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Evaluation of Rapid Antibody Tests for the Diagnosis of *Helicobacter pylori* Infection

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OBJECTIVE: The aim of this study was to compare the performance characteristics of one serum and four whole blood rapid antibody tests for *Helicobacter pylori* infection.

METHODS: A total of 97 outpatients referred for endoscopic evaluation of dyspepsia were included. Antral biopsies were obtained for histology and rapid urease test. Serum was tested with an enzyme-linked immunoassay (HM-CAP) and a rapid serology test (FlexSure HP). A commercially available ^{13}C-urea breath test was performed. Capillary blood obtained by fingerstick was tested with FlexSure HP, QuickVue, Accustat, and StatSimple *pylori* tests. Sensitivity, specificity, and accuracy of each rapid test was calculated relative to a criterion standard of histological gastritis and at least two of the four following tests positive: identifiable organisms on specially stained slides, rapid urease test, urea breath test, or serum immunoassay.

RESULTS: A total of 30 patients (31%) were infected. The FlexSure HP Serum, and FlexSure HP, QuickVue, Accustat, and StatSimple *pylori* whole blood tests had sensitivities of 90%, 87%, 83%, 76%, and 90%; specificities of 94%, 90%, 96%, 96%, and 98%, and accuracies of 93%, 88%, 92%, 87%, and 96%, respectively. Sensitivities were not statistically different. StatSimple *pylori* was more specific than FlexSure HP whole blood ($p < 0.03$), and more accurate than FlexSure whole blood ($p < 0.024$) and Accustat ($p < 0.01$). Serum immunoassay was significantly more sensitive (97%) than FlexSure whole blood, QuickVue, and Accustat ($p < 0.01$), but its specificity (95%) was not statistically different from the rapid tests.

CONCLUSION: Rapid antibody testing provides an accurate diagnosis of *H. pylori* infection. In general, these tests are less sensitive than, but as specific as, standard serology. (Am J Gastroenterol 2000;95:72–77. © 2000 by Am. Coll. of Gastroenterology)

INTRODUCTION

Multiple invasive and noninvasive tests are available for the diagnosis of *Helicobacter pylori (H. pylori)* infection (1–3). Invasive tests rely on endoscopic biopsy of the gastric mucosa. Biopsy specimens can then be cultured for the organism, stained and examined for typical curved bacilli, or tested for urea-splitting activity with a rapid urease test (1). Bacterial culture is rarely performed because of the fastidious nature of the bacteria, leading to inadequate sensitivity (4). Available noninvasive tests include urea breath testing, the stool antigen test, and blood and salivary testing for preformed antibodies to *H. pylori*.

Blood testing for anti-*H. pylori* antibodies was the first minimally invasive test available to diagnose this infection (5). In clinical practice, this required venipuncture, serum preparation and, in most cases, sending the sample to a reference laboratory for an enzyme-linked immunoassay (EIA). Unlike tests that rely on bacterial urease activity, antibody tests can be performed in patients taking proton pump inhibitors (*e.g.*, omeprazole, lansoprazole, rabeprazole, and pantoprazole), antibiotics, or bismuth compounds (*e.g.*, Pepto-Bismol) but are not generally useful in the immediate (<6 months) follow-up after attempted eradication therapy (6–8). The development of devices that qualitatively determine the presence of *H. pylori* antibodies using a precipitin reaction has allowed testing in an office practice setting, providing immediate results (within 10 min) at a cost lower than that of send-out EIA (2, 9). However, these serum-based rapid tests have still required venipuncture and serum preparation (2, 10, 11).

Whole blood antibody tests using capillary blood obtained by fingerstick, are now available and CLIA-waived (12–14). They provide a rapid, in-office diagnosis for $10–15 per test, but are not useful for posttherapy follow-up. Experts anticipate that these tests will be used as screening tools for *H. pylori* infection in patients with dyspepsia (15). Individual tests vary in the antigens used, device design, and ease of use. The relative accuracy of these tests has not previously been reported.

We evaluated four whole blood antibody tests and one rapid serum test in patients undergoing indicated upper endoscopy for the evaluation of dyspepsia: FlexSure HP (whole blood and serum versions), QuickVue, Accustat, and StatSimple *pylori*. We compared these to a criterion standard consisting of antral histology, rapid urease test (RUT), ^{13}C-urea breath test (^{13}C-UBT), and serum EIA.

MATERIALS AND METHODS

Consecutive patients with dyspepsia referred for upper endoscopy at the Portland VA Medical Center or Oregon Health Sciences University Hospital (Portland, OR) were invited to participate. This protocol was approved by the respective Human Studies Committees of the two institutions. Patients were excluded if they had previously been treated for *H. pylori*, or within 4 wk had used a proton pump inhibitor (omeprazole or lansoprazole), antibiotics, or bismuth compounds. Patient demographics, clinical and medication history, and endoscopic findings were recorded. All samples were obtained on the same day as the endoscopy. After obtaining informed consent, routine upper endoscopy was performed in the usual manner under conscious sedation. During endoscopy, standard biopsy forceps were used to obtain two antral and one fundic specimen for histology and one antral specimen for rapid urease test (RUT) using either the CLOtest (Delta West, Bentley, Australia) or Pyloritek (Serim Research, Elkhart, IN) depending upon availability at each study site. These RUT have previously been shown to have equivalent performance characterisitics (16). CLOtests were incubated at 37°C and read at 24 h (17). Pyloritek slides were kept at room temperature and read at 1 h. RUT were read by one of two trained research assistants.

After endoscopy, patients underwent a commercially available ^{13}C-urea breath test (^{13}C-UBT) (Meretek, Houston, TX) according to the manufacturer's instructions, in the fasting state, using a standard 142-g Ensure pudding (Abbott Laboratories, Columbus, OH) test meal, and 125 mg ^{13}C-urea solution. Breath samples at baseline and 30 min after ^{13}C-urea administration were collected into Mylar balloons, transferred into vacutainers, and mailed to the manufacturer for analysis by mass spectrometry. A difference in $^{13}CO_2$ concentration (parts per thousand) between baseline and the 30-min sample >2.4 was considered by the manufacturer to be a positive test.

Serum prepared from venipuncture blood was used for the FlexSure HP Serum test (SmithKline Diagnostics, Palo Alto, CA) and enzyme-linked immunoassay (EIA). Fresh serum was applied to FlexSure cards, developed, and read at 4 min acccording to the manufacturer's recommendations. Frozen serum was mailed to SmithKline Diagnostics, which was blinded to the other diagnostic results, and tested with the HM-CAP EIA. An optical density of >2.2 was considered positive.

Capillary blood was obtained by fingerstick and collected into glass capillary tubes for use with FlexSure HP Whole Blood (SmithKline Diagnostics), QuickVue (Quidel, San Diego, CA) and Accustat (Boehringer Mannheim, Mannheim, Germany) devices. The StatSimple *pylori* (Saliva Diagnostic Systems, Vancouver, WA) consists of a plastic tube containing the reagent strip into which fingerstick blood is directly collected. Test order was randomized for each patient with randomization performed before enrollment. All tests were performed according to the manufacturers' recommendations. The FlexSure, QuickVue, and Accustat devices were all commercially available at the time of the study. The StatSimple *pylori* device became commercially available soon after completion of the study.

Antral specimens were stained with hematoxylin and eosin and alcian yellow–toluidine blue stains. Specimens stained with hematoxylin and eosin specimens were examined for the presence of mononuclear cell and neutrophil infiltration and graded according to the Sydney classification using a published visual analog scale (18). Specimens stained Alcian yellow–toluidine blue were examined for the presence of typical curved bacilli consistent with *H. pylori* (19). All histopathology slides were reviewed by a single expert GI pathologist who was blinded to the clinical history, endoscopic findings, and results of other tests.

Because no single test suffices as a criterion standard, we used the concordance of several tests to diagnose *H. pylori* infection (1). Patients were considered to be *H. pylori* infected if a mononuclear cell infiltrate of the gastric mucosa of at least grade 1 (mild) were present on specimens stained with hematoxylin and eosin (20), and two of the following tests were positive: typical organisms on slides stained with Alcian yellow–toluidine blue, RUT, ^{13}C-UBT, and/or serum EIA. All other patients were considered to be negative for infection.

Sensitivity, specificity, accuracy, 95% confidence intervals, and the chance-adjusted agreement statistic κ were calculated for each test relative to the above criterion standard (21, 22). The Pearson χ^2 test was used to assess for differences between tests and to calculate p values. Tests were considered to be significantly different if the 95% confidence intervals did not overlap the other tests' values, and if $p < 0.05$.

RESULTS

A total of 100 patients with dyspepsia were enrolled and underwent endoscopy with biopsy, RUT, ^{13}C-UBT, and antibody testing. Three patients were subsequently found to have violated the protocol (two had taken bismuth within the previous 4 wk, one had previously been treated for *H. pylori*) and were excluded from analysis. The demographic data of the 97 evaluable patients is shown in Table 1. Most were male (92%) with a mean age of 61 yr (range: 26–86 yr). A total of 30 patients had *H. pylori* infection (prevalence = 31%), as diagnosed by the presence of histological gastritis (mononuclear cell infiltrate) and at least two of the following tests positive: organisms on special stains, RUT, ^{13}C-UBT, or serum EIA. In all, 23 patients (24%) had all four tests positive, four (4%) had three tests positive, and three (3%) had two tests positive. Of 67 *H. pylori* negative patients, 24 had histological gastritis (mild/grade 1 in 20 patients, and moderate/grade 2 in four patients), six of the 24 had one test positive (three ^{13}C-UBT and three EIA), and one patient had two tests positive but without histological gastritis.

Table 1. Demographic Data, History, and Endoscopic Findings (n = 97)

Gender	
Male	89 (92%)
Age (yr)	
Mean (range)	61 (26–86)
H. pylori status	
Positive	30 (31%)
Negative	67 (69%)
Prior history	
Gastric ulcer	24 (25%)
Duodenal ulcer	12 (12%)
GERD	44 (46%)
Histamine H2-receptor antagonist use	55 (57%)
EGD findings	
Esophagitis	23 (24%)
Gastric mucosal abnormality*	40 (41%)
Duodenal mucosal abnormality*	21 (22%)
Gastric ulcer	6 (6%)
Duodenal ulcer	10 (10%)
Barrett's esophagus	8 (8%)

* Erythema/inflammatory changes.

A prior history of gastric or duodenal ulcer was present in 25% and 12% of patients, respectively (Table 1). In all, 46% carried a clinical diagnosis of gastroesophageal reflux disease, and 57% used histamine H2-receptor antagonists. At endoscopy, mucosal abnormalities of the esophagus (esophagitis), stomach and/or duodenum (erythema/inflammatory changes) were noted in 24%, 41%, and 22% of patients, respectively. Gastric ulcer was found in 6%, duodenal ulcer in 10%, and Barrett's esophagus in 8%.

Table 2 shows the performance characteristics of the tests used to evaluate for *H. pylori* as compared to the criterion standard. The results for the tests used as part of the criterion standard are also shown for comparison. Although histological gastritis is invariably present in patients with *H. pylori*, it was only 64% specific for that infection. The presence of typical organisms on specially stained gastric biopsies, or a positive rapid urease test, had similar sensitivities (83% and 87%, respectively) and were each 100% specific. Of the 25 patients with organisms identified on histology, 23 had three confirmatory tests, and two patients had two confirmatory tests. The commercial ^{13}C-UBT used in this study was 100% sensitive for infection but only 87% specific because of nine false-positive tests. Seven of these nine patients had δ values <5 (cutoff for positive = 2.4). Three of the nine had mild gastritis, and one patient without gastritis had a positive EIA as well. The serum EIA was 97% sensitive and 94% specific.

Performance characteristics for the rapid tests are shown in Table 2. Test failures were excluded from analysis: one FlexSure HP Whole Blood, and one Accustat. Three patients did not undergo FlexSure HP serum testing, and five patients did not undergo StatSimple *pylori* testing because of temporary unavailability of the tests. A sufficient capillary blood sample for all four whole blood tests could be obtained from one (n = 48) or two (n = 37) fingersticks, but 12 patients required three or more. The sensitivities of the rapid tests ranged from 76% to 90%, and were not significantly different. The serum EIA was significantly more sensitive than the FlexSure HP Whole Blood, QuickVue, and Accustat tests ($p < 0.01$) but not the FlexSure HP Serum or StatSimple *pylori* tests. Specificities were 90–98% and not different from EIA. StatSimple *pylori* specificity was significantly better than FlexSure HP Whole Blood ($p < 0.03$) and ^{13}C-UBT ($p < 0.01$). Overall accuracy (concordance rate with the gold standard) was 87–96%. StatSimple *pylori* was significantly more accurate than FlexSure HP Whole Blood ($p < 0.024$) and Accustat ($p < 0.01$). The serum EIA was also significantly more accurate than FlexSure HP Whole Blood ($p < 0.04$) and Accustat ($p < 0.02$). The chance adjusted agreement statistic κ confirmed a high degree of concordance between the rapid antibody tests and the criterion standard ($\kappa = 0.74–0.90$). Using a less stringent criterion standard of gastritis plus any *one* positive comparison test (organisms, RUT, ^{13}C-UBT, or EIA) would classify 36 patients as infected, and would reduce the calculated sensitivites of the rapid antibody tests by 8–10% and increase the specificities by 1–2%, compared with the strict standard.

DISCUSSION

The ideal test for *H. pylori* would have several attributes. It would be safe, accurate, noninvasive, easy to perform, free from medication or other effects that would limit accuracy, useful for posttherapy follow-up, provide rapid results, and

Table 2. Performance Characteristics of Tests Used to Diagnose *H. pylori*

	Sensitivity	Specificity	Accuracy	κ*
Gastritis	100% (90–100)	64% (52–76)	75% (67–84)	0.53
Organisms	83% (68–97)	100% (96–100)	95% (90–99)	0.87
Rapid urease	87% (74–100)	100% (96–100)	96% (92–100)	0.90
^{13}C-UBT	100% (90–100)	87% (78–95)	91% (85–97)	0.80
EIA	97% (90–100)	94% (88–99)	95% (90–99)	0.88
FlexSure HP Serum	90% (78–100)	94% (88–99)	93% (87–98)	0.83
FlexSure HP Whole Blood	87% (74–100)	90% (82–97)	88% (81–94)	0.74
Quickview	83% (71–97)	96% (90–100)	92% (86–97)	0.80
Accustat	76% (59–92)	96% (90–100)	87% (82–95)	0.74
StatSimple *pylori*	90% (78–100)	98% (95–100)	96% (92–100)	0.90

Numbers in parentheses are 95% confidence intervals.

* κ = Calculated relative to the criterion standard (see Materials and Methods).

be inexpensive. In most regards, the whole blood antibody tests fulfill these requirements. They are minimally invasive requiring a small blood sample obtained by fingerstick. They are relatively easy to perform although their designs and complexity vary with the Accustat being the most complex to use and the StatSimple *pylori* the least. Unlike tests that rely on bacterial urease activity (UBT and RUT), which may yield false-negative results in patients taking proton pump inhibitors, bismuth compounds, or antibiotics (6, 23, 24), antibody tests are not effected by these medications. The whole blood tests are among the least expensive tests available, costing less than $15 per test. Standard EIA costs $50–100 and there is a delay in diagnosis while the sample is being assessed. Urea breath testing also fulfills many of these criteria, but is more expensive ($125–200 for ^{13}C-UBT, $50–75 for ^{14}C-UBT), usually requires sending the sample for analysis leading to diagnostic delay, and in the case of the ^{14}C-UBT, exposes the patient to a small dose of radiation and therefore cannot be performed in women who may be pregnant (25). There is little current clinical experience in this country with other minimally invasive tests such as stool antigen, saliva antibody, and blood urea tests, but the limitations of the stool antigen and urea tests are likely to be similar to the breath tests, and salivary testing has poor accuracy (12, 26–29). Because detectable antibodies may persist after successful eradication of the organism, qualitative rapid tests using whole blood or serum are not generally useful for posttherapy follow-up, and other tests of *H. pylori* infection (*e.g.*, UBT and endoscopy) should be used in this setting (7, 8).

We determined the performance characteristics of four rapid whole blood tests, and one serum test, in 97 consecutive patients with dyspepsia undergoing indicated upper endoscopy. To determine performance characteristics, an accurate criterion standard for comparison is required. However, for *H. pylori* infection, no single test suffices (1). Tissue-based tests are highly specific but less sensitive because of variations in *H. pylori* density in the gastric mucosa (1, 3, 30). "Global" tests such as UBT or serology, which are free from the sampling errors of tissue-based methods (1), may have improved sensitivity but less specificty, as we found with the ^{13}C-UBT. To avoid these pitfalls, previous authors have used concordance of several tests as the criterion standard (1, 3). We therefore compared the rapid antibody tests to a criterion standard consisting of antral histology (inflammation and presence of organisms on special stain), RUT, ^{13}C-UBT and serum EIA. Histological gastritis is the *sine qua non* of *H. pylori* infection, and we required a mononuclear cell infiltrate of at least grade 1 (Sydney classification) to be present (20). Additionally, to classify a patient as infected, at least two of the four *H. pylori* tests had to be positive. By this standard, 31% of our patients were infected. One additional patient had a positive EIA and ^{13}C-UBT but without histological gastritis and was classified negative for infection. The use of urease-based tests and serum EIA required us to exclude patients previously treated for infection, or recently using proton pump inhibitors, bismuth compounds, or antibiotics. Therefore, whether our results are applicable in these patient groups cannot be ascertained. Additionally, a large proportion of our patients were male and elderly. Although there have been no reports that these tests perform differently in younger adults or in female subjects, the applicability to other patient populations cannot be stated with certainty.

We found both the rapid whole blood and serum antibody tests to be quite accurate for *H. pylori* diagnosis. Concordance (accuracy) with the gold standard was good, ranging from 88–96% with corresponding κ values of 0.74–0.90 [κ values $>$0.75 are considered to reflect a high degree of agreement (22)]. The sensitivities of the tests, although ranging from 76–90%, were not significantly different. Three of the whole blood tests (FlexSure HP, QuickVue, and Accustat) were significantly less sensitive than EIA. The specificities of the rapid tests (90–98%) were similar to that of the EIA (94%). StatSimple *pylori* was significantly more specific than the FlexSure HP whole blood or ^{13}C-UBT. The overall accuracies of the antibody tests were similar, although the StatSimple *pylori* and EIA were each significantly better than the FlexSure HP whole blood or Accustat tests. Using a less stringent criterion standard (gastritis plus one test positive) reduced the calculated sensitivity of each test with little effect on specificity. However, this less strict standard likely misclassifies some patients as positive, inasmuch as several of the tests used as part of the criterion standard have a specificity of $<$100%, and thus it underestimates the true sensitivities of the rapid tests.

Prior evaluations of rapid serum tests have found them to be similar to, but slightly less accuarate, than standard EIA tests, as was found in our study (2, 10, 11, 31–33). Our evaluation of the whole blood tests also yielded results similar to prior reports. The Accustat has previously been reported to have a sensitivity of 88–96% and specificity of 85–95%; Quickvue a sensitivity of 78%, specificity of 93%, and accuracy of 76–89%; and FlexSure HP Whole Blood a sensitivity of 87%, specificity of 74%, and accuracy of 79% (31–36). Three whole blood tests that we did not evaluate, Helisal, Pyloriset, and Chemtrak Hp Chek, have reported sensitivities of 82–92%, 95% and 88%, and specificities of 69–94%, 94%, and 85%, respectively (12–14, 34, 37–39). We chose not evaluate these latter tests to limit the number of fingersticks that our subjects would undergo. There have been no published reports of the StatSimple *pylori* test, and no studies comparing different whole blood tests.

For comparison purposes, we also calculated performance characteristics for the tests used as part of the criterion standard. There is an inherent bias in these calculations because, to an extent, these tests are being compared to themselves, which may overestimate the true values. Nonetheless, some conclusions can be drawn. Histological gastritis, although a sensitive indicator of *H. pylori* infection, is not specific, inasmuch as mild degrees of inflammatory cell infiltration may be present in uninfected patients (20). The

tissue-based tests, examining for typical organisms or rapid urease testing, were each moderately sensitive but highly specific. We employed special stains of antral specimens that were examined by an expert GI pathologist, since specialist review may be more accurate (2). The special stain we used, Alcian yellow–toluidine blue, highlights bacteria and has been shown to have similar performance characteristics as Giemsa and Steiner stains (19). Although sensitivities reported with the Genta and Warthin-Starry stains have been higher than we found with Alcian yellow–toluidine blue, others have not found special stains (including the Genta stain) to increase the accuracy of histology (1, 30, 40). The HM-CAP serum EIA was quite accurate and similar to previously reported EIA results using similar criterion standards (1, 3). It should be noted that the EIA was performed by the manufacturer where expertise and attention to quality control are high.

The Meretek ^{13}C-UBT was less specific than expected (1, 3, 41), because of the occurrence of nine false-positives. It is possible that some of these patients were, in fact, infected (*i.e.*, true positive): three of the patients had mild gastritis (although without a confirmatory *H. pylori* test) and one patient without gastritis had a positive EIA antibody test. More likely, the delta $^{13}CO_2$ value has either been set too low, or, as with the ^{14}C-UBT, an indeterminate range needs to be defined (2). Seven of the nine false positives had δ values <5. If the cutoff value were raised from 2.4 to 3.2, the sensitivity and specificity would have been 94% and 93%, respectively. Other investigators have found urea breath testing to be less sensitive but more specific, but they used different cutoff values and did not use commercially available tests (1, 3, 41).

We have found the rapid antibody tests to be accurate for the diagnosis of *H. pylori* infection in the outpatient setting. They should not be used after attempted eradication therapy, as persistent antibodies may cause a false-positive result (8, 10). In general, these tests are somewhat less sensitive but as specific as standard serology. Differences among tests include device design and ease-of-use, but costs are similar and inexpensive. The StatSimple *pylori* test had better specificity and accuracy then several of the other devices, and, with the blood collection tube and test strip combined in one apparatus, was the easiest to use. For population screening, a sensitivity of $>90\%$ is often desired. If used for this purpose, the fact that many of these tests have less than this sensitivity, needs to be considered (34). Nonetheless, based on performance, applicability to office-based practice, and cost, rapid antibody testing is the optimal modality for the outpatient assessment of *H. pylori* in most patients with dyspepsia.

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