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Comparison of Commercial Serological Tests for Detection of *Helicobacter pylori* Antibodies

NICHOLAS J. TALLEY,[1,2]* LOUIS KOST,[1] ANNE HADDAD,[1]† AND ALAN R. ZINSMEISTER[2]

Gastroenterology Unit and Division of Gastroenterology and Internal Medicine[1] and Department of Health Sciences Research,[2] Mayo Clinic, Rochester, Minnesota 55905

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Serological testing for *Helicobacter pylori* infection is one of the diagnostic methods of choice. Various commercial kits that use different antigens have been developed, but data on their diagnostic accuracy and direct comparisons between the tests are lacking. We aimed to evaluate the sensitivity, specificity, and predictive value of three immunoglobulin G enzyme-linked immunosorbent assay kits: Pylori stat, Helico-G, and Premier *H. pylori*. Serum samples and gastric biopsy findings from 76 patients were evaluated. We found by using a priori cutoff values that the Pylori stat, Helico-G, and Premier kits had overall sensitivities of 96, 96, and 88%, respectively, and specificities of 94, 86, and 96%, respectively, compared with gastric biopsy findings. For 232 serum samples, the Pylori stat test and a previously validated standard serological assay on which the test was based disagreed in 3% of the cases, while for 76 samples that were tested, Helico-G and a previously validated standard assay on which it was based disagreed in 8% of the cases. The intra- and interassay precision of each of the test kits was high. We conclude that serology based on any of these commercial tests represents a reliable and valid method for the diagnosis of *H. pylori* whether or not highly purified antigens are used.

Serological tests for diagnosing the presence of *Helicobacter pylori* infection have been developed for research purposes and may in the future have applications in clinical practice (15, 18). Serological tests are useful in *H. pylori* infection because virtually all patients colonized with this organism undergo a local antibody response directed against antigens covering the surface and flagella of the organisms; in the majority of cases this antibody response is also detectable in the serum (3, 5, 8, 10, 12, 19, 24, 27–29). In population-based studies, serodiagnosis remains one of the methods of choice for detecting the prevalence of infection (1, 6). Moreover, serological testing may be useful for diagnostic screening and for the monitoring of treatment in some circumstances (9, 11, 22, 23, 26), although this remains to be carefully evaluated.

In view of the potential importance of *H. pylori* infection, commercial kits based on enzyme-linked immunosorbent assay (ELISA) methods have been developed. The ELISA technique is currently the method of choice because of its cost, simplicity, and ability to quantitatively determine the level of antibody (15, 18). We have previously reported that the ELISA immunoglobulin G (IgG) antibody test developed by Perez-Perez et al. has a sensitivity of 96% and a specificity of 94% (24) in our population. A commercial kit (Pylori stat; Biowhittaker, Walkersville, Md.) based on similar methods has subsequently been developed by these investigators and is available in the United States. We have also shown that an IgG ELISA developed by Newell et al. had a sensitivity and specificity of 93 and 96%, respectively, in our patients (24), and a commercial kit (Helico-G; Porton Cambridge) based on this method has also been developed in the United Kingdom (12). The Helico-G kit utilizes an antigen derived from whole extracts of *H. pylori* (a crude antigen) (12), while the Pylori stat kit uses a defined mixture of *H. pylori* proteins for the antigen (2). Furthermore, Evans and coworkers have developed an ELISA for anti-*H. pylori* antibody that detects serum IgG antibodies directed against the high-molecular-weight cell-associated proteins of *H. pylori*; they reported that this assay had a sensitivity and specificity of 99% (3). A commercial kit (Premier *H. pylori*) using this methodology is also now available in the United States.

However, before such kits can be applied in the research or clinical setting, it needs to be confirmed that the commercial methods are reliable and valid. Moreover, while it has been postulated that serological assays that make use of whole extracts of *H. pylori* antigens are likely to be less sensitive and specific because of shared antigens with other organisms (3), direct comparisons between different methods are generally lacking. Furthermore, very few data on the effect of repeated freezing and thawing of serum samples on the reliability of detection of antibody to *H. pylori* are available.

We therefore aimed to evaluate the sensitivity, specificity, and predictive value of three commercial kit methods (Pylori stat, Helico-G, and Premier *H. pylori*). In addition, we wished to test for interassay variation to determine whether

TABLE 1. Diagnostic value of commercial kits compared with gastric biopsy results (n = 76)

Test	Sensitivity (%)	Specificity (%)	Predictive value (%)		Accuracy (%)
			Positive	Negative	
Pylori stat	96.3	93.9	89.7	97.9	94.7
Helico-G	96.2	85.7	78.1	97.7	89.3
Premier *H. pylori*	88.5	95.9	92.0	94.0	93.3

* Corresponding author.
† Deceased.

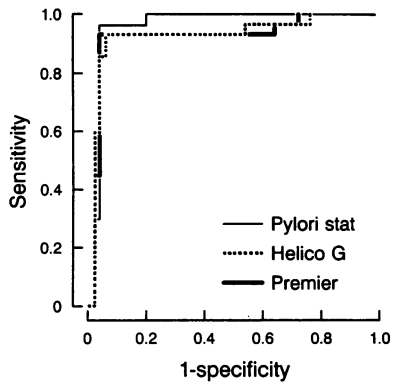

FIG. 1. ROC curves for the Pylori stat, Helico-G, and Premier tests compared with the gold standard (gastric biopsy material) for 76 patients.

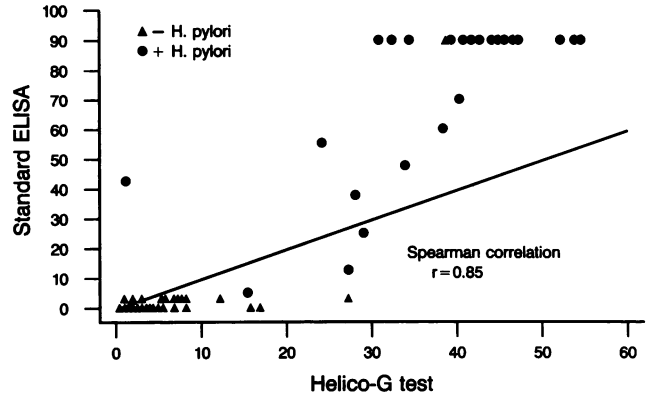

FIG. 3. Correlation between the standard ELISA (antigen 1 IgG) and the Helico-G test (in nuits per milliliter) for the 76 patients evaluated who also had gastric biopsy results. The Spearman rank correlation coefficient equals 0.85 ($P < 0.001$). The $y = x$ line is shown.

freeze-thawing affected the reliability of the results and also to test for intra-assay variation.

MATERIALS AND METHODS

Patient population. A total of 232 patients were evaluated; there were two distinct study populations. The first group comprised 76 patients who underwent upper-gastrointestinal endoscopy and biopsy. The validity of noncommercial serology testing compared with that of gastric biopsy findings in this group has been previously reported (24). The mean age was 50 years (range, 15 to 79 years), and 47% were males. All subjects had blood withdrawn for serological testing at the time of endoscopy, and the sera were stored in aliquots at −20°C.

Biopsies for the 76 patients were evaluated by a single histopathologist who was unaware of the *H. pylori* status of the subjects. Biopsies were stained with hematoxylin and eosin and with Giemsa or Warthin-Starry silver stain for evaluation. *H. pylori* was identified after examination of the slide sections (24). Cultures were also obtained for 27 of these 76 patients; the methodology has been previously described in detail (17, 24). *H. pylori* organisms were identified when highly curved gram-negative bacilli that were urease, oxidase, and catalase positive were found. Patients were classified as *H. pylori* positive if either histology or (when available) culture reflected the presence of the organisms; 36% were *H. pylori* positive. The patients were classified as *H. pylori* negative if histology (and culture when available) were negative (24). We have previously demonstrated a high degree of concordance between histology and culture for the diagnosis of *H. pylori* (24).

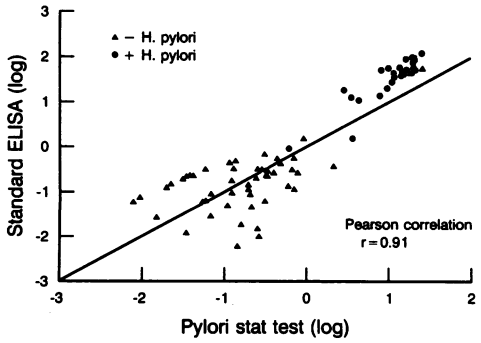

FIG. 2. Correlation between the standard ELISA (antigen A IgG) and Pylori stat test (log values) for the 76 patients evaluated who also had gastric biopsy results. The Pearson correlation coefficient equals 0.91 ($P < 0.001$). The $y = x$ line is shown.

The second group comprised 156 heterogeneous patients who had serum stored in the Mayo Clinic National Cancer Institute serum bank at −70°C. A total of 47 had benign esophageal diseases, 60 had benign musculoskeletal disorders, and 49 had benign lung diseases. The population characteristics and serological test results with one noncommercial ELISA method for this group have also been previously reported; the mean age was 62 years, 47% were males, and 44% were seropositive for *H. pylori* (25). Gastric biopsy material from these patients was not available in the serum bank, but this group was used to compare one of the commercial methods (Pylori stat) with the available reference ELISA and to further evaluate the agreement among all three commercial methods. All studies were approved by the Institutional Review Board of the Mayo Clinic.

Serological testing. The serum samples were all tested in the Mayo Clinic Gastroenterology Research Unit with the three commercial ELISA kits. The investigators coded and tested all samples independently and were unaware of the clinical or *H. pylori* status of the samples. To estimate the precision of the commercial tests, intra- and interassay variation was evaluated for four samples that were tested four to five times on three separate days with each of the commercial kits. To further evaluate whether freeze-thawing affected the results, the Pylori stat test was also repeated with 76 samples on three separate occasions over 3 months (day 1, day 15, and day 90).

The commercial ELISA results from the Pylori stat and Helico-G tests were each compared with those from previously validated noncommercial assays (24). The 232 samples were initially tested in M. Blaser's laboratory by using the method described by Perez-Perez et al. (19); all samples had been coded so that the investigators were unaware of the *H. pylori* status of the patients during the testing phase (24, 25). The antigen used was derived from a pool of sonicated *H. pylori* isolates from five patients representing a diverse range of antigens (and is referred to here as antigen A IgG) (19). The serum samples were diluted 1 in 800 for the IgG assay.

TABLE 2. Intra- and interassay precision of Pylori stat test[a]

Serum sample	Day 1			Day 2			Day 3			Interassay (n = 3)		
	Mean assay score	SD	% CV	Mean assay score	SD	% CV	Mean assay score	SD	% CV	Mean assay score	SD	% CV
1	4.85	0.28	5.69	4.33	0.03	0.80	4.61	0.20	4.43	4.60	0.26	5.74
2	3.41	0.17	5.07	3.33	0.07	2.21	3.24	0.12	3.75	3.32	0.09	2.63
3	1.56	0.07	4.13	1.67	0.10	5.87	1.51	0.12	8.13	1.59	0.09	5.77
4	0.23	0.00	0.35	0.23	0.00	0.35	0.22	0.00	0.37	0.23	0.01	2.55

[a] Cutoff score for seropositive result, 1.0; SD, standard deviation; CV, coefficient of variation. For each assay day, n = 4.

The second antibody used was peroxidase-conjugated goat anti-human IgG. The cutoff score for positivity was defined as an optical density ratio value greater than or equal to 1 in serum; this has been shown to be a highly sensitive and specific cutoff score (1, 19). These 232 samples were also independently tested at the Mayo Clinic by using the Pylori stat test. A total of 76 serum samples from all the patients who had undergone gastric biopsy were initially analyzed in D. Newell's laboratory by using methods previously described (11, 24); these data provided standard serology test results to compare with those of the Helico-G kit that was independently tested at the Mayo Clinic. The standard serology test was derived from acid-extractable surface antigens of NCTC 11638 (referred to here as antigen 1 IgG), and the cutoff score was based on previously published results (12, 24). No serum sample data were available for directly comparing the Premier kit with standard serology.

Statistical analysis. Sensitivity, specificity, and predictive values were calculated for each commercial kit by using the gastric biopsy results as the "gold standard" (4). The cutoff scores for a positive result were based on the recommended values provided by the manufacturers. Receiver operator characteristic (ROC) curves based on separate logistic regression models with age, gender, and each of the assays were constructed to summarize sensitivity and specificity estimates. The mean, standard deviation, and coefficient of variation were calculated on separate occasions for four samples with four to five replicates, performed on three consecutive days, to evaluate the intra- and interassay precision of the commercial tests.

RESULTS

The diagnostic value of each commercial test compared with gastric biopsy findings is presented in Table 1. Compared with gastric biopsy (the gold standard), the Pylori stat test had an accuracy of 95%, while Helico-G had an accuracy of 89% and Premier had an accuracy of 93%. There was excellent discrimination of *H. pylori* status on the basis of the ROC curves for the Pylori stat, Helico-G, and Premier tests, compared with gastric biopsy findings adjusted for age and gender (Fig. 1).

The Pylori stat test and the standard ELISA (antigen A IgG) disagreed in only eight cases (3.4%) in the 232 patients tested (76 who also had gastric biopsy data and 156 who had not undergone gastric biopsy). The correlation between the log values for the two tests when all 232 patients were compared was 0.86 ($P < 0.001$), while for the 76 patients with gastric biopsy data, the correlation was 0.91 ($P < 0.001$) (Fig. 2).

For the 76 serum samples from individual patients that were tested on three separate occasions 3 months apart to assess whether long-term freeze-thawing affected the results, there was disagreement between one of the Pylori stat values and the standard serology test (antigen A IgG) in four cases (5.3%). For one patient, the standard serology test was positive while the Pylori stat test was positive on one occasion but was negative the other two times. For two patients, the standard serology test was negative while the Pylori stat test was positive once but negative the other two times. For the fourth patient, the standard serology test was negative while the Pylori stat test was positive on all three occasions.

The Helico-G test and the standard ELISA (antigen 1 IgG) for the 76 patients tested disagreed in six cases (7.9%). The correlation coefficient for the two tests was 0.85 ($P < 0.001$) (Fig. 3). For the 231 patients who had all three commercial kit tests performed (in one case there was not enough serum remaining), the Pylori stat test and the Premier test disagreed for only 4.8% of the samples, while the Pylori stat test and the Helico-G test disagreed for 8.7% of the samples.

The intra- and interassay testing revealed minimal variation for each of the commercial kits (Tables 2 to 4).

DISCUSSION

This study suggests that the Pylori stat, Helico-G, and Premier tests for detecting the presence of *H. pylori* antibodies are all highly accurate methods and that such kits can be used for research and clinical purposes. A useful way to

TABLE 3. Intra- and interassay precision of Helico-G test[a]

Serum sample	Day 1			Day 2			Day 3			Interassay (n = 3)		
	Mean assay score	SD	% CV	Mean assay score	SD	% CV	Mean assay score	SD	% CV	Mean assay score	SD	% CV
1	48.50	0.84	1.74	54.41	0.63	1.15	56.15	1.82	3.24	53.02	4.01	7.55
2	46.26	1.36	2.95	51.05	0.65	1.27	55.35	0.89	1.61	50.89	4.54	8.93
3	23.36	1.32	5.64	22.59	1.74	7.70	25.57	1.49	5.81	23.84	1.54	6.47
4	1.91	0.14	7.45	3.41	0.68	20.0	2.43	0.19	7.95	2.58	0.76	29.40

[a] Cutoff score for seropositive result, 10.0; SD, standard deviation; CV, coefficient of variation. For each assay day, n = 5.

TABLE 4. Intra- and interassay precision of Premier *H. pylori* test[a]

Serum sample	Day 1			Day 2			Day 3			Interassay (n = 3)		
	Mean assay score	SD	% CV	Mean assay score	SD	% CV	Mean assay score	SD	% CV	Mean assay score	SD	% CV
1	7.63	0.48	6.26	8.70	0.34	3.92	10.26	0.32	3.08	8.86	1.32	14.89
2	6.96	0.14	1.96	8.19	0.15	1.87	8.25	0.81	9.84	7.80	0.73	9.35
3	2.05	0.05	2.27	2.47	0.17	6.76	2.25	0.19	8.29	2.26	0.21	9.16
4	0.42	0.01	2.52	0.39	0.01	3.57	0.36	0.01	3.61	0.39	0.03	7.69

[a] Cutoff score for seropositive result, 2.2; SD, standard deviation; CV, coefficient of variation. For each assay day, n = 4.

express the relationship between the sensitivity and the specificity of a test is to construct a ROC curve (24). In using such a curve, it can be seen that tests that discriminate the best are placed towards the upper left corner of the curve. Moreover, the overall accuracy can be described by the area under the curve. The ROC curves indicate that the commercial kit serological tests are accurate over a range of cutoff points. Moreover, repeated freeze-thawing over a 3-month period did not seriously affect the reliability of the Pylori stat test.

The practical applications of serodiagnostic testing remain to be carefully defined. It is recognized that the prevalence of *H. pylori* infection increases with age in asymptomatic persons in developed countries, although this tends to plateau at around the age of 60 years and is related to socioeconomic status and ethnicity (1, 6). The high prevalence of *H. pylori* infection in otherwise healthy persons confounds the interpretation of serological testing in clinical practice. We also found that, depending on the test kit used, 3 to 9% of patients appear to have false-positive ELISA results compared with gastric biopsy findings, and others have reported similar results (7, 13). The reasons for this are uncertain. Bacteria with antigens that cross-react with *H. pylori* might produce antibodies, such as the urease of *Gastrospirillium hominis*, but other studies have shown that the standard serological ELISA developed by Perez-Perez et al. had little or no cross-reactivity with *Campylobacter jejuni* or *Campylobacter fetus* (19, 20), and the test based on high-molecular-weight cell-associated proteins should also avoid this problem (3). It is possible that biopsy results can be negative even though patients have had a past infection because patients return slowly to seronegativity (11, 26). Perhaps most important, using biopsy material as the gold standard may be inadequate, as infection is usually patchy and therefore biopsies may sometimes fail to identify truly positive patients. Indeed, there was little disagreement between the ELISAs evaluated here, consistent with other data (24). Thus, use of ELISA may be a preferable gold standard for documenting the presence of current or past infection. Our results also indicate that, depending on the test kit, only about 1 to 5% of patients appear to have false-negative serology results when gastric biopsy is used as the gold standard. It is possible that these patients do not produce a circulating antibody response which is detectable with complex antigens such as are used by the commercial kits. Interestingly, the use of more-purified antigens did not significantly enhance the specificity in this study as might be expected (2, 14). It is also possible that false-negative results may occur occasionally for patients who are in the acute phase of infection before an IgG response has developed (15, 18).

Whether patients who have dyspepsia should be screened in clinical practice for the presence of *H. pylori* infection with commercial kits such as the ones tested here remains controversial. It has been proposed that patients with dyspepsia could be screened for *H. pylori* status before endoscopy is recommended (22, 23). As *H. pylori* occurs in over 95% of patients with chronic duodenal ulceration and in up to 80% of patients with chronic gastric ulceration (16, 21), it has been proposed that such an approach would help reduce the need for endoscopy as well as cost. If such a policy were adopted, only seropositive patients would undergo endoscopy. A recent study suggested using endoscopy for only those patients who are seropositive, are over 45 years of age, or are taking nonsteroidal anti-inflammatory drugs would avoid up to 23% of endoscopies while as few as 3% of ulcers would be missed (23). However, further large prospective clinical studies are needed before such an approach can be widely accepted. Indeed, for such a strategy to work, it is required that some clear management plan for *H. pylori*-negative patients be available, as otherwise many negative patients would be investigated anyway.

It has also been proposed that serological tests could be used for monitoring treatment in some circumstances. It is recognized that levels of antibodies to *H. pylori* remain elevated for long periods even after successful eradication of the infection, but usually there is a trend for the antibody level to slowly decrease; this fall can be detected by 1 month after successful treatment but may be more reliably detected at 3 months (11). It has been suggested that the fall of specific-IgG levels over a 3-month period from the start of the treatment is a good predictor of successful treatment (9, 11, 26), but this remains to be confirmed.

In conclusion, we have shown that commercial ELISA kits that measure the level of IgG antibody to *H. pylori* are accurate and perform equally well whether a more purified antigen is used or not. The clinical application of serological testing using commercial kits remains to be delineated; before such testing can be recommended for screening dyspeptic patients in clinical practice, further prospective studies will need to show that such an evaluation is cost-effective.

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