, diseases, and environmental factors.[18]

From a study using a survey of 26 experts from nine Southeast Asian countries (Cambodia, Indonesia, Laos, Malaysia, Myanmar, the Philippines, Singapore, Thailand, and Vietnam), the rapid urease test (RUT) was the most common method used to diagnose *H. pylori* infection, followed by UBT. Most Southeast Asian countries used a test-and-treat strategy for patients with dyspepsia without alarming symptoms, except Laos and the Philippines. In these cases, stool antigen and urea breath tests were commonly used. Among health centers and regions in the same countries, there were significantly different proportions of patients with findings of endoscopic gastritis who underwent RUT and histological evaluation.[19]

COMPLICATIONS OF *H. PYLORI* INFECTION

Colonization with *H. pylori* is known to increase the risk of certain diseases, such as duodenal ulcer, gastric ulcer, non-cardiac gastric carcinoma, B-cell lymphoma, and possibly thrombocytopenic purpura. A case-control study was conducted by Darnindro et al. between June 2014 and August 2014 in Jakarta with 69

cases and 71 controls using medical record and histopathology evaluation. *H. pylori* infection can cause atrophy and metaplasia of the gastric mucosa. According to histopathological findings, active chronic gastritis was found in 62.3% of *H. pylori* (+) patients, compared with only 12.7% of *H. pylori* (-) patients (OR = 11.31; 95% CI: 4.86-26.7). Mild and moderate atrophy was higher among *H. pylori* (+) patients, though the difference was not statistically significant (p = 0.09). The frequency of gastric mucosal metaplasia was found to be higher in *H. pylori* (+) patients (10.1% vs 1.4%; p = 0.03).[20]

Increased metaplasia in the *H. pylori* (+) population was also observed by Tenggara et al. Of 1127 patients who underwent endoscopy between 2001 and 2011 in North Jakarta, metaplasia was found in 3.31% of *H. pylori* (-) patients and 9.23% of *H. pylori* (+) patients. Only 7 patients had gastric malignancies, and all of them were *H. pylori* (-). They concluded that there was an association between metaplasia and *H. pylori* infection. However, there was no association between gastric malignancy and *H. pylori* infection.[21]

According to Quach et al., the prevalence of gastric cancer is the highest in Vietnam (17/100.000) and the lowest in Indonesia (1/100.000). In Indonesia, ethnicities including Chinese, Bataknese, and Minahasanese were considered as high-risk factors for the development of gastric cancer. In most Southeast Asian countries, a familial history of gastric cancer and precancerous gastric lesions were considered risk factors for gastric cancer development.[20]

It was suggested that *H. pylori* infection decreases the risk of gastroesophageal reflux disease and its complications, including Barret's esophagus, adenocarcinoma of the esophagus, and gastric cardia. A study conducted by Miftahussurur et al. in Surabaya involved 104 patients with dyspeptic syndrome in Indonesia between October 2015 and November 2015 who underwent endoscopic evaluation. GERD was diagnosed by endoscopic evaluation, and patients were asked to complete GERD-Q questionnaires. The presence of *H. pylori* strains was identified on the basis of histology, culture, and immunohistochemistry. Of all patients, 53.8% were confirmed to have GERD. Only two patients (1.9%) were diagnosed as *H. pylori* positive, although both were also diagnosed with GERD. In conclusion, this study found a high prevalence of GERD in areas with a low *H. pylori* prevalence, although the association could not be measured due to an insufficient number of cases.[12]

CURRENT TREATMENT MODALITIES FOR *H. PYLORI* INFECTION

The currently available guidelines for dyspepsia with *H. pylori* infection management in Indonesia by Syam et al. (2017) recommend a minimum 7-day course of either triple or quadruple therapy for the first-line regimen, depending on the rate of resistance to clarithromycin in the affected area.[22] The combination of a proton pump inhibitor (PPI), such as rabeprazole, lansoprazole, omeprazole, pantoprazole, or esomeprazole, to reduce gastric acid production and antibiotics effective against *H. pylori* is reported to be beneficial to eradicate the infection.

Triple therapy with PPI, amoxicillin, and clarithromycin/metronidazole remains the treatment of choice in areas with a rate of resistance of less than 20% to clarithromycin.[21] Meanwhile, those residing in areas with high resistance to clarithromycin are suggested to undergo a culture and resistance test with samples isolated from an endoscopic specimen, or a molecular test directly through gastric biopsy, prior to treatment initiation. A quadruple therapy comprising bismuth subsalicylate, PPI, metronidazole, and tetracycline is recommended in such areas. Under circumstances where bismuth is not available, the same regimen can still be used without including bismuth.

When the first-line clarithromycin-based regimen fails, bismuth quadruple or triple therapy with PPI, levofloxacin, and amoxicillin are favorable as the second-line treatment, whereas in areas with high resistance to clarithromycin, the PPI-levofloxacin-amoxicillin regimen may be the first line of treatment.[22]

A confirmation test needs to be conducted within at least 4 weeks after each treatment

course.[22] A UBT or *H. pylori* stool antigen monoclonal test can be beneficial to identify any treatment failure.

ANTIBIOTIC RESISTANCE IN *H. PYLORI* INFECTION

The high prevalence of clarithromycin-, levofloxacin-, and metronidazole-resistant *H. pylori* remains a burden of many Asia-Pacific countries, as reported in a meta-analysis by Kuo et al.[22] Among many other reasons, such as genetic polymorphisms and patient compliance, antibiotic resistance has been proposed as a major factor contributing to the low eradication rate of *H. pylori* infection after standard therapy.[24] Therefore, in *H. pylori* Management in ASEAN: The Bangkok Consensus Report, Mahachai et al. recommend that the first-line regimen should be customized for each region in accordance with its antibiotic resistance pattern.[25]

Miftahussurur et al.[26] conducted a prospective study to evaluate resistance rates from August 2012 to November 2015 involving 849 adult dyspeptic patients who underwent endoscopy examinations in 11 cities spreading across the five largest islands of Indonesia. Among them, 77 strains of H. Pylori were isolated to undergo sensitivity assays for metronidazole, clarithromycin, levofloxacin, amoxicillin, and tetracycline. There were high rates of antibiotic resistance to metronidazole and levofloxacin (46.8% and 31.2%, respectively), whereas a lower prevalence of resistance to clarithromycin (9.1%), amoxicillin (5.2%), and tetracycline (2.5%) were observed. The patterns of resistance were also found to vary significantly among several ethnicities and regions. The highest rate of resistance to levofloxacin was found in Java (50%) and Sumatera (44.4%), while Sumatera also showed a significantly higher rate of metronidazole resistance (88.9%) than other islands. Of all ethnic groups, Ambonese were associated with significantly higher rates of metronidazole and tetracycline resistance compared with others. Moreover, high levels of clarithromycin resistance were also observed in Ambonese, Chinese, and Balinese. Only strains isolated from Dayak individuals were found to be sensitive to all antibiotics. The study suggested that standard triple therapy based on metronidazole and levofloxacin may not be effective at eradicating *H. pylori* infection in Indonesia.

To investigate this matter further, Miftahussurur et al.[26] initiated a follow-up study where a total of 105 strains isolated from 1,039 dyspeptic subjects from August 2012 to February 2016 were analyzed in order to investigate possible alternative regimens for *H. pylori* infection in Indonesian regions with high rates of metronidazole and levofloxacin resistance. Sensitivity to five alternative antibiotics comprising rifaximin, rifabutin, furazolidone, garenoxacin, and sitafloxacin were assessed in this study. It was revealed that all strains were sensitive to rifabutin, furazolidone, and sitafloxacin. A mild rate of resistance to garenoxacin was found, whereas those treated with rifaximin showed a much higher rate (6.7% and 38.9% respectively). The resistance rates to both drugs were found to be the highest in Java. Garenoxacin resistance was found neither in Bali, Kalimantan, and Timor nor in those belonging to Ambonese, Balinese, Dayak, Javanese, Minahasanese, and Timor ethnic groups. In contrast, rifaximin resistance was found to be evenly distributed among all ethnicities. The study suggested that alternative therapies with furazolidone, rifabutin, and sitafloxacin might be considered as the treatment of choice to eradicate *H. pylori* in Indonesian regions with metronidazole and levofloxacin, as well as clarithromycin resistance.

In an attempt to identify the virulence factors that might contribute to the high prevalence of antibiotic-resistant *H. pylori* strains in Indonesia, genetic sequencing assays were conducted in both studies. An association between *H. pylori* resistance to several antibiotics and their genotypes were then discovered.[26,27] Tetracycline-resistant *H. pylori* was shown to be significantly associated with CagA-positive strains, whereas those with genetic expression of VacA were associated with rifaximin resistance.

CONCLUSION

The prevalence of *H. pylori* infection in Indonesia is relatively low in comparison with

other Southeast Asian and Asian countries, as is the incidence of gastric cancer. We suggest that this phenomenon is due to East-Asian-type-cagA strains as a predominant strain in Indonesia that possesses a 6-bp deletion, resulting in less virulent disease. In areas with limited resources, the test-and-treat strategy is preferred to diagnose dyspeptic patients without alarming symptoms. To date in Indonesia, there is still no noninvasive examination proven to be significantly valuable for evaluating gastric mucosal status in *H. pylori* infected patients. Triple therapy remains the mainstay of treatment in areas of low resistance rates to clarithromycin, while a PPI-levofloxacin-amoxicillin regimen should be used in high-resistance areas. However, the Indonesian population also has high resistance rate to levofloxacin, especially in the regions of Java and Sumatera. Therefore, in these cases, furazolidone, rifabutin, and sitafloxacin might be considered as drugs of choice to eradicate *H. pylori*. A multicenter study involving a large number of samples should be conducted to determine the optimal *H. pylori* treatment regimen in Indonesia.

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