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Original Article

A novel one-step *Helicobacter pylori* saliva antigen test

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Abstract

Background: A rapid, reliable, and sufficiently accurate test for diagnosing *Helicobacter pylori* infection is required for screening dyspeptic patients before a referral for endoscopy. The purpose of this article is two-fold: first, to evaluate the accuracy of a one-step *H. pylori* saliva antigen (HPS) test; and second, to compare noninvasive and invasive *H. pylori* tests in Taiwanese population.
Methods: A total of 104 consecutive dyspeptic patients admitted for gastroenterology into the outpatient department underwent a one-step HPS test, rapid urease test, histology, and ^{13}C-urea breath test ^{13}C-UBT (proto C-13 urea kit). The accuracy of the HPS test was compared with a gold standard defined by at least two positive *H. pylori* test results from three *H. pylori* tests (histology, rapid urease test, and ^{13}C-UBT).
Results: The 104 patients eligible for analysis (mean age: 58 years, range 22-87 years), 21 (20%) were gold standard positive. Among them, the positive of the one-step *H. pylori* saliva Ag test, rapid urease test, ^{13}C-UBT, histology were (52; 50%), (17; 16%), (27; 25%) and (22; 21%) respectively. The sensitivity and specificity of the HPS tests, rapid urease test, ^{13}C-UBTs, and histology were 71.43% and 55.42%, 76.19% and 98.80%, 100% and 92.77%, and 85.71% and 95.18%, respectively, relative to the gold standard. The one-step HPS test exhibited a sensitivity of 71.43%, nearly equivalent to that of the rapid urea test.
Conclusion: The one-step HPS test exhibited a high sensitivity and low specificity compared with the other tests, indicating that it is not sufficiently accurate for use in a clinical setting for diagnosing *H. pylori* infection. However, the test is simple to use (requiring only a saliva sample), inexpensive, and noninvasive in its application, and thus appealing for use in population-based prevalence surveys of the epidemiology of *H. pylori* infection.

Keywords: *Helicobacter pylori*; one-step *H. pylori* saliva antigen test

1. Introduction

Helicobacter pylori infection is common worldwide. The prevalence of *H. pylori* among developing countries, developed countries, and Taiwan are approximately 80−90%, 50%, and 55%, respectively.[1] *H. pylori* is a Gram-negative, microaerophilic bacterium found in the stomach. It was identified in 1982 by Barry Marshall and Robin Warren, who observed that it was present in patients with chronic gastritis and gastric ulcers. *H. pylori* infection is a major factor in the etiology of peptic ulcer disease, chronic gastritis, gastric cancer, and gastric mucosa-associated lymphoid tissue lymphoma. Because of its widespread prevalence and clinical significance, *H. pylori* infection constitutes a major public health concern.[2]

Diagnostic methods for *H. pylori* infection have generally been divided into direct (invasive) and indirect (noninvasive) tests.[3] The invasive method is based on directly identifying the

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microorganism by studying samples obtained using gastric biopsy. Noninvasive tests can be performed on serum,[4] saliva,[5] stool,[6] or breath sample.[7] When patients are screened for the presence of the microorganism prior to referral for upper gastrointestinal endoscopy, this allows resources to be directed toward patients who are likely to develop severe pathology. It has been shown that *H. pylori* status as determined by serology predicts endoscopic findings more accurately than formal questioning.[8] In this study, we have proposed a novel, rapid, reliable, and accurate test for diagnosing *H. pylori* infection which could be efficacious for screening dyspeptic patients prior to a referral for endoscopy.[8]

2. Methods

This study compared the performance of several candidate screening tests, including the noninvasive one-step *H. pylori* saliva antigen (HPS) Test (Ameritek, Everett, WA, USA), the ^{13}C-urea breath test (^{13}C-UBT; proto C-13 urea kit, Synmosa Biopharma Corporation, Taipei, Taiwan), and the invasive histology and rapid urease test (HelicotecUT; Strong Biotech, Taipei, Taiwan). Subsequently, the accuracy of the new one-step *H. pylori* saliva Ag test was also evaluated.

2.1. Study population

Participants were selected from patients admitted for gastroenteropathy into the Outpatient Department at the D*epartment of* Gastroenteropathy*, Cheng-Hsin General Hospital, in Taipei, Taiwan* between June 1, 2012 and December 31, 2012. A total of 140 gastroenteropathy OPD patients, aged 20−80 years and presenting with abdominal discomfort as well as dyspeptic symptoms were admitted for upper gastrointestinal panendoscopy.

The criteria applied for exclusion from the study included: (1) the use of antimicrobials, proton-pump inhibitors (PPIs), H_2 blockers, and bismuth derivatives within 1 month before the study; (2) previous upper digestive hemorrhages and gastric cancer; and (3) presence of any underlying systemic diseases such as heart disease, combined with ingesting antiplatelet and anticoagulants.

The study followed the standards of the Declaration of Helsinki and has been approved by the Institutional Review Board (IRB) of *Cheng-Hsin* General Hospital [CHGH-IRB: (298) 101-11-1]. As the dataset used in this study consists of de-identified data from a retrospective cohort, written informed consent from the patients receiving upper gastrointestinal panendoscopy services was waived by the approval of the IRB.

During enrollment, patients had their medical histories taken and charts reviewed in the endoscopy room of the D*epartment of* Gastroenteropathy*, Cheng-Hsin General Hospital. This was undertaken* to determine the participants' medical history, such as peptic ulcer disease, heart disease, previous *H. pylori* infection, and drug history, such as the use of anticoagulants, antiplatelet, antibiotics, or PPIs.

Prior to each patient undergoing endoscopy, a well-trained representative from the saliva test's company performed a saliva test as follows: No food or drink was allowed 1 hour before the test. To perform the test, approximately 2−3 mL of saliva were extracted from each participant and mixed with 6−8 drops of an extraction buffer. After mixing, a pipette was used to transfer four drops of the mixture into the sample well of the test cassette. As the test kit begins to work, a purple color moves across the result window in the center of the test disk. The results are observed within 5−30 minutes. The occurrence of two bands (T band and C band) in the test and control zones was positive for *H. pylori*. The occurrence of one band in the control zone was negative for *H. pylori*. If there was no band in the control zone (invalid result) the samples were retested.

After extracting saliva from the participants, a consultant physician performed an endoscopy. Four antral mucosal biopsy specimens were extracted from each patient. Three biopsies obtained from around the antrum (of 4 quadrants) within 3 cm of the pylorus were sent for histology. The presence of *H. pylori* was determined by staining with hematoxylin and eosin. If no *Helicobacter* organisms were observed, then a modified Giemsa stain was applied. The remaining antral biopsy specimen was used for a slide biopsy rapid urease test (HelicotecUT Biotech). The test was checked 30 minutes after insertion of the biopsy, and then reviewed at 24 hours, after which the result was recorded.

Immediately after the endoscopies, each participant underwent the ^{13}C-UBT.[7] The patients were required to exhale two breath samples into two individual sample bags [i.e., a normal breath and a second breath after consuming a lemon-flavored ^{13}C-urea solution (PROTOC-13 urea kit)]. The mechanism of the ^{13}C-UBT is used to measure the urease activity of *H. pylori*.[7] The bacterium produces copious amounts of urease, which breaks down the ^{13}C-labeled urea to produce labeled CO_2 and ammonia. The CO_2 is dissolved in the blood stream and transported to the lungs for removal. Exhaled CO_2 was collected in a bag and then processed and analyzed using the advanced Ap 2005 - ^{13}C-Breath Gas Analysis (Analytical Precision Limited, Windsor House Northwich, Cheshire CW9 7TN), Isotope Ratio Mass Spectrometer.[7] A quick report was generated in 7 minutes.

2.2. Statistical analysis

Gold standard positives were defined as those with at least two positive test results among the rapid slide biopsy urease test, histology, and ^{13}C-UBT. Gold standard negatives were defined as those with negative results for all three tests (or 2 tests if the ^{13}C-UBT was not conducted).[9] Performance of tests in diagnosing *H. pylori* infection was examined by using area under the receiver operator characteristic curves (AUROC), which was expressed as plots of the test sensitivity vs. 1−specificity. A significance level of 0.05 was used for all statistical calculations. Using the gold standard test as a reference, sensitivity, specificity, positive and negative predictive values, and precisely associated 95% confidence intervals (CIs) were calculated for the saliva test, rapid urease test, ^{13}C-UBT, and pathology of the participants.

3. Results

After excluding 36 patients because of recent consumption of antiplatelet ($n = 11$), antibiotics ($n = 9$), PPIs ($n = 13$), and absence from the ^{13}C-UBT ($n = 3$), 104 patients were eligible for analysis (Fig. 1). Table 1 shows the characteristics of the 104 patients who underwent endoscopy. The mean age of the participants was 58 years, and 61% were female. Among the 104 participants, 21 (20%) were gold standard positives for the one-step *H. pylori* saliva Ag test ($n = 52$; 50%), rapid urease test ($n = 17$; 16%), ^{13}C-UBT ($n = 27$; 25%), and histology ($n = 22$; 21%); and 83 (80%) were gold standard negatives (Table 2).

The sensitivity of the one-step saliva test in relation to the invasive tests ranged from 71.43% to 85.7% (Table 3). The one-step HPS test exhibited a sensitivity of 71.43%, nearly equivalent to that of the rapid urease test.

Comparison of the AUROC of the four tests (HPS, HelicotecUT test, ^{13}C-UBT, and pathology) in relation to the gold standard were 0.634 (95% CI, 0.504–0.764), 0.875 (95% CI 0.764–0.986), 0.964 (95% CI, 0.930–0.998), and 0.904 (95% CI, 0.813–0.996), respectively, with $p \leq 0.05$ (Table S1). In relation to AUROC, ^{13}C-UBT (AUROC −0.964) is best for testing diagnostic accuracy, although the HPS test (AUROC −0.634) is also sufficient. From this result, we could calculate the minimal required sample size as 144.

4. Discussion

Diagnostic methods for *H. pylori* infection have generally been divided into direct (invasive) and indirect (noninvasive) tests.[7] The invasive test is based on directly identifying the microorganism by studying samples obtained using gastric biopsy.[3] Noninvasive tests can be performed on serum, saliva, stool, or breath samples.

The choice of a diagnostic test should depend on the clinical circumstances, the pretest probability of infection, sensitivity and specificity of the test (or more correctly, the likelihood ratio of a positive and negative test), the cost effectiveness of the testing strategy, and the availability of the test.[10] Certain clinical circumstances warrant invasive studies: patients who have failed eradication therapy might require culture and antimicrobial sensitivity testing to help determine an appropriate regimen, and older patients presented with new onset dyspepsia and those with "alarm" symptoms (such as bleeding and weight loss) that raise concerns of malignancy.

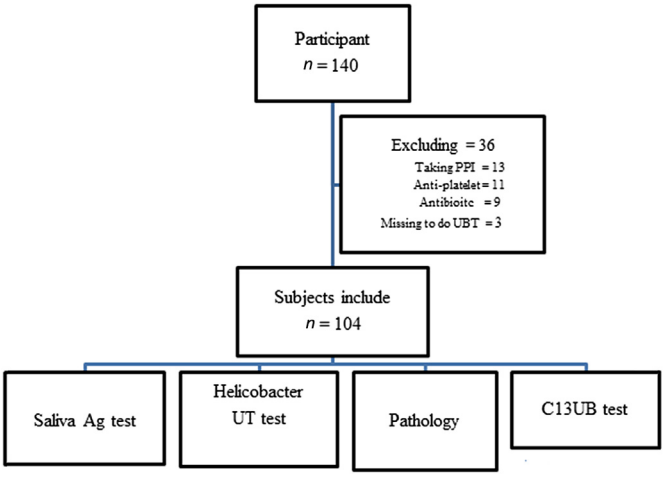

Fig. 1. Flow chart of the study.

Table 1
Characteristics of 104 patients enrolled in Cheng-Hsin Hospital undergoing esophagogastroduodenoscopy between 2012/06 and 2012/12.

Characteristic	% (*n*)
Mean age (min, max)	58 y (22, 87)
Sex (M/F)	49/61% (40/64)
Medical chart review	
History of peptic ulcer disease	10% (11)
Previous EGD	29% (30)
Previous treated for *H. pylori*	5% (6)
Naïve patient	54% (57)
Endoscopic evaluation during EGD	
Esophagitis	22% (23)
Hemorrhagic gastritis	26% (28)
Atrophic gastritis	4% (5)
Erosive gastritis	16% (17)
Superficial gastritis	7% (8)
Ulcers (gastric ulcer, duodenal ulcer)	20% (21)
Negative	1% (2)

Noninvasive protocols are preferred for epidemiological studies and for young children.[4,10,11] In addition to facilitating epidemiological research, noninvasive *H. pylori* testing can be successfully used for pre-endoscopic screening of patients referred to a gastroenterology[12] service for investigating dyspepsia as well as therapeutic monitoring after eradication therapy. Using noninvasive tests to screen young patients and children[4,10] who present with dyspepsia has been advocated on the basis of a decrease in overall endoscopy workload and resultant financial savings.[12]

Recently, some noninvasive methods of testing for *H. pylori* have become available: (1) the ^{13}C- or ^{14}C-labeled UBT; (2) serology (based on detection of a specific anti-*H. pylori* IgG antibody in the patient's serum); and (3) *H. pylori* stool antigens test. Several novel methods of detecting *H. pylori* have recently been described and include detecting antibodies in saliva and urine and detecting antigens in stool.[13]

That *H. pylori* can be transmitted by both oral to oral and stomach to oral routes has been recognized since 1989 when Shames et al[14] first isolated *H. pylori* from the dental plaque of patients with gastric diseases related to *H. pylori* infection. Several studies have suggested that oral *H. pylori* is associated with the presence of gastric *H. pylori*[14,15] infection, and

Table 2
Percent positive for *Helicobacter pylori* by test type among 104 patients enrolled in Cheng-Hsin Hospital for *H. pylori* infection study, June–December 2012.

Test type	% of *H. pylori* positive (*n*)
Saliva antigen test	50 (52)
HelicotecUT test	16 (17)
Histology	21 (22)
^{13}C-UBT	25 (27)
Gold standard	20 (21)

Table 3
Sensitivity and specificity of *Helicobacter pylori* tests in relation to gold standard in 104 patients from Cheng-Hsin Hospital.

	Positive, *n* (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Saliva antigen test	52 (50)	71.43	55.42	29.11	88.33
HelicotecUT test	17 (16)	76.43	98.8	94.1	94.3
^{13}C-UBT	27 (25)	100	92.77	77.8	100
Histology	22 (21)	85.71	95.18	81.8	96.3
Gold standard	21 (20)				

NPV = negative predictive value; PPV = positive predictive value; UBT = urea breath test.

patients who test positive for oral *H. pylor*i have a lower success rate of gastric *H. pylori* eradication than oral *H. pylori*-negative individuals.[16,17]

A search using PubMed found 305 articles that have "*Helicobacter pylori*" and "saliva" in the title, 26 titles that also include antigen in the title, and only three titles that are about detection of oral *H. pylori* antigen in humans.

Namiot et al[18] screened 155 patients with no history of *H. pylori* infection and found that 65.6% were positive for *H. pylori* in dental plaque using the Oxoid IDEA Hp StAR amplified immunoassay test (which uses monoclonal antibodies to detect fecal antigen).

Yee et al[17] screened 201 participants; they were then separated into UBT+ and UBT− groups. They found that oral screening test could identify persons with no symptoms but with antigenic evidence of possible oral *H. pylori* infection who are at risk for developing gastric disease. In Yee et al's[17] experiment, the HPS test results were compared with the UBT, serum antibody, campylobacter-like organism test, silver stain, culture, and stool antigen test results. Oral antigen tests were positive in 41 UBT− people, indicating that they may have *H. pylori* antigen in the mouth in the absence of disease.

Song and Li[16] screened 391 patients with dyspepsia who underwent gastroscopy and histopathological examination of gastric mucosa. To evaluate *H. pylori* in the oral cavity, the authors used an HPS test based on detection of *H. pylori* antigen in saliva using rapid immune–chromatographic assay. For evaluation of *H. pylori* in stomach mucosa, the authors used the ^{13}C-UBT. The results showed that the eradication of *H. pylori* in the mouth cavity using mouth rinse and peridental treatment could kill the oral *H. pylori* and improve the eradication rate of gastric *H. pylori* by triple therapy (Table 4).[16–18]

The accuracy of a test is crucial in diagnosing a condition or assessing a marker for disease.[15] A greater scope is possible in the population-based setting to adjust for known test inaccuracies in the reporting of rates and their comparisons.[9] In large-scale studies of *H. pylori*, the saliva-based test is a particularly attractive alternative to serum-based tests because, in addition to eliminating the need to employ trained personnel to draw blood, saliva sampling might provide a better response rate than serum sampling in studies using volunteers. Antibody levels persist in the blood for extended periods of time. The persistent antibody causes increasingly frequent false positive test rate.[19] Serology has been the most widely used test, but the sensitivity and specificity of this test is comparatively low. The UBT is the most accurate noninvasive test, but is expensive and difficult to perform.[7]

This study provides essential information on the AUROC of four tests commonly used in clinical practice for diagnosing *H. pylori* infection. Clinicians use a variety of tests to diagnose *H. pylori* infection in patients presented with abdominal symptoms. These data were used to compare the sensitivity, specificity, and AUROC of each test and gold standard test. We evaluated the performance of *H. pylori* tests in a population of Taiwanese adults by using various methods and evaluated the AUROC of the new one-step HPS test.

In this study, we proposed a novel rapid, reliable, and accurate test for diagnosing *H. pylori* infection required for screening dyspeptic patients prior to a referral for endoscopy.

Table 4
The results based on *Helicobacter pylori* saliva antigen test.

Reference	Patients (number)	Tests	Study design	Results
Namiot et al[18]	155	*H. pylori* antigens in supragingival plaque	Used the immunological method (a kit for detection of *H. pylori* antigens in stool samples.) to test *H. pylori* antigens in supragingival plaque despite no history of *H. pylori* infection	65.6% were positive for *H. pylori* in dental plaque
Yee et al[17]	201	HPS, UBT, serum antibody, *Campylobacter*-like organism test, silver stain, culture, and stool antigen test	HPS results were compared in parallel with the UBT, serum antibody, *Campylobacter*-like organism test, silver stain, culture, and stool antigen test results	Oral antigen tests were positive in 41 UBT− people, indicating that they may have *H. pylori* antigen in the mouth in the absence of disease
Song and Li[16]	391	233 patients who were ^{13}C-UBT+were divided Into four	Treated with	Eradication rate of gastric *H pylori*
		O-G+t (53)	triple therapy	42 (93.3)
		O+G+t (53)	triple therapy	40 (78.4)
		O+G+tm (65)	triple therapy + mouth rinse	54 (90.0)
		O+G+tmp (62)	triple therapy + mouth rinse + periodontal treatment	54 (94.7)

G = gastric test by UBT; HPS = saliva *H. pylori* antigen test; O = oral test by HPS; t = treated with triple therapy; tm = triple therapy + mouth rinse; tmp = triple therapy + mouth rinse + periodontal treatment; UBT = C-13 urea breath test.

The one-step HPS test is an immune-sandwich assay, highly sensitive to *H. pylori* urease, developed to use saliva as a specimen for detecting *H. pylori* colonization in the gastrological tract and oral cavity.[17] The monoclonal antibody used in the assay reacts with only *H. pylori* urease; thus, it has a high sensitivity and specificity. The analytical sensitivity of the test is 10 ng/mL of *H. pylori* urease.[17] There was no interference or cross reactivity with the other bacteria in the oral cavity and there was statistical correlation between oral antigen and serum antibody test results.

Our results showed that the positive rate of HPS was 71.43%, nearly equivalent to that of the saliva *H. pylori* test's 74.9% in Song and Li's study[16] and demonstrating that the mouth is another storage site for *H. pylori*. In this study, the gastric *H. pylori* eradication rate in HPS+ positive patients was lower than that in HPS− patients (78.4% vs. 93.3%). The test results of gastric and oral *H. pylori* were not consistent in this study. Previous studies have shown that *H. pylori* does not colonize in the mouth of a person with good oral hygiene (e.g., no periodontal disease, no gingival band, or plaque). In this situation, the oral *H. pylori* titer is low and does not reach the threshold of gastric *H. pylori* infection. Therefore, a saliva test to detect gastric *H. pylori* infection would give negative results. For gastric *H. pylori*-positive patients with good oral hygiene, although gastric *H. pylori* may be refluxed into the mouth; the bacterium may not survive in the mouth.

In this study, the HPS test had a high sensitivity, which enabled it to detect a low titer of *H. pylori*.[17] Therefore, the positive rate for oral *H. pylori* infection was higher than that for gastric *H. pylori* infection.

The sensitivity of the one-step HPS test in relationship to the invasive tests and the gold standard ranged from 72% to 88%. The one-step HPS test had exhibited a sensitivity of 71.43%, nearly equivalent to that of the rapid urea test. The salivary assessment achieved a relatively high sensitivity and low specificity, compared with the other tests, indicating that it is not sufficiently accurate for use in a clinical setting for diagnosing current *H. pylori* infection. However, because it is easy to use (requiring only a saliva sample), inexpensive, and noninvasive, it is attractive for use in population-based prevalence surveys for *H. pylori* infection. In addition, HPS can diagnose oral *H. pylori* in individuals with no symptoms. It further identified those with no symptoms but with antigenic evidence of possible oral *H. pylori* infection who are thus at risk for developing gastric disease and recurrence infection.[16,17] It is a simple and rapid method to test for and eliminate oral *H. pylori*. This method can be used to prove the elimination of gastric *H. pylori*, and it is practical for use in the clinical environment as well.[16]

There are certain limitations to our study. First, this study included all outpatients who presented with epigastralgia; thus, the prevalence of *H. pylori* was low. Second, the sample size of this study was lower than the effective sample size. Third, the HPS test achieved relatively high sensitivity and low specificity. Nevertheless, further large population studies are still needed to validate this result.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jcma.2014.11.004.

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