



Stool Antigen Examination as a Diagnostic Tool for Dyspeptic Patient caused by *Helicobacter pylori* Infection: A Case-based Literature Review

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ABSTRACT

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Today, the gold standard for diagnosing *Helicobacter pylori* infection is by urea breath test (UBT). However, UBT tests are not widely available in several remote areas in Indonesia. Stool antigen test (SAT) is an alternative diagnostic test for *H. pylori* infection. However, it is unclear whether the performance of SAT to diagnose *H. pylori* infection can be comparable with UBT accuracy. This report was aimed to determine the accuracy of SAT to diagnose *H. pylori* infection as an alternative to UBT. Our case-based literature review indicates that SAT has high sensitivity (79–96.4%); therefore, SAT can help doctors in ruling out *H. pylori* infection. SAT also demonstrates remarkable specificity of stool antigen examination (98.6–100%), suggesting that SAT can help doctors in ruling in *H. pylori* infection.

Introduction

Dyspepsia is a complex symptom that arises in the upper gastrointestinal tract. The symptoms include epigastric pain or discomfort, heartburn, excessive burping, excessive belching, acid regurgitation, slow digestion, nausea, bloating, and early satiety. The etiology of dyspepsia consists of acid secretion such as a duodenal ulcer or gastroesophageal reflux disease, impaired gastrointestinal motility, functional, hypersensitivity, neuromuscular dysfunction, and specific stimuli in example caused by *Helicobacter pylori* [1]. *H. pylori* infection is very common in the world. Several studies for Asia's *H. pylori* infection prevalence rates ranging from 20% to 84%, Africa's prevalence rates 41.3% 91.3%, and USA's prevalence rates among the low-income population is about 79% [2], [3], [4], [5], [6], [7], [8], [9]. In Indonesia, *H. pylori* infection prevalence is 22.1% [10]. Today, the gold standard to diagnose *H. pylori* infection is by urea breath test (UBT) [11].

H. pylori produce active urease that converts urease to ammonium and converts CO₂ in the stomach.

UBT uses isotope-labeled urea consumed by the patient that will be broken down by *H. pylori*. UBT is divided into two types, ¹³C, and ¹⁴C tests. The ¹³C is non-radioactive, while ¹⁴C uses radioactive isotope. UBT's function is to confirm the colonization and to monitor *H. pylori*'s eradication [12]. In Indonesia, UBT is not widely available. The ¹³C-UBT is available in cities such as Jakarta, Surabaya, Medan, and Makasar, meanwhile ¹⁴C available in North Sumatra, West Java, Jakarta, Yogyakarta, East Java, Bali. UBT is relatively expensive [13].

Stool antigen test (SAT) is an alternative diagnostic test for *H. pylori* infection. SAT has several advantages, such as non-invasive, more accessible, faster, and does not require expensive chemicals and equipment. Hence, the price is less costly than UBT (the cost is about USD 20). Also, the SAT is widely used in Indonesia. The first method of SAT is the enzyme immunoassay (EIA), which is a method based on polyclonal antibodies and has been shown to have high accuracy. EIA-based assays, such as the commercial kit Premier Platinum HpSA, can be used in Indonesia [6], [7]. Although it is well known that the SAT has high accuracy,

it is not clear whether the performance of the SAT to diagnose *H. pylori* infection can be comparable with UBT accuracy. Therefore, this case-based review will discuss the comparison of the accuracy of SAT and UBT in diagnosing *H. pylori* infection.

Case Presentation

A 40-year-old male patient presented with worsening epigastric pain since three days ago came to a nearby clinic. The pain had appeared for 4 months but had gotten worse in the last 3 days. It was described as heartburn that appears intermittently. Nausea, vomiting, and decreased appetite were reported. The patient took antacids to alleviate his symptoms, but they did not get better. He did not have a history of consumption of over-the-counter medications. The patient's vital signs were within the normal range.

The doctor diagnosed the patient with dyspepsia and suspected it is caused by *H. pylori* infection due to its high prevalence in the area. However, the UBT to confirm the infection is not available in the city, and the nearest hospital is 12 h away. The doctor had read an alternative to diagnose *H. pylori* infection by detecting its antigen in stool, considered doing a SAT on the patient rather than referring the patient. Nevertheless, the doctor wondered if SAT performance in diagnosing *H. pylori* infection was comparable to the UBT.

Methods

Search strategy

We searched for studies from five databases (PubMed, Cochrane, Scopus, EBSCO, and Proquest) using keywords: Dyspepsia, SAT, UBT, *H. pylori* infection, and their synonyms, respectively. The keywords used on each search at different databases are shown in Table 1.

Eligibility criteria

The studies were determined to be eligible for this review using inclusion and exclusion criteria. The inclusion criteria cover the type of the study (systematic review/meta-analysis of cross-sectional study or cross-sectional study) and the relevance of the research which includes: (1) The SAT used in the study is immunoassay (EIA) and (2) the reference test used in the study is the UBT. As for the exclusion criteria, we excluded studies with animals, studies with

Table 1: Search strategy and keywords used

Database	Search terms	Hits articles	Selected articles
PubMed	(((((dyspepsia[Title/Abstract]) OR (dyspeptic[Title/Abstract]) OR (indigestion[Title/Abstract]) OR (dyspepsia[MeSH Terms]) OR (indigestion[MeSH Terms])) AND (((stool antigen examination[Title/Abstract]) OR (stool antigen test[Title/Abstract]) OR (fecal antigen examination[Title/Abstract]) OR (fecal antigen test[Title/Abstract]) OR (stool antigen[Title/Abstract]) OR (fecal antigen[Title/Abstract])) AND ((urea breath test) OR (UBT))) AND (((helicobacter pylori[MeSH Terms]) OR (helicobacter pylori infection[Title/Abstract]) OR (h. pylori[Title/Abstract]) OR (h. pylori infection[Title/Abstract]))	73	2
Cochrane	(dyspepsia OR dyspeptic OR indigestion) in Title Abstract Keyword AND (stool antigen examination OR fecal antigen examination OR stool antigen OR fecal antigen OR stool antigen test OR fecal antigen test) in Title Abstract Keyword AND (urea breath test OR UBT) in Title Abstract Keyword AND (helicobacter pylori OR h. pylori OR helicobacter pylori infection) in Title Abstract Keyword- (Word variations have been searched)	19	0
Scopus	TITLE-ABS-KEY (dyspepsia OR dyspeptic OR indigestion) AND (stool AND antigen AND examination OR fecal AND antigen AND examination OR stool AND antigen AND test OR fecal AND antigen AND test OR stool AND antigen OR fecal AND antigen) AND (urea AND breath AND test OR ubt) AND (h. pylori OR h. pylori AND infection OR helicobacter AND pylori OR helicobacter AND pylori AND infection)	100	1
EBSCO	(TI Urea Breath Test OR TI UBT OR AB Urea Breath Test OR AB UBT) AND (TI H. pylori OR TI H. pylori infection OR TI helicobacter pylori OR TI helicobacter pylori infection OR AB H. pylori OR AB H. pylori infection OR AB helicobacter pylori OR AB helicobacter pylori infection) AND (TI stool antigen examination OR TI fecal antigen examination OR TI stool antigen OR TI fecal antigen OR TI stool antigen test OR TI fecal antigen test OR AB stool antigen examination OR AB fecal antigen examination OR AB stool antigen OR AB fecal antigen OR AB stool antigen test OR AB fecal antigen test) AND (TI Dyspepsia OR TI Indigestion OR TI Dyspeptic OR AB Dyspepsia OR AB Indigestion OR AB Dyspeptic)	33	0
Proquest	(ti(("h. pylori infection") OR ("helicobacter pylori infection") OR ("h. pylori") OR ("helicobacter pylori")) OR ab(("h. pylori infection") OR ("helicobacter pylori infection") OR ("h. pylori") OR ("helicobacter pylori"))) AND (ti(("urea breath test") OR ("UBT")) OR ab(("urea breath test") OR ("UBT"))) AND (ti(("stool antigen examination") OR ("fecal antigen examination") OR ("stool antigen test") OR ("fecal antigen test") OR ("stool antigen") OR ("fecal antigen")) OR ab(("stool antigen examination") OR ("fecal antigen examination") OR ("stool antigen test") OR ("fecal antigen test") OR ("stool antigen") OR ("fecal antigen"))) AND (ti(("dyspep") OR ("indigestion")) OR ab(("dyspep") OR ("indigestion")))	121	0

a language other than English, and studies with no full text available.

Critical appraisal

The selected studies were appraised critically using the combination of Critical Appraisal Tools for Diagnostic Studies checklist from <http://www.cebm.net> (Oxford University).

Data extraction

The data extracted from each study included validity (evidence level, blinding, the spectrum of patients, and reference standard), importance (sensitivity, specificity, positive predictive value, and negative predictive value), and applicability of the study in our setting.

RESULTS

Search selection

Articles on five different journal databases were performed using search terms provided in Table 1. These comprehensive searches were done to find articles regarding the SAT as a diagnostic tool for *H. pylori* infection compared to UBT. Then, articles obtained were screened using predefined selection and eligibility criteria.

Figure 1 shows the search and selection flow of studies selected in this EBCR. The study was carried out on five databases. After removing duplication articles between databases, 187 articles were obtained with the following details: 72 articles from PubMed, ten articles from Cochrane, 85 articles from Scopus, 12 articles from EBSCO, and 8 articles from Proquest. A hundred eighty-seven articles were obtained, and then screened for titles and abstracts using eligibility criteria, and 18 articles met the criteria. After assessing 18 full-text articles using eligibility criteria, three studies were obtained (Hooton *et al.* [14], Chen *et al.* [15], and Braden *et al.* [16]). Subsequently, we appraised the three studies for their validity, importance, applicability, and level of evidence (Table 2)

Discussion

Validity tests were done in all three studies, and we concluded that all three articles were valid. In

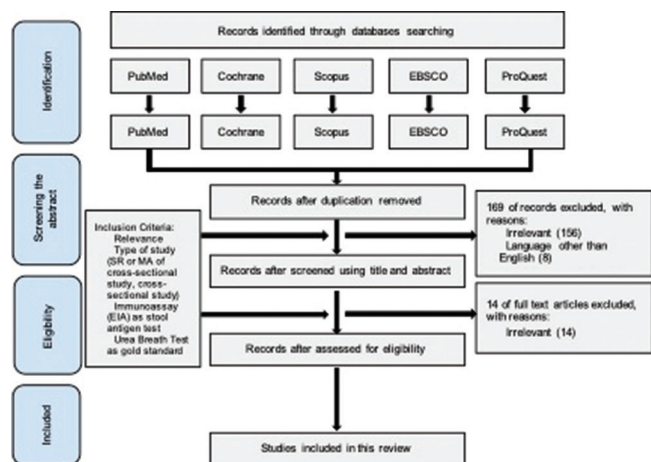


Figure 1: Flowchart of the searching strategy and study selection

Table 2: Validity, importance, applicability, and LoE of papers appraised in this study

Article	Validity			Importance			Applicability			LoE				
	Representative spectrum of patients	Independent, blind comparison between the index test and the reference test	Reference test applied regardless of the index test result	Sensitivity	Specificity	Likelihood ratio for a positive test result	Likelihood ratio for a negative test result	Positive predictive value	Negative predictive value		Availability, affordability, accuracy, and precision of diagnostic test in our setting	Estimate of our patient pretest probability	Resulting post-test probabilities	The consequences of the test helping our patient
Hooton et al.,	+	-	+	79%	100%	Undefined ^a	0.21	100%	83.5%	+	0.22	Undefined ^a	+	2
Chen et al.	-	-	+	96.4%	100%	Undefined ^a	0.04	100%	88%	+	0.22	Undefined ^a	+	2
Braden et al.	+	-	+	91.6%	98.6%	65.4	0.09	91.6%	98.6%	+	0.22	0.86	+	2

^aUndefined is resulted since specificity is 100%, therefore it could be interpreted that the likelihood ratio for a positive result is very high. LoE: Level of evidence.

the study conducted by Hooton *et al.*, the spectrum of patients is representative of those in whom it would be used in practice, including patients with dyspepsia. In the study, both the UBT and the SAT were done to every patient who was included in the trial, so the reference standard (in this case, UBT) was applied regardless of the index test result (SAT). However, blinding to the comparison of the UBT and SAT was not stated in the study [14]. In the second study done by Chen *et al.*, the spectrum of patients included both patients with dyspepsia and asymptomatic patients. However, since the data analysis of patients with dyspepsia and asymptomatic patients is separated, it is still representative of those in whom it would be used in practice. In this study, every patient was tested with serology, UBT, HpSA ELISA test, and HpSA rapid test. Blinding to the comparison of these tests was not stated in the study [15]. In the study by Braden *et al.*, the spectrum of patients included patients with abdominal pain, which is representative of those in whom it would be used in practice since one of the main signs of dyspepsia is abdominal pain. All patients were screened for *H. pylori* infection using the UBT and HpSA, so the reference standard test was used regardless of the index test result. The author also did not state the blinding to the comparison of both tests [16]. Although all three studies do not indicate the blinding to the comparison between the reference standard and the index test, the result of both tests (UBT and SAT) that were used is objective, so the chance of bias is low, therefore blinding to the comparison of these two tests is not necessary [14], [15], [16].

The sensitivity of the stool antigen examination presented in the three studies ranged from 79% to 96.4%. The results indicate that the studies have high sensitivity, so SATs can help doctors rule out *H. pylori* infection. The three studies also demonstrate the remarkable specificity of stool antigen examination, ranging from 98.6% to 100%. These results suggested that the SAT can help doctors in ruling in *H. pylori* infection (especially in the first two studies, the specificity is similar to the gold standard). For positive Likelihood Ratio (LR), Hooton *et al.* and Chen *et al.* have undefined results; meanwhile, Braden *et al.* has 65.4. Still, all of the studies show us a robust probability to find positive results in positive patients than in negative patients. In Hooton *et al.*, Chen *et al.*, and Braden *et al.*'s, the negative LR is 0.21, 0.04, and 0.085, respectively. Although Hooton *et al.*'s result showed the probability of around -30%, studies done by Chen *et al.* and Braden *et al.* give us a strong probability to find negative results in negative patients than in positive *H. pylori*-infected patients due to the low score, which are lower than 0.1. Positive predictive value in each Hooton *et al.*, Chen *et al.*, and Braden *et al.*'s studies is 100%, 100%, and 91.6%, respectively. The results are incredibly high, which means that there is a high probability for patients with positive results to be infected by *H. pylori*. Besides, negative predictive value for Hooton *et al.* is 83.5%,

for Chen *et al.* is 88%, and for Braden *et al.* is 98.6%. Although not as high as the positive predictive value, these scores are high enough to increase physician's confidence that negative patients are not infected by *H. pylori*. From these importance measurements, we can conclude that EIA SAT is as useful as UBT (almost have perfect scores) to be tools for ruling in the diagnosis of *H. pylori* infection, and is sufficient enough to be tools for ruling out the diagnosis of *H. pylori* infection aside from UBT test as the gold standard [17], [18].

Therefore, the application of the SAT as a choice in diagnosing *H. pylori* infection is reasonable. The SAT, in this case, the EIA, is widely available in Indonesia and inexpensive compared to UBT. Moreover, the SAT is found to be high in sensitivity and specificity. Furthermore, based on its LR, the SAT would generate moderate to significant changes to the pretest probability, which in turn would play a role in the doctor's decision to initiate treatment — in our setting, the pretest probability, solely determined by the prevalence of *H. pylori* infection in Indonesia, which is 0.22 [10], [19]. In respect of that, the post-test probability would be above 0.86, which is relatively high. In conclusion, the SAT would help manage patients suspected of infection by *H. pylori*.

Conclusion

We conclude that SAT accuracy on diagnosing dyspeptic patients caused by *H. pylori* is comparable to UBT. Moreover, the SAT is more widely available and inexpensive than UBT.

Authors contribution

HML, JG, NT, NAT, and TR contribute in article collection, writing, and critical appraisal. ML involved in expert opinion, writing, and manuscript finalization.

References

1. Koduru P, Irani M, Quigley EM. Definition, pathogenesis, and management of that cursed dyspepsia. *Clin Gastroenterol Hepatol.* 2018;16(4):467-79. <https://doi.org/10.1016/j.cgh.2017.09.002> PMID:28899670
2. Ozen A, Furman A, Berber M, Karatepe HO, Mutlu N, Sarçoban HE, *et al.* The effect of *Helicobacter pylori* and economic status on growth parameters and leptin, ghrelin, and insulin-like growth factor (IGF)-I concentrations in

- children. *Helicobacter*. 2011;16(1):55-65. <https://doi.org/10.1111/j.1523-5378.2010.00814.x>
PMid:21241414
3. Thankachan P, Muthayya S, Sierksma A, Eilander A, Thomas T, Duchateau GS, et al. *Helicobacter pylori* infection does not influence the efficacy of iron and Vitamin B12 fortification in marginally nourished Indian children. *Eur J Clin Nutr*. 2010;64(10):1101-7. <https://doi.org/10.1038/ejcn.2010.126>
PMid:20683455
 4. Cherian S, Burgner DP, Cook AG, Sanfilippo FM, Forbes DA. Associations between *Helicobacter pylori* infection, co-morbid infections, gastrointestinal symptoms, and circulating cytokines in African children. *Helicobacter*. 2010;15(2):88-97. <https://doi.org/10.1111/j.1523-5378.2009.00740.x>
PMid:20402811
 5. Abdollahi A, Morteza A, Khalilzadeh O, Zandieh A, Asgarshirazi M. The role of *Helicobacter pylori* infection in gastro-oesophageal reflux in Iranian children. *Ann Trop Paediatr*. 2011;31(1):53-7. <https://doi.org/10.1179/1465328110y.0000000004>
PMid:21262110
 6. Tanih NF, Okeleye BI, Ndip LM, Clarke AM, Naidoo N, Mkwetshana N, et al. *Helicobacter pylori* prevalence in dyspeptic patients in the Eastern Cape Province race and disease status. *S Afr Med J*. 2010;100(11):734-7. <https://doi.org/10.7196/samj.4041>
PMid:21081026
 7. Joutei HA, Hilali A, Fechtali T, Rhallabi N, Benomar H. *Helicobacter pylori* infection in 755 patients with digestive complaints: Pasteur Institute, Morocco, 1998-2007. *East Mediterr Health J*. 2010;16(7):778-82. <https://doi.org/10.26719/2010.16.7.778>
 8. Hestvik E, Tylleskar T, Kaddu-Mulindwa DH, Ndeezi G, Grahnquist L, Olafsdottir E, et al. *Helicobacter pylori* in apparently healthy children aged 0-12 years in urban Kampala, Uganda: A community-based cross-sectional survey. *BMC Gastroenterol*. 2010;10(1):62. <https://doi.org/10.1186/1471-230x-10-62>
 9. Epplein M, Signorello LB, Zheng W, Peek RM, Michel A, Williams SM, et al. Race, African ancestry, and *Helicobacter pylori* infection in a low-income United States POulation. *Cancer Epidemiol Biomarkers Prev*. 2011;20(5):826-34. <https://doi.org/10.1158/1055-9965.epi-10-1258>
PMid:21357376
 10. Syam AF, Miftahussurur M, Makmun D, Nusi IA, Zain LH, Zulkhairi, et al. Risk factors and prevalence of *Helicobacter pylori* in five largest Islands of Indonesia: A preliminary study. *PLoS One*. 2015;10(11):e0140186. <https://doi.org/10.1371/journal.pone.0140186>
PMid:26599790
 11. Syam AF, Simadibrata M, Makmun D, Abdullah M, Fauzi A, Renaldi K, et al. National consensus on management of dyspepsia and *Helicobacter pylori* infection. *Acta Med Indones*. 2017;49(3):279-87.
PMid:29093241
 12. Ferwana M. Accuracy of urea breath test in *Helicobacter pylori* infection: Meta-analysis. *World J Gastroenterol*. 2015;21(4):1305-14. <https://doi.org/10.3748/wjg.v21.i4.1305>
PMid:25632206
 13. Miftahussurur M. Noninvasive *Helicobacter pylori* diagnostic methods in Indonesia. *Gut Liver*. 2020;14(5):553-9. <https://doi.org/10.5009/gnl19264>
PMid:31693853
 14. Hooton C, Keohane J, Clair J, Azam M, O'Mahony S, Crosbie O, et al. comparison of three stol antigen assays with the ¹³C-urea breath test for the primary diagnosis of *Helicobacter pylori* infection and monitoring treatment outcome. *Eur J Gastroenterol Hepatol*. 2006;18(6):595-9. <https://doi.org/10.1097/00042737-200606000-00004>
PMid:16702847
 15. Chen MJ, Fang YJ, Wu MS, Chen CC, Chen YN. Application of *Helicobacter pylori* stool antigen test to survey the updated prevalence of *Helicobacter pylori* infection in Taiwan. *J Gastroenterol Hepatol*. 2020;35(2):233-40. <https://doi.org/10.1111/jgh.14828>
PMid:31408909
 16. Braden B, Posselt HG, Ahrens P, Kitz R, Dietrich CF, Caspary WF. New immunoassay in stool provides an accurate non-invasive diagnostic method for *Helicobacter pylori* screening in children. *Pediatrics*. 2000;106:115-7. [https://doi.org/10.1016/s0016-5085\(00\)84138-4](https://doi.org/10.1016/s0016-5085(00)84138-4)
PMid:10878159
 17. Chey WD, Wong BC. American college of gastroenterology guideline on the management of *Helicobacter pylori* infection. *Am J Gastroenterol*. 2007;102(8):1808-25.
PMid:17608775
 18. Avisiena A, Nusi IA, Maimunah U, Rahaju AS, Setiawan PB, Purbayu H, et al. Diagnostic values of *Helicobacter pylori* stool antigen immunochromatographic method compared to histopatholgy in dyspepsia patient. *New Armen Med J*. 2019;3(1):13-9.
 19. Syam AF. Current situation of *Helicobacter pylori* infection in Indonesia. *Med J Indones*. 2016;25(4):263-6.