Brief Communication

Current situation of *Helicobacter pylori* infection in Indonesia

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ABSTRAK

Data epidemiologi infeksi Helicobacter pylori (H. pylori) terus berubah dalam beberapa dekade terakhir. Indonesia dilaporkan memiliki prevalensi infeksi H. pylori yang rendah dibandingkan dengan negara lain di Asia. Beberapa penelitian di Indonesia melaporkan bahwa sanitasi yang buruk, usia, agama, etnis merupakan faktor risiko untuk infeksi H. pylori. Dibandingkan dengan tes diagnostik lainnya, tes urine merupakan tes yang dapat diandalkan untuk mendeteksi H. pylori di Indonesia karena tes tersebut bersifat non-invasif dengan harga yang cukup terjangkau dan memiliki akurasi yang tinggi. Meskipun banyak penelitian telah dilakukan mengenai prevalensi infeksi H. pylori pada beberapa etnis di Indonesia, peneliti masih memiliki beberapa pertanyaan yang belum terjawab mengenai infeksi H. pylori di Indonesia. Oleh karena itu, diperlukan untuk membangun pusat penelitian H. pylori yang menyediakan fasilitas untuk kultur, evaluasi resistensi antibiotik, dan memperoleh informasi genotipe yang dapat menjelaskan perbedaan dalam infeksi H. pylori di antara berbagai etnis di Indonesia.

ABSTRACT

The epidemiology of *Helicobacter pylori* (*H. pylori*) has been changing over the past decades. Indonesia was reported have a low prevalence of *H. pylori* infection compared to other countries in Asia. Some studies in Indonesia have evaluated that poor sanitation, age, religion, ethnicity are the risk factors for *H. pylori* infection. Compared to other diagnostic tests, the urine test will be reliable for the detection of *H. pylori* in Indonesia because it is non-invasive and low cost with high accuracy. Although we have already performed studies on the prevalence of *H. pylori* infection in several ethnics, we still have some questions that remain unclear regarding *H. pylori* infection in Indonesia. Therefore, we have a need to build a *H. pylori* center that provide facilities for culturing, evaluating antibiotic resistance, and obtaining the genotype information that may explain the differences in *H. pylori* infection among ethnic groups in Indonesia.

As a developing country in Southeast Asia, Indonesia is an archipelago with a multi-ethnic society (more than 1,000 ethnic and sub-ethnic groups). The age-standardized incidence of gastric cancer in Indonesia has been reported to be 2.8/100,000, which is low compared with the one recorded among other Asian countries.[1] Indonesia, with its different ethnicities, cultures, life-styles and religions, presents an appropriate model to examine the effects of migration and co-evolution on the bacteria-host interactions involved in the *Helicobacter pylori (H. Pylori)* infection

Until March 2013, only 313 hospitals provided gastrointestinal endoscopy services in Indonesia. Although these hospitals were distributed in 33 provinces in the country, 72% (98/136) of them were located on Java island.[2] This uneven distribution makes it difficult for our physicians to establish a diagnosis of *H. pylori*.

The epidemiology of *H. pylori* has been changing over the past decades, with a decrease in the prevalence of infection in most countries. The changing epidemiology of the bacterium has been associated with a decline in peptic ulcer disease and gastric cancer. A Malaysian study reported by Leow et al[3] found that in the period of 1989–1990, the overall prevalence of *H. pylori* was 51.7%. This prevalence decreased to 30.3% in the second period, 1999–2000, and to 11.1% in the third period, 2009–2010 (p<0.001).[3]

Syam et al reported a prevalence of *H. pylori* infection of 22.1% (59/267).[4] In contrast to other countries in Asia, we have a low prevalence of *H. pylori* infection. We attempted to identify the risk factors for *H. pylori* infection, but found inconsistencies in terms of locations. Hence, questions remain about *H. pylori* infection in Indonesia are, first, what are the risk factors for the *H. pylori* infection in Indonesia? And second, why does the incidence of the *H. pylori* infection remain low in Indonesia?

In addition to these problems, we aim to identify the best test for *H. pylori* screening in Indonesia.

What are the risk factors for the *H. pylori* infection in Indonesia?
Some studies have evaluated the risk factors for *H. pylori* in Indonesia. The latest study reported

by Darnindro et al[5] found that the incidence of *H. pylori* infection in patients with poor sanitation was higher compared with patients who had a good sanitation status. The lower the sanitation status, the higher the risk of *H. pylori* infection (OR=2.5; 95% CI=1.01–6.19; p=0.044). Furthermore, the use of public toilets can increase the spread of infection because of individual's lack of hygienic behaviour. Also, the use of wells, especially shallow wells, as a water source increases the risk of transmission of *H. pylori*.[5] Darnindro et al[5] reported that the incidence of *H. pylori* infection in areas with a low clean water index was higher than in areas with a high clean water index. The lower the index, the greater the risk of *H. pylori* infection (OR=1.524; 95% CI=0.57–4.04; p=0.396). Darnindro et al[5] also showed that 13.5% of their sample had a high crowding index, although the association between *H. pylori* infection and crowding did not achieve statistical significance (OR=1.2; 95% CI=0.37–4.49).[5]

Our study, conducted from January 2014 to February 2015, involved a total of 267 patients with dyspeptic symptoms on Java, Papua, Sulawesi, Borneo, and Sumatra islands. The patients aged 50–59 had a significantly higher *H. pylori* infection rate than did the 30–39-year-old group (OR=2.98; p=0.05). The Protestants had a significantly higher *H. pylori* infection rate than did the Catholics (OR=4.42; p=0.008). The infection rate was also significantly lower among people who used tap water as their source of drinking water compared with those who drank from wells or rivers (OR=9.67; p=0.03).[4]

The major ethnicities in the study of Darnindro et al[5] were Javanese (45.9%), Bugis (18%), and Sundanese (15.3%). The incidence of *H. pylori* infection among Javanese in their study was 17.9%, whereas it was 30% among Bugis, and 29.4% among Sundanese.[5] Our epidemiology study in five major islands in Indonesia yielded a similar trend.[4] There were significant differences in the prevalence of *H. pylori* infection in terms of ethnic groups (p<0.001). The highest prevalence of *H. pylori* infection was found among Papuan patients: 9/21 (42.9%) tested positive for *H. pylori*. This compared with 28/70 (40.0%) of Batak patients, 11/30 (36.7%) of Buginese patients and just 7/54 (13.0%) of Chinese patients. There was

no significant difference in the *H. pylori* infection rate between Surabayan Chinese (15.4%, 4/26) and Pontianak Chinese (12.5%, 3/24; *P*=0.93). Three Dayak patients (7.5%) were positive for *H. pylori* infection. The comparison of these two studies allowed us to conclude that ethnicity is one of the risk factors for *H. pylori* infection.[4]

Why does the incidence of *H. pylori* infection remain low in Indonesia?

The causes of the low *H. Pylori* infection rate in Indonesia remain unknown. We would expect *H. pylori* infection to be as high in this country as in other developing countries, because the sanitation infrastructure remains to be constructed. Most of Indonesians still do not have direct access to clean water. Table 1 presents a summary of previous studies that examined the prevalence of *H. pylori* infection and gastric cancer in Indonesia. Although a number of researchers have investigated this, the results are controversial and contradictory (0–68%).[6,7] This could be attributable to the different study populations and different tests used for *H. pylori* diagnosis.[8] Moreover, most of these studies investigated only the largest ethnic group, the Javanese.[6,7,9,10] In a previous study, Miftahussurur et al confirmed that the prevalence of *H. pylori* infection in Surabaya (Java island) was low, only 11.5%, diagnosed using five different methods.[8]

It is still to be expected that our genetic-polymorphism evaluation of the possibility that some ethnic groups, such as the Javanese and most of the ethnic groups in Sumatra (Acehnese, Minang, and Palembang), might have immunity against *H. pylori* infection. It is also possible that some diets may be useful in preventing *H. pylori* infection. In addition to the remaining question of why the prevalence of *H. pylori* is low in Indonesia, another enigma emerges: why do some ethnic groups, such as the Papuans, Bugis (South Celebes) and Batak (North Sumatra), have a high prevalence of *H. pylori* infection compared with other ethnicities?

What is the best tool for establishing the diagnosis of *H. pylori* infection in Indonesia?

We performed several studies to identify the best *H. pylori* diagnostic test for the Indonesian population, such as Pronto Dry, *H. pylori* stool antigen (HpSA), or a urine test.

In 2003–2004, we evaluated the rapid urease test (Pronto Dry) in patients with dyspepsia in several endoscopic centers in Indnesia. The study was conducted in patients with dyspepsia who underwent endoscopic examination in the endoscopic centers of several cities in Indonesia, as follows: Cipto Mangunkusumo Hospital Jakarta, Hasan Sadikin Hospital Bandung, Sardjito Hospital Yogyakarta, Soetomo Hospital Surabaya, Adam Malik Hospital Medan and Sanglah Hospital Denpasar. The study took place from January 2003 to April 2004. Out of 525 cases, 56 cases were considered *H. pylori* positive based on the criteria used, 39 tested positive using Pronto Dry, and 17 tested negative using Pronto Dry. The overall sensitivity and specificity of Pronto Dry were 69.7% and 95.7%, respectively. Its positive predictive value was 66.1%, its negative predictive value was 96.4% and its overall accuracy rate was 92.9%. When we calculated the sensitivity and specificity at each endoscopic center, the results varied.[11]

Our study evaluating the HpSA test found that the area under the receiver operating characteristic (ROC) curve was 0.722 (95% CI=0.518–0.927). Using a cut-off value of 0.274 instead of 0.16 (as recommended by the manufacturer), the sensitivity and specificity were 66.7% and 78.9%, respectively.[9]

To confirm the accuracy of the urine test (RAPIRUN), we compared the results

Table 1. Summary of the prevalence of gastric cancer and *H. pylori* infection reported by several studies

Author	Study period	Area	n	Gastric cancer	*H. pylori* positive rate
Syam AF et al[10]	2003–2004	5 cities	550	1/550 (0.2%)	10.2%
Syam AF et al[11]	2001	Jakarta	63	1/63 (1.6%)	9.5%
Syam AF et al[4]	2014–2015	6 cities	267	1/267 (0.4%)	22.1%
Saragih et al[9]	1998–2005	Jakarta	2903	47/2903 (1.61%)	9.0%
Siregar G et al[12]	2003	Medan	50	3/50 (6%)	60%

of the test with histology confirmed by immunohistochenmistry (IHC) and culture. From this study, we could confirm the high accuracy of RAPIRUN, which is a rapid immunochromatographic method for the determination of anti-*H. pylori* IgG in urine. We found identical results between histology confirmed by IHC and culture (12/88, 13.6%). Only two samples tested positive using the urine test, but were found to be negative using the two gold-standard tests. Conversely, four samples tested negative using the urine test but were found to be positive using histology confirmed by IHC and culture. The overall sensitivity and specificity of RAPIRUN were 83.3% and 94.7%, respectively. Its positive predictive value was 71.4%, its negative predictive value was 97.3% and its overall accuracy rate was 93.2%. This urine test will be reliable for the detection of *H. pylori* in Indonesia.[12] This result was also in agreement with a previous report from North Sulawesi which found that the results of urine tests using a similar kit were identical to those obtained using the anti-*H. pylori* antibody serum test.[13] As a non-invasive test, the urine test is user friendly and combines low cost with high accuracy; therefore, it is the best option for measuring *H. pylori* status in remote areas that lack of an endoscopy system, such as much of Indonesia. This urine test can also be very useful for mass screening.

What should be done?

We have the means to establish a center dedicated to the study of *H. pylori* infection in Indonesia. We expect to collect samples from the five largest islands in Indonesia. We have a system to manage the samples, including their storage at -20 or -80°C. We have experience in culturing other bacteria and using them in molecular biology studies. We have already performed studies and obtained updates on the prevalence of *H. pylori* infection in several ethnic groups; we now need to build a *H. pylori* center to address the remaining unanswered questions, based on the following steps (1) providing a facility for culturing *H. pylori* and evaluating antibiotic resistance to *H. pylori* and (2) providing a facility to perform molecular biology studies and to obtain genotypic information that may partly explain the differences in *H. pylori* infection rates among ethnic groups in Indonesia.

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