Diagnostic Value of 14c Urea Breath Test for Helicobacter pylori Detection in Indonesian Dyspeptic Patients

by Muhammad Miftahussurur

Submission date: 28-Jul-2020 02:40PM (UTC+0800)
Submission ID: 1363150709
File name: 2._Paper_Validasi_14C_UBT_final_AcxYAR_280720.docx (79.2K)
Word count: 3328
Character count: 19441

Diagnostic Value of ^{14}c Urea Breath Test for *Helicobacter pylori* Detection in Indonesian Dyspeptic Patients

Short title: *H. pylori* Diagnostic Value of ^{14}C Urea Breath Test

Muhammad Miftahussurur[1,2*], Adinta Windia[1], Iswan Abbas Nusi[1], Ricky Indra Alfaray[2,3], Kartika Afrida Fauzia[2,3], Hartono Kahar[4], Herry Purbayu[1], Titong Sugihartono[1], Poernomo Boedi Setiawan[1], Ummi Maimunah[1], Ulfa Kholili[1], Husin Thamrin[1], Amie Vidyani[1], Dalla Doohan[2,3], Langgeng Agung Waskito[3], Yudith Annisa Ayu Rezkita[2,5], Yoshio Yamaoka[1,3]

[1]Gastroentero-Hepatology Division, Department of Internal Medicine, Faculty of Medicine, Universitas Airlangga Surabaya, East Java, 60286, Indonesia

[2]Institute of Tropical Disease, Universitas Airlangga, Surabaya, East Java, 60115, Indonesia

[3]Department of Environmental and Preventive Medicine, Oita University Faculty of Medicine, Yufu, 879-5593, Japan

[4]Department of Clinical Pathology, Faculty of Medicine, Universitas Airlangga, Surabaya, East Java, 60286, Indonesia

[5]Faculty of Medicine, Muhammadiyah University of Surabaya, Surabaya, East Java, 60113, Indonesia

***Corresponding author**

Muhammad Miftahussurur, MD., PhD

2
Gastroentero-Hepatology Division, Department of Internal Medicine, Faculty of Medicine-Dr. Soetomo Teaching Hospital, Universitas Airlangga, Surabaya
Jalan Mayjend Prof. Dr. Moestopo No. 6-8 Surabaya 60286, Indonesia.
Tel: +6231-502-3865; Fax: +6231-502-3865
E-mail: muhammad-m@fk.unair.ac.id

ABSTRACT

Introduction: Histopathology method is often used as a gold standard diagnostic for *H. pylori* infection in Indonesia. However, it requires an endoscopic procedure which is limited in Indonesia. A non-invasive method, such as ^{14}C *Urea Breath Test* (UBT) is more favorable; however, this particular method has not been validated yet.

Methods: A total of 55 dyspeptic patients underwent gastroscopy and ^{14}C-UBT test. We used Heliprobe® UBT for UBT test. As for the histology, May-Giemsa staining of two gastric biopsies (from the antrum and corpus) were evaluated following the Updated Sydney System.

Results: The Receiver Operating Characteristics analysis showed that the optimum cut-off value was 57 with excellence Area under Curve = 0.955 (95% CI = 0.861-1.000). By applying the optimum cut-off value, Heliprobe® UBT showed 92.31% for sensitivity, 97.62% for specificity, 92.31% for positive predictive value, 97.62% for negative predictive value, 38.77 for positive likelihood ratio, 0.0788 for negative likelihood ratio, and 96.36% for the accuracy.

Conclusion: The ^{14}C-UBT is an accurate test for *H. pylori* diagnosis with excellent sensitivity, specificity, and accuracy. The different optimum cut-off points suggested a validation is absolutely necessary for new test prior application to the new population.

INTRODUCTION

Helicobacter pylori have infected approximately 50% of the worldwide population, with a higher prevalence in developing countries (1). This bacterium can induce progressive gastric mucosal inflammation leading to several cascades in gastric diseases starting with chronic gastritis, atrophic gastritis until the end phase is gastric adenocarcinoma (2, 3). One of the gold standard methods to diagnose *H. pylori* infection in Indonesia is histopathology examination, which endoscopy examination is necessary to collect the gastric biopsy (4). Unfortunately, there are only less than 400 hospitals with endoscopy system in Indonesia and mostly located in big cities in Java Island (5, 6). This number is not sufficient considering the total population of Indonesia is approximately 250 million. Ideally, 2500 consultant gastroenterologists are needed, but in recent years only 10 gastrointestinal endoscopy training centers were established (5). Thus, the use of histopathology examination for *H. pylori* detection is still a challenge in Indonesia. Thus, the non-invasive method for *H. pylori* detection is more favorable to cover all Indonesian populations.

Urea Breath Test (UBT) is a non-invasive diagnostic method that widely used to diagnose *H. pylori* infection. This test is based on the mechanism that ingested "labeled carbon-containing urea" can be broken down to carbon dioxide (CO_2) and ammonia (NH_4-OH) by *H. pylori* as the urease-producing microorganism in the gastric mucosa (7). The tagged carbon within CO_2 will be detected in exhaled breath patients (8, 9). There are two carbon isotopes (^{13}C and ^{14}C), which are used for the UBT. The ^{13}C isotope need more complex equipment, including a mass spectrophotometer, that makes difficult for conducting the test compare to ^{14}C isotope that only required a portable compact beta-scintillation counter (8). Thus, it is more convenient to perform UBT using ^{14}C isotope. In

addition, compared to other non-invasive diagnostic methods, UBT has advantages on the less time required to perform the test, quick result, and less technical handling.

Based on national consensus, ^{13}C-UBT still becomes one of the recommended diagnostic tests for *H. pylori* infection (4, 10). Previous studies reported that ^{13}C-UBT method has 99% sensitivity and 98% specificity respectively (4, 10). In contrast, studies in other Asian countries showed that ^{13}C-UBT could have lower sensitivity (64.2%) and lower specificity (89.1%) (11, 12). Despite many publications had assessed the diagnostic value of ^{13}C-UBT, studies about ^{14}C-UBT remain scarce. Furthermore, to our knowledge, ^{14}C-UBT has not yet been validated in the Indonesian population. A validation study is necessary to get information regarding the diagnostic value of ^{14}C-UBT in Indonesia, so the practitioners can apply this test as an alternative method rather than the invasive methods. Here, we conducted a prospective study to validate ^{14}C-UBT as an alternative *H. pylori* diagnostic method in Indonesia.

METHODS

Study population

We conducted a cross-sectional study and recruited patients for endoscopic examination from November 2018 to April 2019 in Surabaya, Indonesia. A total of 55 dyspeptic patients with endoscopy indications were included. Among all participants, none had received antibiotics and bismuth drugs for 4 weeks and 2 weeks before the procedure, respectively. In addition, none of these patients had a history of gastric surgery, endoscopy contraindication, and bleeding gastrointestinal tract 4 weeks prior to the procedure. Patients were fasting before endoscopy and UBT. Before the UBT test, patients were interviewed with a standard questionnaire to obtain demographic data. One day after the UBT test, upper-endoscopy was performed by experienced endoscopists. During the endoscopic examination procedure, the endoscopist diagnosed the patients based on the endoscopic observation. In addition, we obtained two gastric specimens (one from the lesser curvature of the antrum, approximately 3 cm from the gastric pyloric ring, and one more from the greater curvature of the corpus). Those two specimens were used for the histological examination by professional histopathologist. This study was approved by Dr. Soetomo General Hospital Ethics Committee and written informed consent obtained from all patients.

Histology evaluation of *H. pylori* infection

The *H. pylori* status was based on histopathological examination by May-Giemsa staining as the reference standard to classify the *H. pylori*-positive and the *H. pylori*-negative groups (13). Briefly, all biopsy materials for histological examination were fixed in 10% buffered formalin and embedded inside paraffin. Serial sections were stained with May–Giemsa

stain. The stained specimens then were evaluated using the Updated Sydney System (14). Samples with bacterial load score ≥ 1 would be considered as positive for *H. pylori*.

^{14}C-Urea Breath Test (UBT)

Patients had to avoid smoking and sparkling water or soft drinks on the day of the test and fast at least 4 hours before the test. For the UBT examination, we used Heliprobe® ^{14}C-UBT (Heliprobe, Stockholm, Sweden), and all the procedures we followed the manufacturer's instructions. The patient swallowed a HeliCap® capsule containing ^{14}C urea (1 μCi) and wait 10 minutes before exhaling into Heliprobe® Breath Card where the reactivity filters absorb the CO_2. The indicator changes color from orange to yellow to indicate when the reactivity filters are saturated and sampling completed. Then the Heliprobe® Breath Card were inserted to the Heliprobe® Analyzer to obtain the measurement value.

Statistical analysis

Discrete variables were tested using Pearson's chi-squared test. The normality of the continuous variables was analyzed by the Shapiro–Wilk normality test. Receiver-operating characteristic (ROC) curves were determined to calculate the best cut-off values, including the area under the curve for discriminating *H. pylori* positivity. The statistical analysis was performed by R. Studio (R. Studio, Inc., Boston, USA) and SPSS statistical software version 23.0 (IBM Corp., Armonk, NY, USA) to calculate diagnostic test value: sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio, negative likelihood ratio, as well as their accuracy.

RESULTS

Patients characteristic

We included 55 subjects, consisted of 36 males (65.5%) and 19 females (34.5%) with a mean age of 48.27 ± 11.4 years old. The majority of the patients were age more than 40 years old with age group between 40-49 years old became the predominant age group (17/55, 27.3%). Most of the patients were Javanese (38/55, 69.0%) because the patients were from Surabaya city that is located on Java island.

Diagnostic value of ^{14}C-UBT and cut-off determination

The manufacture cut-off recommendation for the ^{14}C U BT was 50. The analysis using this cut-off showed the value of sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of 92.31%, 95.24%, 85.71%, 85.71%, and 94.54% respectively. The value of positive possibility ratio and negative possibility ratio were 19.380 and 0.079, respectively.

Following the recommendation for validating the new diagnostic modality for a new population (8, 15), we investigated the best cut-off value for the Indonesia population. The ROC analysis showed the area under the curve of the ^{14}C-UBT was 0.955 (95% CI=0.861-1.000). The optimum cut-off value was 57, with sensitivity, specificity, positive predictive value, negative predictive value, and accuracy values of 92.31%, 97.62%, 92.31%, 97.62%, and 96.36% respectively (Table 1). The value of positive likelihood ratio and negative likelihood ratio were 38.770 and 0.0788, respectively. We could obtain similar sensitivity but slightly higher specificity by applying a new cut-off point of 57, suggesting the cut-off value of 57 is more suitable to be applied in the Indonesian population. Therefore, further analysis in this study was using cut-off 57.

Table 1. The diagnostic value between two different cut-offs

Diagnostic parameter	Diagnostic value	
	Cut-off 50	Cut-off 57
Sensitivity	92.31%	92.31%
Specificity	95.24%	97.62%
PPV	85.71%	92.31%
NPV	97.56%	97.62%
Accuracy	94.54%	96.36%

Diagnostic test results and patients' demographic data

We compared the prevalence of *H. pylori* infection by using ^{14}C-UBT with a new cut-off 57 and histopathology analysis (Table 2). A similar prevalence of *H. pylori* (13/55, 23.6%) was observed between these methods. The characteristic of sex and age were similar between these methods. The number of males (7/13, 53.8%) was more than female (6/13, 46.2%) in the *H. pylori*-positive patients' group. The predominant age group of *H. pylori*-positive patients was 40-49 years old (5/13, 38.5%). In addition, Javanese people become the most dominant in the positive case of the *H. pylori* group between these methods.

Table 2. Diagnostic test results and patients' demographic data

Characteristics	^{14}C-UBT *				Histology			
	Hp Positive (%)		Hp Negative (%)		Hp Positive (%)		Hp Negative (%)	
Total patients	13	(23.6)	42	(76.4)	13	(23.6)	42	(76.4)
Sex								
Male	7	(53.8)	29	(69.0)	7	(53.8)	29	(69.0)
Female	6	(46.2)	13	(31.0)	6	(46.2)	13	(31.0)
Age								
<29	0	(0.0)	4	(9.5)	0	(0.0)	4	(9.5)
30-39	0	(0.0)	7	(16.7)	0	(0.0)	7	(16.7)
40-49	5	(38.5)	12	(28.6)	5	(38.5)	12	(28.6)
50-59	3	(23.1)	12	(28.6)	3	(23.1)	12	(28.6)
>60	5	(38.5)	7	(16.7)	5	(38.5)	7	(16.7)
Ethnic								
Ambon	0	(0.0)	2	(4.8)	0	(0.0)	2	(4.8)
Bugis	0	(0.0)	1	(2.4)	0	(0.0)	1	(2.4)
Javanese	11	(84.6)	27	(64.3)	10	(76.9)	28	(66.7)
Dayak	0	(0.0)	1	(2.4)	0	(0.0)	1	(2.4)
Madura	1	(7.7)	5	(11.9)	2	(15.4)	4	(9.5)

Sunda	0	(0.0)	1	(2.4)	0	(0.0)	1 (2.4)
Chinese	1	(7.7)	5	(11.9)	1	(7.7)	5 (11.9)

*Diagnosis based on UBT was using the cut-off value of 57

Endoscopy finding among *H. pylori*-infected patients

The endoscopy finding revealed that among *H. pylori*-uninfected patients (Table 3), the most predominant observation was superficial gastritis (52.4%), followed by gastro-duodenitis (23.8%) and erosive gastritis (19.0%). Meanwhile, among *H. pylori*-infected patients, erosive gastritis was predominant (46.2%), followed by peptic ulcer (30.8%) and superficial gastritis (15.4%).

Table 3. Endoscopy results among *H. pylori*-infected patients

Endoscopic finding	***H. pylori*-negative (%)**	***H. pylori*-positive (%)**
	N = 42	N = 13
Normal	1 (2.4)	0 (0.0)
Superficial gastritis	22 (52.4)	2 (15.4)
Erosive Gastritis	8 (19.0)	6 (46.2)
Gastroduodenitis	10 (23.8)	1 (7.7)
Peptic Ulcer	1 (2.4)	4 (30.8)

DISCUSSION

This is the first study to determine the diagnostic performance of ^{14}C-UBT in the Indonesian population. The standard measurement according to the manufacturer recommendation had yielded a good value of sensitivity, specificity, positive predictive value, negative predictive value, positive possibility ratio, negative possibility ratio, and accuracy compared to gold standard histopathology. However, even in this state a validation of new test prior application to the new population is necessary. Our ROC analysis resulted in the optimum cut-off point was 57, which is slightly higher than the manufacturer recommendation. By applying this new cut-off point we could get similar sensitivity, but slightly better specificity, suggesting the ability to determine the true negative patients is increasing. Our result was in line with a systematic review study that insisted all results of UBT have to be adjusted for cut-off value for a new population (8, 15). The adjustment of cut-off value may increase the performance of the diagnostic test (15). A review study revealed that overall the specificity and sensitivity of the UBT are mostly more than 95% and better than when using higher cut-off (16). In addition, a study from Iran and Europe showed a better diagnostic performance was obtained when applied a higher cut-off point (8, 17), suggesting this method combining with higher cut-off value would give accurate, reliable, and useful for the diagnosis of *H. pylori* infection in routine clinical practice. The higher Heliprobe® cut-off value should depend on the population, because different population has different prevalence of *H. pylori* due to many factors such as ethnics and life style. Therefore, different population has different optimum cut-off value. Further study is interesting to do because Indonesia has many kinds of population with different characteristic and variety of *H. pylori* prevalence.

The new cut-off application of ^{14}C-UBT and histopathology method yielded the same positive and negative results in diagnosing *H. pylori* infection. A previous study showed that around 20% to 30% of the *H. pylori*-infected individuals may develop peptic ulcer disease, and then end-stage of the infection might be developed to gastric cancer (2, 3). Endoscopy following by histopathology method has been widely performed for gastrointestinal disorders and become a pivotal approach for *H. pylori* infection diagnosis (16), but this method still becomes a challenge in Indonesia because the gastroenterology and endoscopic facilities remain limited and not enough to cover total population (5, 6). Moreover, this invasive method also spends a relatively long time, higher cost, and more inconvenient compare to the non-invasive method. In addition, our UBT validation result showed an excellent AUC value of 0.955, suggesting only less than 5% case was no concordance between test and gold standard diagnostic method. This value was greater than other diagnostic methods that had been validated in Indonesia, such as serology anti-IgG (AUC = 0.913) (18). Compared to RAPIRUN®, the overall accuracy of Heliprobe® in Indonesia showed better performance (19). These results confirmed that UBT is an excellent non-invasive *H. pylori* infection diagnostic method, even compared to other non-invasive modalities.

In this study, we found that the most case found from *H. pylori*-uninfected patients was superficial gastritis. Meanwhile, erosive gastritis was predominant in the *H. pylori*-infected patients. Comparison between these two groups showed that the prevalence of superficial gastritis and gastroduodenitis were more dominant in *H. pylori*-uninfected patients than *H. pylori*-infected patients, while the more severe condition that is a peptic ulcer, was more dominant in *H. pylori*-infected patients. This result can be explained form *H. pylori* infection pathogenesis. *H. pylori* can make inflammation and further damage that

create erosive gastritis (20). If this condition continues, erosive gastritis might become a gastric ulcer, gastric atrophy, and even develop into gastric adenocarcinoma (21).

There were several limitations to this study. The sample number of this study might be not enough to represent the country needed due to data only take from one city. Therefore, further study with a higher number of samples collected from several different locations in Indonesia might be needed. In addition, the subjects only taken from dyspepsia patients that underwent endoscopy in the hospital. This could not fully represent *H. pylori* infection prevalence because infected patients also can be asymptomatic.

CONCLUSION

The ^{14}C-UBT is an accurate test for *H. pylori* diagnosis with excellent sensitivity, specificity, and accuracy. The different optimum cut-off points applied in Indonesian samples suggested that validation is absolutely necessary for new test prior application to the new population.

CONFLICT OF INTEREST

No competing interests declared.

FINANCIAL SUPPORT

This report is based on work supported in part by grants from the Grants-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science, and Technology (MEXT) of Japan (15H02657, 16H05191, 16H06279, 18KK0266, and 19H03473) (YY) and the National Institutes of Health (DK62813) (YY). This work was also supported by the Japan Society for the Promotion of Science (JSPS) Institutional Program for Core-to-Core Program; B. Asia-Africa Science Platform (YY). DD, KAF and

RIA are PhD students supported by the Japanese Government (MEXT) scholarship program for 2016, 2017, and 2019, respectively. This study was also funded by the Hibah Riset Mandat 2020, grant from Universitas Airlangga (377/UN3.14/PT/2020).

REFERENCES

1. Salih BA. Helicobacter pylori infection in developing countries: the burden for how long? Saudi journal of gastroenterology : official journal of the Saudi Gastroenterology Association. 2009;15(3):201-7.
2. Kusters JG, van Vliet AH, Kuipers EJ. Pathogenesis of Helicobacter pylori infection. Clin Microbiol Rev. 2006;19(3):449-90.
3. Basso D, Plebani M, Kusters JG. Pathogenesis of Helicobacter pylori infection. Helicobacter. 2010;15 Suppl 1:14-20.
4. 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 medica Indonesiana. 2017;49(3):279-87.
5. Makmun D. Present status of endoscopy, therapeutic endoscopy and the endoscopy training system in Indonesia. Dig Endosc. 2014;26 Suppl 2:2-9.
6. Miftahussurur M, Doohan D, Nusi IA, Adi P, Rezkitha YAA, Waskito LA, et al. Gastroesophageal reflux disease in an area with low Helicobacter pylori infection prevalence. PloS one. 2018;13(11):e0205644.
7. Graham DY, Miftahussurur M. Helicobacter pylori urease for diagnosis of Helicobacter pylori infection: A mini review. Journal of advanced research. 2018;13:51-7.
8. Mansour-Ghanaei F, Sanaei O, Joukar F. Clinical Validation of an Office-Based C-UBT (Heliprobe) for H. pylori Diagnosis in Iranian Dyspeptic Patients. Gastroenterology research and practice. 2011;2011:930941.
9. Moosavi SSL. Urea Breath Test: StatPearls Publishing LLC; 2019 June 1, 2019.
10. Gisbert JP, Pajares JM. Review article: 13C-urea breath test in the diagnosis of Helicobacter pylori infection -- a critical review. Alimentary pharmacology & therapeutics. 2004;20(10):1001-17.
11. Abd Rahim MA, Johani FH, Shah SA, Hassan MR, Abdul Manaf MR. ¹³C-Urea Breath Test Accuracy for Helicobacter pylori Infection in the Asian Population: A Meta-Analysis. Ann Glob Health. 2019;85(1):110.
12. Peng N-J, Lai K-H, Liu R-S, Lee S-C, Tsay D-G, Lo C-C, et al. Capsule 13C-urea breath test for the diagnosis of Helicobacter pylori infection. World journal of gastroenterology. 2005;11(9):1361-4.
13. Lee JY, Kim N. Diagnosis of Helicobacter pylori by invasive test: histology. Annals of translational medicine. 2015;3(1):10.
14. Dixon MF, Genta RM, Yardley JH, Correa P. Classification and grading of gastritis. The updated Sydney System. International Workshop on the Histopathology of Gastritis, Houston 1994. Am J Surg Pathol. 1996;20(10):1161-81.
15. Leal YA, Flores LL, Fuentes-Panana EM, Cedillo-Rivera R, Torres J. 13C-urea breath test for the diagnosis of Helicobacter pylori infection in children: a systematic review and meta-analysis. Helicobacter. 2011;16(4):327-37.
16. Talebi Bezmin Abadi A. Diagnosis of Helicobacter pylori Using Invasive and Noninvasive Approaches. Journal of pathogens. 2018;2018:9064952.
17. Jonaitis LV, Kiudelis G, Kupcinskas L. Evaluation of a novel 14C-urea breath test "Heliprobe" in diagnosis of Helicobacter pylori infection. Medicina. 2007;43(1):32-5.

18. Miftahussurur M, Yamaoka Y. Diagnostic Methods of Helicobacter pylori Infection for Epidemiological Studies: Critical Importance of Indirect Test Validation. Biomed Res Int. 2016;2016:4819423.
19. Syam AF, Miftahussurur M, Uwan WB, Simanjuntak D, Uchida T, Yamaoka Y. Validation of Urine Test for Detection of Helicobacter pylori Infection in Indonesian Population. Biomed Res Int. 2015;2015:152823.
20. Lee I. Critical pathogenic steps to high risk Helicobacter pylori gastritis and gastric carcinogenesis. World journal of gastroenterology. 2014;20(21):6412-9.
21. Ishaq S, Nunn L. Helicobacter pylori and gastric cancer: a state of the art review. Gastroenterology and hepatology from bed to bench. 2015;8(Suppl 1):S6-S14.

Diagnostic Value of 14c Urea Breath Test for Helicobacter pylori Detection in Indonesian Dyspeptic Patients

ORIGINALITY REPORT

13%	3%	12%	0%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	Joyce Matie Kinoshita da Silva, Cibele Aparecida Villares, Maria do Socorro Monteiro, Carlos Colaúto et al. "Validation of a rapid stool antigen test for diagnosis of Helicobacter pylori infection", Revista do Instituto de Medicina Tropical de São Paulo, 2010 Publication	2%
2	Ari Fahrial Syam, Muhammad Miftahussurur, Willy Brodus Uwan, David Simanjuntak, Tomohisa Uchida, Yoshio Yamaoka. " Validation of Urine Test for Detection of Infection in Indonesian Population ", BioMed Research International, 2015 Publication	2%
3	Fariborz Mansour-Ghanaei, Omid Sanaei, Farahnaz Joukar. " Clinical Validation of an Office-Based C-UBT (Heliprobe) for Diagnosis in Iranian Dyspeptic Patients ", Gastroenterology Research and Practice, 2011 Publication	1%

4	Tsogt-Ochir Byambajav, Namdag Bira, Gotov Choijamts, Duger Davaadorj et al. "Initial Trials With Susceptibility-Based and Empiric Anti-H. pylori Therapies in Mongolia", Frontiers in Pharmacology, 2019 Publication	1 %
5	Syam, Ari Fahrial, Muhammad Miftahussurur, Dadang Makmun, Iswan Abbas Nusi, Lukman Hakim Zain, Zulkhairi, Fardah Akil, Willi Brodus Uswan, David Simanjuntak, Tomohisa Uchida, Pangestu Adi, Amanda Pitarini Utari, Yudith Annisa Ayu Rezkitha, Phawinee Subsomwong, Nasronudin, Rumiko Suzuki, and Yoshio Yamaoka. "Risk Factors and Prevalence of Helicobacter pylori in Five Largest Islands of Indonesia: A Preliminary Study", PLoS ONE, 2015. Publication	1 %
6	gastrores.org Internet Source	1 %
7	Takahiro Uotani, Kosuke Murakami, Tomohisa Uchida, Shingo Tanaka et al. " Changes of tight junction and interleukin - 8 expression using a human gastroid monolayer model of infection ", Helicobacter, 2019 Publication	1 %
8	Ramesh Rana, Sheng Lan Wang, Jing Li, Ying Xin Wang, Qian Wen Rao, Chang Qing Yang.	1 %

"Helicobacter pylori infection: A recent approach to diagnosis and management", Journal of Biomedicine, 2017
Publication

---

9 Makmun, Dadang. "Present status of endoscopy, therapeutic endoscopy and the endoscopy training system in Indonesia : Present endoscopy status in Indonesia", Digestive Endoscopy, 2014. 1%
Publication

---

10 Hamed Said Habib, Moustafa Abdelaal Hegazi, Hussam Aly Murad, Elamir Mahmoud Amir, Taher Fawzy Halawa, Basem Salama El-Deek. "Unique features and risk factors of Helicobacter pylori infection at the main children's intermediate school in Rabigh, Saudi Arabia", Indian Journal of Gastroenterology, 2014 <1%
Publication

---

11 Nagashima, Hiroyuki, Shun Iwatani, Modesto Cruz, José A. Jiménez Abreu, Lourdes Tronilo, Eduardo Rodríguez, Mildre Disla, Hideo Terao, Tomohisa Uchida, Varocha Mahachai, Ratha-korn Vilaichone, Lotay Tshering, Takahiro Mitsui, Seiji Shiota, David Y. Graham, and Yoshio Yamaoka. "Differences in interleukin 8 expression in Helicobacter pylori–infected gastric mucosa tissues from patients in <1%

Bhutan and the Dominican Republic", Human Pathology, 2015.
Publication

12	mdpi.com Internet Source	<1%
13	statpearls.com Internet Source	<1%
14	Vincenzo Savarino, Giuseppe Sandro Mela, Patrizia Zentilin, Giuliana Bisso et al. "Comparison of Isotope Ratio Mass Spectrometry and Nondispersive Isotope-Selective Infrared Spectroscopy for 13C-Urea Breath Test", American Journal of Gastroenterology, 1999 Publication	<1%
15	issuu.com Internet Source	<1%
16	link.springer.com Internet Source	<1%
17	e-sciencecentral.org Internet Source	<1%

Exclude quotes	Off	Exclude matches	< 10 words
Exclude bibliography	On		

Diagnostic Value of 14c Urea Breath Test for Helicobacter pylori Detection in Indonesian Dyspeptic Patients

GRADEMARK REPORT

FINAL GRADE

/0

GENERAL COMMENTS

Instructor

PAGE 1

PAGE 2

PAGE 3

PAGE 4

PAGE 5

PAGE 6

PAGE 7

PAGE 8

PAGE 9

PAGE 10

PAGE 11

PAGE 12

PAGE 13

PAGE 14

PAGE 15

PAGE 16