REVIEW

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Noninvasive *Helicobacter pylori* Diagnostic Methods in Indonesia

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Although the prevalence of *Helicobacter pylori* infection in Indonesia is lower than that in other countries, *H. pylori* is still an essential pathogen associated with severe gastric mucosal damage and dyspeptic symptoms. Invasive diagnostic methods are not ideal due to the lack of endoscopic centers and high costs without full coverage by social insurance. Among the noninvasive methods, the urea breath test is widely available in Indonesia and has been suggested as the primary option to ensure the successful eradication of *H. pylori*. There has been no local validation for the urea breath test utilizing ^{13}C or ^{14}C. The stool antigen test is inexpensive and suitable for use in active infections before and after eradication; however, customs and habits are obstacles to delivering fresh stool on time. Only polyclonal antibodies and qualitative stool antigen test kits with low sensitivity are available. Serology is a widely validated method and has good accuracy, but it cannot distinguish between active and inactive infections. According to our observations, serology is the main choice of experts and patients, as it is simple, inexpensive and widely known. The urine test is an alternative for reducing costs and endoscopic workload, with high accuracy but low sensitivity. Further studies are necessary to prove the validity of the urine test to be used throughout Indonesia, especially in areas with a low prevalence of *H. pylori* infection. In conclusion, the validated urea breath test and the stool antigen test are considered noninvasive practical approaches for the detection of *H. pylori* infection in Indonesia, with serological and urine tests as alternatives. **(Gut Liver 2020;14:553-559)**

Key Words: Noninvasive; *Helicobacter pylori*; Urea breath test; Stool antigen test; Serology

INTRODUCTION

Some invasive diagnostic methods, such as the rapid urease test, histopathology and culture, have been developed to detect *Helicobacter pylori*, a Gram-negative bacterium that is the primary cause of chronic gastritis, gastric atrophy and gastric cancer.[1] Invasive tests are accurate and commonly used in daily practice. However, inexpensive, simple, convenient and user-friendly indirect tests, such as the urea breath test (UBT), the stool antigen test (SAT) and serology, have been introduced to diagnose *H. pylori* infection.[2]

Indonesia consists of 18,108 islands inhabited by 267,842,292 people, the fourth largest population in the world. The prevalence of *H. pylori* infection in Indonesia is 22.1%,[3] which is relatively low compared with neighboring countries such as Malaysia, Thailand and the Philippines, with prevalence of 24.3% to 49%, 54.1% to 76.1% and 60%, respectively.[4-6] Water source, age, and religion are risk factors for *H. pylori* infection among several ethnic groups in Indonesia.[3] The m2 type of *vacA* middle region, East Asian type *cagA* with 6-bp deletion and EPIYT motif, *dupA* negative, and double-positive *jhp0562/β-(1,3)galT* are the predominant virulence factors that may associated with lower incidence of gastric cancer.[7] We found that the complete integrating conjugative elements TFSS 4b type were less predominant and tended to have higher severity in the gastric mucosa.[8] In Indonesia, the prevalence of metronidazole- and levofloxacin-resistant strains is high, but the prevalence of amoxicillin- and tetracycline-resistant strains is low. We suggest that in some regions of Indonesia, clarithromycin- or metronidazole-based triple therapy should be carefully considered for eradicating *H. pylori*.[9] To counter high rates of metronidazole and clarithromycin resistance, furazolidone-, rifabutin- and sitafloxacin-based therapies might become alternative regimens, while sitafloxacin should be considered for eradication of levo-

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floxacin-resistant strains.[10]

Dyspepsia is the fifth-highest prevalent diseases among inpatients and the sixth-highest among outpatients in Indonesia.[11] In addition, a high prevalence of gastroesophageal reflux disease was found in an area of Indonesia with a low prevalence of *H. pylori* infection, with high rates of several risk factors, including smoking, a history of proton pump inhibitor (PPI) use and higher economic group.[12] However, the use of gastrointestinal (GI) endoscopy in Indonesia is still limited. In 2013, there were only 515 accredited GI endoscopists among 252 million people, for a ratio of 1:489,320.[11,13] In comparison, the ratio of endoscopists to the total population is 1:37,037 in the United States and 1:49,000 in England.[11] The number of hospitals in Indonesia that are able to provide GI endoscopy services is limited to only 313 hospitals in 33 provinces, most of them on Java Island.[11] Thus, the use of invasive diagnosis in Indonesia has many obstacles due to the limited availability of endoscopy. In this review, we summarize the current status of noninvasive diagnosis of *H. pylori* infection in Indonesia and make some recommendations (Table 1).[14-16]

UREA BREATH TEST

During infection, *H. pylori* has the ability to produce highly active urease, an enzyme that converts urea to ammonium and labelled CO_2 in the stomach.[14,15] In the UBT, isotope-labelled urea is consumed by the patient, and then *H. pylori* breaks down urease enzyme products in the stomach.[16] The labelled CO_2 diffuses into epithelial cells, is absorbed into the blood and is excreted through the lungs.[14] The labelled CO_2 is detected in the exhaled breath after 10 minutes and serves as an indicator of the presence of *H. pylori*.[16,17] With a sensitivity and specificity of more than 90%, the UBT is the best noninvasive method, although it is less reliable in patients with a history of gastric resection or use of PPIs.[14]

In the UBT test, urea is labelled by the stable heavy isotope ^{13}C or the radioactive isotope ^{14}C.[18] ^{13}C-UBT is noninvasive and accurate, but it is relatively expensive due to the requirement for mass spectrometric analysis, which is only available in large cities. ^{13}C-UBT is safer in pediatric patients and pregnant women because it does not use a radioactive isotope. Among 34 provinces of Indonesia, ^{13}C-UBT is available in only 10 centers in four main cities: three centers in Jakarta and two centers in

Table 1. *Helicobacter pylori* Noninvasive Tests and the Current Situation in Indonesia

Diagnostic test	Sensitivity[14-16]	Specificity[14-16]	Advantage	Disadvantage	Situation in Indonesia
UBT	95%	95%	High accuracy Detect current infection	Less reliable in patients with history of gastric resection or PPI consumption	^{13}C-UBT and ^{14}C-UBT remain restricted to 4 and 6 cities, respectively Expensive and uncovered by social insurance Ongoing validation
SAT	94%	92%	Inexpensive and not age dependent Novel monoclonal antibodies are not influenced by PPI ICA-based, does not require special equipment or experts	Inconsistent accuracy based on antigens Accuracy influenced by incubation time and stool condition	Most centers use ICA-based tests, but with low sensitivity Collecting stools is more difficult than collecting blood samples
Serology	90%	80%	Saves costs and reduces endoscopic workload	Less accurate in children Wide range of cutoff values Cannot distinguish between current and past infections Lower accuracy than ICA-based tests	Most widely used Validated for some kits
Urine test	93%	92%	Easy sampling method without special skills and tools Sampling cheaper than serum sampling	False negative results with low concentrations of IgG	Lower accuracy Requires more time to interpret Lack of availability

UBT, urea breath test; PPI, proton pump inhibitor; SAT, stool antigen test; ICA, immunochromatographic assay; IgG, immunoglobulin G.

Surabaya on Java Island, three centers in Medan on Sumatera Island, and two centers in Makassar on Sulawesi Island. In addition, this test is not covered by Indonesian social insurance. With a cost of Indonesian Rupiah (IDR) 1,200,000 (U.S. Dollar [USD] 85 estimated in July 2019), this method is relatively expensive and may not become a common method for detection of *H. pylori*. Recently, ^{13}C-UBT has been performed using a simpler infrared spectrophotometer, which is more compact, cost effective and easy procedure than the mass spectrometer.[12] Most Indonesian gastroenterologists use this method to evaluate *H. pylori* positivity after eradication beside of SAT.[19,20] According to the Asia-Pacific consensus to improve the accuracy of the test, the patients should stop taking bismuth salts and antibiotics for 4 weeks, PPI for 2 weeks and fast for at least 4 hours.[18,21] These preparations are not convenient for most patients, especially those with severe symptoms. Because UBiT®-IR300 infrared spectrophotometers are not currently available, most Indonesian centers use a new type of infrared spectral analyzer (POCone FT-IR®; Otsuka Pharmaceutical Co. Ltd., Tokyo, Japan), which is claimed to be simpler, easy to maintain, faster and accurate. We use a 75-mg tablet of ^{13}C-urea, not a 100-mg tablet as previously described.[22] In contrast to the recommendation for gurgling to avoid catalytic positive bacteria in the oral cavity and oropharynx,[23] a film-coated tablet-based UBT (UBIT, Otsuka Pharmaceutical Co. Ltd.) is used without gargling.

Validation in the United States and Europe suggested a lower dose of ^{13}C-UBT (75 to 125 mg) than the original recommendation (350 mg), but not lower than 75 mg to avoid poor results.[24] The reduction a dose of 50 mg in children was found in several studies that have been used to diagnose *H. pylori* infection.[22,25] At the same dose of ^{13}C-urea, low production of endogenous CO_2 in younger children has a relatively high isotope ratio of $^{13}CO_2$ to $^{12}CO_2$.[25] However, in Indonesia we use a similar dose for adults and children. Based on the manufacturer's instructions, we do not administer citric acid. A previous study suggested the use of citric acid to increase sensitivity and specificity,[26] especially with long-term use of PPI. In addition, when citric acid pretreatment was not performed, the accuracy was decreased.[27] We do not have data about modification of the lateral recumbent position for patients with partial gastrectomy.[28] Collected breath samples were analyzed for ^{13}C-UBT with a cutoff value of 2.5%, as recommended by the manufacturer. Unfortunately, this cutoff has not been validated for adults and children and we are trying to validate it. The calculated optimal cutoff points of UBT are important in populations that have a low prevalence of *H. pylori* infection, because they (e.g., healthy volunteers) are able to express higher delta over baseline (DOB) values. In contrast, in patients with dyspepsia in whom the prevalence of infection is higher than in the normal population, low DOB values must be considered.[29]

The use of ^{14}C during pregnancy is not usually recommended because of radiation hazards.[18] However, it has been reported that a lower dose of ^{14}C-UBT can be used safely in children.[25] In Indonesia, 16 centers provide ^{14}C-UBT: nine centers in North Sumatera on Sumatera Island; one center in Jakarta, two centers in West Java, two centers in East Java and one center in Yogyakarta on Java Island; and one center on Bali Island. All the centers use the HUBT-20A1 analyzer (Headway, Shenzhen, China) with a ^{14}C-urea capsule containing 27.8 kBq of radiation. Following the manufacturer's instructions, we use a cutoff value of 50% to detect *H. pylori* infection. Currently, we are validating ^{14}C-UBT in difference rate of *H. pylori* infection. In areas such as Indonesia with a lack of access to endoscopy, the use of UBT could minimize the number of endoscopies and the associated expenses to the healthcare system and patients' discomfort. Modifications of the ^{14}C-urea dose and breath-collection times may solve the problem of the use of ^{14}C-UBT in pregnant women and children, although the use of ^{14}C-UBT in these patients is still not accepted in Indonesia.

STOOL ANTIGEN TEST

The SAT is noninvasive and inexpensive, and its diagnostic accuracy is not dependent on age.[30] Enzyme immunoassay (EIA) based on polyclonal antibodies was the first method of SAT and had high accuracy.[31] However, most of the results were inconsistent, and a monoclonal antibody-based approach was developed, which has been shown to reduce false positive findings and increase specificity.[32] The pretreatment monoclonal antigen technique was superior to polyclonal technique, with a specificity of 97% versus 94%, sensitivity of 96% versus 90%, positive predictive value of 96% versus 91% and negative predictive value of 97% versus 85%.[33] Four to eight weeks of antisecretory therapy also showed that the monoclonal antigen was better than the polyclonal antigen.[33,34] In Indonesia, the SAT does not require expensive special equipment and chemicals and is cheaper than UBT. It is widely used throughout the country with a cost of IDR 300,000 (USD 20 estimated July 2019). In addition, the SAT does not require fasting and, with novel monoclonal antibodies, does not require discontinuation of PPIs.[35]

EIA and immunochromatographic assay (ICA) are both methods of SAT. EIA has better accuracy than ICA, even though the latter uses monoclonal antibodies.[36,37] EIA-based assays, such as the commercial kit Premier Platinum HpSA (Meridian Diagnostic, Cincinnati, OH, USA) may be applicable in Indonesia. After mixing the stool sample with 200 μL of sample diluents, enzyme conjugate is added to the microplate. The mix was incubated for 1 hour at room temperature and washed five times. The results are read by spectrophotometry after one drop of stop solution is added to end the reaction. The manufacturer's recommendations indicate a positive result if absorbance (450/630) ≥0.160.[38] A cutoff value of 0.300 is reported to provide the best diagnostic value, with sensitivity of 93.9%, specificity of 95.7% and accuracy of 94.8%; a cutoff value of 0.130 provides less sensitivity

(89.5%) and specificity (83.3%).[39,40] However, most commercial laboratories in Indonesia are not interested in using this method because of higher costs and thus reduced potential profits.

ICA has the advantage of providing rapid diagnosis of *H. pylori* infection. ICA may be useful in developing countries with many remote areas, such as Indonesia. A proper accuracy of ICA-based SAT can be in stock in many hospitals in Indonesia, and the examination can be carried out in small laboratories, as this test does not require special equipment and experts. When it was applied in clinical practice for the first time, an acceptable sensitivity of 88% and a specificity of 94% were achieved.[41] Most of our centers and commercial laboratories use a rapid SAT method with monoclonal antibodies based on recently developed lateral flow ICA, such as On-Site *H. pylori* Ag Rapid Test-cassette (CTK Biotech Inc., San Diego, CA, USA).[18,32] This test is very suitable for daily practice because it has more practical steps.[26] The manufacturer's instructions recommend applying 5 to 10 mL of faces to the device that contained with the antibody. If *H. pylori* antigen is present in the stool, a reaction between the antigen-antibodies and the dye will appear within 15 minutes as a red line in the instrument test zone. The negative result was determined if one red line appears in the control zone while the positive result was determined if two red lines appear in both control and test zone. The result is invalid if there is no red line in the control zone and the examination need to be repeated using a new tape. In addition, the *H. pylori* strain used in this test is different from that in Indonesia,[42] several factors affect the results of SAT. Low amounts of antigen due to low colonization in the stool and low ability to react can produce false negative results.[20] In a country such as Indonesia, with a low prevalence of *H. pylori*, the density number of *H. pylori* is also low, suggesting a high risk of low sensitivity of the SAT. Incubation time also is an important factor. The sensitivity of readings at 30 and 60 minutes can reach 76.9% and 78.6%, respectively, compared with 59.1% at 20 minutes.[25] Formless or watery stools can reduce the accuracy of the test due to dilution of antigens.[37] If the sample is not tested within a short time (less than 7 days), it must be stored at low temperature (–5°C to –25°C). Testing of stool samples stored at –80°C for 225 days still provided good sensitivity and specificity.[37] In Indonesia, collecting stools is more difficult than collecting blood samples. People cannot predict their defecation time well, and many may not feel comfortable about the delivery process.

The accuracy of the SAT for *H. pylori* is a concern. A validation study of Pronto Dry (Medical Instruments Corporation, Solothurn, Switzerland) at Cipto Mangunkusumo Hospital in Jakarta reported sensitivity and specificity of only 66.7% and 78.9%, respectively, with 0.274 as the cutoff value.[43] In addition, of 54 of 63 dyspeptic patients (85.7%) who tested positive based on several methods, 42 tested positive by the SAT only, which suggests a potential for false positive results. Therefore, the local validation test is very important, because differences in the antigenicity of *H. pylori* strains affect the result of the SAT.[32]

SEROLOGY

In general, detection of specific antibodies following exposure to various *H. pylori* antigens can be a useful method in clinical practice because it is acceptable to patients, cheap and fast.[18] An important study reviewed 36 commercial kits used in 26,812 patients in different populations; the sensitivity ranged from 57% to 100% and the specificity from 31% to 100%.[44] Thus, a validated serological test is useful for initial screening before the diagnosis is confirmed by histology or culture, especially in a country with a shortage of endoscopic centers.[45] However, it must be noted that the test and treat strategy is not recommended in areas with a low prevalence of *H. pylori*. Our group showed that an enzyme-linked immunoassay (ELISA) kit (Eiken Co. Ltd., Tokyo, Japan) had low sensitivity when the cutoff value from the manufacturer's instructions (positive if ≥10 U/mL, with sensitivity and specificity of 66.7% and 97.2%, respectively) was used. We suggested using a cutoff value of ≥5.5 U/mL, which increased the sensitivity to 86.7%.[13] The use of serological tests for screening patients with dyspepsia can save costs and reduce endoscopic workload by up to 30%.[33] Nevertheless, serological tests are not recommended for children because of the problem of the level of *H. pylori*-specific antibodies.[30]

Antibody preparations are closely related to the diagnostic accuracy of different kits.[46] Kits made in Eastern countries will be more accurate in detecting *H. pylori* strains in Eastern countries than kits made in Western countries. The accuracy of diagnostic kits from Western countries was low when applied to Japanese patients.[47,48] In a study that compared the diagnostic accuracy of ELISA kits from Western and Eastern countries for detection of immunoglobulin G (IgG) antibodies to *H. pylori* in Japan, the accuracy of the Western kit was 86.8% and the accuracy of the Eastern kit was 92.3%.[49] Therefore, the use of antigens of local *H. pylori* strains will affect the success of serological tests in Indonesia.

Serological tests use blood samples to detect IgG antibodies by ELISA. Similar to the SAT, the accuracy of EIA-based serological tests is better than that of ICA-based tests. A study that compared 29 commercial serological tests showed that nine of 17 EIA-based tests but only one in 12 ICA-based tests had an accuracy of more than 90%.[2] Immunoblot assay has higher specificity but lower sensitivity than EIA. This method requires special expertise and has high costs, so it is not used in clinical laboratories in Indonesia.[17] ELISA is the most commonly used method in Indonesia. After *H. pylori* has been successfully treated, IgG antibodies to *H. pylori* will last for several months.[50] In addition, serological tests can result in false negatives, which may occur with new infections when antibody levels are not sufficiently elevated, because IgG antibodies appear approxi-

mately 21 days after *H. pylori* infection.[51] We are currently validating an ICA-based kit (MP Diagnostics ASSURE®; MP Biomedicals, Santa Ana, CA, USA) against histopathology as the gold standard. They proposed a recombinant current infection marker as an indication of current infection for covering the lack of serology.

URINE TEST

Several tests for detection of antibodies to *H. pylori* using urine and saliva samples have shown high sensitivity and specificity.[52-54] Sampling of urine and saliva can be performed easily without the need for special skills or tools and is cheaper than sampling of serum. However, a major problem is that the concentrations of *H. pylori* antibodies in saliva and urine are lower than in serum.[17] False negative results can occur with urine-based ELISA. *H. pylori*-specific IgG has low concentration in the urine. A study showed that a commercial kit (RAPIRUN® stick, Otsuka Pharmaceutical Co., Ltd.) to detect *H. pylori* antibodies in urine was reliable for detecting *H. pylori* infection in Indonesia.[55] In this test, 0.3 mL of fresh urine is mixed with 0.3 mL of dilute solution to make an approximately 2-fold dilution, and a test stick is placed in the mixture. A colloidal gold-conjugated anti-human IgG (Fc) polyclonal antibody (goat) is enclosed inside the test stick. *H. pylori* antigen is used to immobilize the test line of the evaluation section, and the anti-human IgG polyclonal antibody is used as the control line.[56] If two red bands appear on the test line after the sample is applied for 15 minutes at 25°C to 30°C, the result is considered positive. The result is considered negative if a red band appears on the control line only. The result is considered invalid due to error in the assay steps or excessively diluted urine if the red band is absent in the control line. The RAPIRUN® test validation result in Indonesia found sensitivity, specificity, positive predictive value, negative predictive, and accuracy of 83.3%, 94.7%, 71.4%, 97.3%, and 93.2%, respectively. In Japan and Vietnam, rapid urine tests had a sensitivity of 93.1%, a specificity 92.3% and an accuracy of 92.0%.[14] Our group also used RAPIRUN® among minor ethnic groups in remote areas of North Sulawesi and found identical results to serological test findings.[57] When the urine test showed a positive result, we used a disposable gastric brush to obtain gastric juice and a small amount of gastric tissue for *H. pylori* culture. However, in our experience, RAPIRUN® had less accuracy in areas with low prevalence of *H. pylori* in Indonesia[58] and required more time to interpret rather than manual instruction.

CONCLUSIONS

The use of noninvasive *H. pylori* testing in Indonesia may reduce the overall endoscopic workload and the financial burden on Indonesian social insurance. Validated UBT and SAT are considered practical approaches for the detection of *H. pylori* infection in Indonesia, with serological and urine tests as alternative strategies.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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