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Realities of Diagnosing *Helicobacter pylori* Infection in Clinical Practice: A Case for Non-invasive Indirect Methodologies

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Background: The current, arbitrarily defined gold standard for the diagnosis of *H. pylori* infection requires histologic examination of two specially stained antral biopsy specimens. However, routine histology is potentially limited in general clinical practice by both sampling and observer error. The current study was designed to examine the diagnostic performance of invasive and non-invasive *H. pylori* detection methods that would likely be available in general clinical practice.

Methods: The diagnostic performance of rotating clinical pathology faculty using thiazine staining was compared with that of an expert gastrointestinal pathologist in 38 patients. *In situ* hybridization stains of adjacent biopsy cuts were also examined by the expert pathologist for further comparison. Receiver operator characteristic (ROC) analysis was performed to evaluate whether the diagnostic performance of the expert pathologist differed depending upon the histologic method employed. A similar analysis was made to evaluate the diagnostic performance of pathology trainees relative to the expert. In the absence of an established invasive gold standard, non-invasive testing methods (rapid serum antibodies, formal Elisa antibodies and carbon-14 urea breath testing) were evaluated in 74 patients by comparison with a gold standard defined using a combination of diagnostic tests.

Results: Using either rapid urease testing of biopsy specimens or urea breath testing as the gold standard for comparison, the diagnostic performance of the rotating clinical pathology faculty was inferior to that of the expert gastrointestinal pathologist especially with regard to specificity (e.g., 69 percent for the former versus 88 percent, with the latter relative to rapid urease testing). Although interpretation of *in situ* hybridization staining by the expert appeared to have an even higher specificity, ROC analysis failed to show a difference. The mean ROC areas for thiazine and *in situ* hybridization staining for trainee pathologists relative to the expert were 0.88 and 0.94, respectively. In untreated patients, urea breath testing had a sensitivity and specificity of 100 percent as compared with thiazine staining with a sensitivity of 83 percent and a specificity of 97 percent. Post-therapy, breath testing had a sensitivity of 100 percent but a specificity of only 86 percent as compared with invasive testing with a sensitivity and specificity of 100 percent. Rapid serum antibody testing and formal Elisa antibody testing agreed in 93 percent of cases (Kappa 0.78) with the rapid test being correct in three of the four disagreements

Conclusions: The current study illustrates a number of realities regarding *H. pylori* diagnosis. There is no diagnostic gold standard in general clinical practice. Accurate interpretation of specially stained slides is a learned activity with a tendency towards overdiagnosis early on. Urea breath testing is likely to be the

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[b]*Abbreviations:* PCR, polymerase chain reaction; ROC, receiver operator characteristic; DPM, disintergrations per minute.

diagnostic method of choice for untreated patients in general clinical practice although antibody testing is almost as accurate. Rapid antibody tests are at least as accurate as formal Elisa antibody tests. Urea breath testing is useful for confirming cure after therapy, but false-positive results may occur in some patients.

INTRODUCTION

The current arbitrarily defined gold standard for the diagnosis of *Helicobacter pylori* infection consists of histologic examination of two specially-stained antral biopsy specimens [1, 2]. Studies with the Giemsa, Warthin Starry or Genta stains have revealed an accuracy that may be as high as 98 percent in expert hands [2, 3]. However, histology may be less accurate in general clinical practice for a variety of reasons. Sampling error is commonly cited as a potential cause of inaccurate histological diagnosis so that certain authorities have recommended that additional specimens be taken from the lesser curve and/or the gastric body to increase the diagnostic yield [4]. Additional biopsy specimens may be especially important in patients taking antisecretory therapy. Histology is also potentially limited in clinical practice by inter- and intra-observer variability depending on the expertise of the examining pathologist [5, 6]. Moreover, none of the currently accepted special stains used to identify *H. pylori* infection are specific for the organism so that diagnosis is made upon morphologic characteristics alone [1, 2]. The most specific method for diagnosing *H. pylori* infection is culture of biopsy specimens, but this method is highly insensitive because of the fastidiousness of the organism [1, 2]. Consequently, routine culture cannot be considered an acceptable gold standard for general clinical practice. Other specific invasive methodologies such as polymerase chain reaction (PCR)[b] or immunohistochemistry are also limited in clinical practice because of the expertise required to perform these studies [7, 8].

A variety of highly accurate, non-invasive diagnostic tests for *H. pylori* infection have recently become available [1, 2]. These include rapid office-based antibody tests, formal Elisa antibody testing, and urea breath testing (both carbon 13 and carbon 14 tests) [1, 2, 6, 9-12]. In the absence of a true gold standard for diagnosis, these newer methodologies have been compared against a battery of other methods to demonstrate their accuracy [11, 12]. From a statistical point of view, this approach is limited by the inclusion of the test method under consideration in the arbitrarily defined gold standard itself, so that it can be argued that the method under consideration is actually being compared with itself. An alternative approach is to compare the test methodology with a gold standard that is defined by concordance of two or more other methodologies (for example, histology, rapid urease testing or breath testing) [9]. An obvious limitation of this approach is that patients with discordant gold standard component test results have to be excluded from analysis. Little is known about the accuracy of these newer, non-invasive methodologies in general clinical practice since they too may be limited by interpretation bias (for example, where to define the transition from positive to negative in terms of the magnitude of the test response).

The aims of the current study were to determine the accuracy of invasive and non-invasive *H. pylori* detection methods in general clinical practice. We chose to examine methods that would likely be available in most diagnostic centers and that would require minimal expertise for accurate interpretation of results.

METHODS

General

All patients presenting to the Gastroenterology Division of the University of Pennsylvania for upper endoscopy were invited to participate in the current study. Patients who were pregnant, breast feeding, had used antibiotics or bismuth preparations within four weeks or proton pump inhibitors within one week, or had previously undergone gastric surgery were excluded. Patients who had received specific anti-*H. pylori* therapy in the past were included providing that this treatment had been completed at least four weeks prior to testing. Three antral biopsy specimens (within 3 cm of the pylorus) were taken in all patients at the time of their endoscopy. Two specimens were submitted for histological analysis, and one was used for rapid urease testing (CLO test, Delta West, Bentley, Australia). To determine the intra-observer reproducibility of histology for the diagnosis of *H. pylori* infection, the expert gastrointestinal pathologist read 16 randomly selected antral biopsy slides on three separate days over a four-week period in a different random order at each session. There was disagreement as to the presence or absence of *H. pylori* organisms in two of 16 cases. In each case, the slides were read as negative twice but positive once with an organism burden of one on a scale of 0 to three on both occasions. There was complete agreement amongst all three readings in the remaining 14 cases. The intra-class correlation coefficient was 0.82 with a P value for a difference between replicates of 0.62 [6]. All studies had the approval of the committee on studies involving humans and the radiation safety committee of the University of Pennsylvania and were only performed after the patients provided informed consent.

Invasive testing

In order to assess the diagnostic performance of standard histological methods for *H. pylori* diagnosis in general clinical practice, we compared the sensitivity and specificity of thiazine staining for *H. pylori* diagnosis (relative to rapid urease testing and urea breath testing) as assessed by rotating clinical pathology faculty with the results obtained by the expert gastrointestinal pathologist in 38 Bouin's-fixed paraffin-imbedded antral biopsies. To further evaluate the diagnostic performance of the expert gastrointestinal pathologist using standard histology, the latter's sensitivity and specificity with thiazine staining were compared with *in situ* hybridization staining of adjacent cuts of all 38 biopsy specimens [13]. *In situ* hybridization was performed using a 22 base biotin-labeled oligonucleotide probe complementary to a portion of the *H. pylori* 16 s ribosomal RNA at a final concentration of 1 μg/ml using manual capillary action technology on the Microprobe Staining System (Fisher Scientific, Boston, Massachussetts) with modifications as previously described. Receiver operator characteristic (ROC) analysis of thiazine staining and *in situ* hybridization for *H. pylori* detection relative to rapid urease and urea breath testing was determined for the experienced gastrointestinal pathologist for a more detailed comparison of standard histological methods with our *in situ* hybridization technique for *H. pylori* detection [14]. ROC analysis is independent of disease prevalence making it possible to determine sensitivity and specificity over all "cut-off" points. In the absence of a "true" gold standard for *H. pylori* diagnosis, we chose to keep the rapid urease and urea breath tests as invariant tests for these comparisons since it is generally easy to distinguish positive from negative tests with these methods. This in no way implies that either the rapid urease or urea breath test is the "true" gold standard for diagnosis. Instead, one test must be kept constant such that relative comparisons can be made. ROC analysis was also performed on five resident pathologists in training relative to the expert gastrointestinal pathologist in order to determine how much experience was required for accurate *H.*

pylori detection. For each ROC analysis, the observers graded on a scale of 1 through 5 their surety of the presence of *H. pylori* organisms (one being definitely not present, five being definitely present). The area under the ROC curve was calculated for each analysis. This value is a measure of diagnostic performance with a value of 0.5 representing chance and 1.0 representing perfect test performance [14]. The grading of thiazine and *in situ* stains were done on separate occasions.

Non-invasive testing

The diagnostic performance of non-invasive testing methodologies was assessed first by defining the gold standard using a combination of results from all tests in 74 study subjects in a manner similar to those described by Cutler [11] and the Division of Anti-infective Drug Products Center for Drug Evaluation and Research of the US Food and Drug Administration (Dr. A. Hopkins, personal communication). These tests included evaluation of two antral biopsy specimens stained with thiazine for the presence of organisms, two antral biopsies stained with hematoxyllin and eosin for the presence of chronic inflammation on routine histology [12] and one antral biopsy specimen, which was used for rapid urease testing. Histological interpretation was performed by the same expert gastrointestinal pathologist who performed the invasive testing studies (see above). In addition, all patients underwent urea breath testing after ingestion of a capsule containing 1 μCi (37 ßEq) carbon 14 urea (Trimed specialties, Charlottesville, Virginia) with subsequent collection of breath samples at five-minute intervals for 30 minutes [6]. Radioactivity of exhaled breath was measured in a scintillation counter in auto-DPM mode with a calculated efficiency of greater than 98 percent and expressed as disintegrations per minute (DPM). A positive test with breath testing was defined as an increase over baseline of more than 100 DPMs. Antibody testing was performed on all patients using two methodologies, the Flexure HP rapid serum test (SmithKline Diagnostics, San Jose, California), which was performed in the office, and the HM CAP Elisa antibody test (Enteric Products, Inc., Stony Brook, New York), which was performed on serum that was mailed to a reference laboratory. For the former test, supernatant was removed after centrifugation at 3200 RPM for 20 minutes and placed on Flexure HP cards [15]. A positive test result was defined as the appearance of a pink colored test line in addition to a visible control line. The latter test was performed after additional serum samples were coded and transferred to SmithKline Diagnostics for quantitative Elisa assay using the HM CAP antigen [16]. Elisa values greater than 2.2 were considered positive for *H. pylori* infection.

Using a combination of these testing methods, a pre-therapy true-positive diagnosis was defined as the presence of four or more positive tests while a true-negative required one or none positive. Patients with either two or three positive tests were considered non-evaluable and were excluded from analysis. For post-therapy diagnosis, the second antibody test was removed from the above scheme, and a positive diagnosis post-therapy required three or more of the four remaining tests to be positive. A negative diagnosis required one or none of the four tests to be positive, and patients with two positive tests were excluded from analysis. Statistical analysis were performed using Statistica 4.0 (Statsoft Inc., Tulsa, Oklahoma). Estimates of sensitivity and specificity were computed in the usual manner, and comparisons between the two serological tests were performed using percentage agreement and the chance adjusted agreement statistic, Kappa.

RESULTS

Rapid urease testing and urea breath testing detected *H. pylori* infection in 15/38 (39 percent) and 19/38 patients (50 percent), respectively. Using the rapid urease test as the

Table 1. Sensitivity and specificity of histology for *H. pylori* diagnosis (n = 38).

	Relative to rapid urease test		Relative to urea breath test	
	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)
Routine pathology (Thiazine stain)	87	69	75	68
GI pathologist (Thiazine stain)	87	88	75	91
GI pathologist (*In situ* hybridization)	80	100	60	100

gold standard, thiazine staining of antral biopsy specimens had a sensitivity of 87 percent and a specificity of 69 percent for *H. pylori* detection when evaluated by the rotating clinical pathology faculty (Table 1). When the same slides were examined by the expert gastrointestinal pathologist, the sensitivity of thiazine was unchanged but the specificity increased to 88 percent. The sensitivity and specificity of *in situ* hybridization in the expert pathologist's hands was 80 percent and 100 percent, respectively, as compared with the rapid urease test results (Table 1). Using urea breath testing as the gold standard, a similar trend occurred, although the sensitivity of histology was somewhat lower for all calculations because urea breath testing identified more patients with *H. pylori* gastritis than any other modality.

In order to determine whether the relative diagnostic performance of thiazine and *in situ* hybridization staining for *H. pylori* diagnosis was truly different in expert gastrointestinal pathologists' hands, ROC analysis was performed. ROC values did not differ significantly between the two histological methods indicating equivalent test performance (Table 2).

The relative diagnostic performance of thiazine staining and *in situ* hybridization for five pathologists in training, with the expert gastrointestinal pathologist serving as the gold standard, is shown in Table 3. The mean ROC areas for thiazine staining and *in situ* hybridization were 0.88 and 0.94, respectively. In addition, when asked which of the two diagnostic methods was easier to interpret, four of the five trainees felt the *in situ* hybridization stain to be superior, and the one trainee who felt that the thiazine stain was superior actually performed better relative to the expert gastrointestinal pathologist with the *in situ* stain (data not shown).

Table 2. Relative diagnostic performance of thiazine and in situ hybridization staining for *H. pylori* diagnosis by the expert gastrointestinal pathologist (n = 38).

	Relative to rapid urease test (ROC[1] values)	Relative to urea breath test (ROC[1] values)
Thiazine stain	0.86	0.74
In situ hybridization	0.87	0.79

[1] ROC = receiver operator characteristic

Table 3. Relative diagnostic performance of two histological methods for *H. pylori* diagnosis by five pathologists in training (n = 38).

Observer	Thiazine stain relative to expert GI pathologist (ROC[1] values)	*In situ* hybridization relative to expert GI pathologist (ROC[1] values)
1	0.86	0.89
2	0.91	1.0
3	0.9	0.97
4	0.93	0.99
5	0.8	0.85
Average	0.88	0.94

[1] ROC = receiver operator characteristic.

Table 4. Sensitivity and specificity of various testing methods *H. pylori* diagnosis (n = 74).[1]

Pre-therapy (n = 54)	Thiazine stain	Rapid urease test	Chronic gastritis	Urea breath test	Elisa antibody test	Rapid serum antibody test
Sensitivity (%)	83	91	91	100	91	91
Specificity (%)	97	100	100	100	94	100
Post-therapy (n = 15)						
Sensitivity (%)	100	100	100	100	N/A[2]	N/A[2]
Specificity (%)	100	100	93	86	N/A[2]	N/A[2]

[1] The gold standard for diagnosis is defined according to the scheme outlined in Methods.
[2] N/A, not applicable.

Table 5. Analysis of discordant antibody tests.

Patient number	Rapid serum antibody test	Elisa[1] value	Rapid urease test	Thiazine stain	Urea breath test	Correct test
7006	Positive	1.6	Positive	Positive	Positive	Rapid antibody
7026	Negative	2.5	Negative	Negative	Negative	Rapid antibody
7029	Negative	2.5	Positive	Positive	Positive	Elisa test
7051	Negative	2.5	Negative	Negative	Negative	Rapid antibody

[1] A value greater than 2.2 is considered positive.

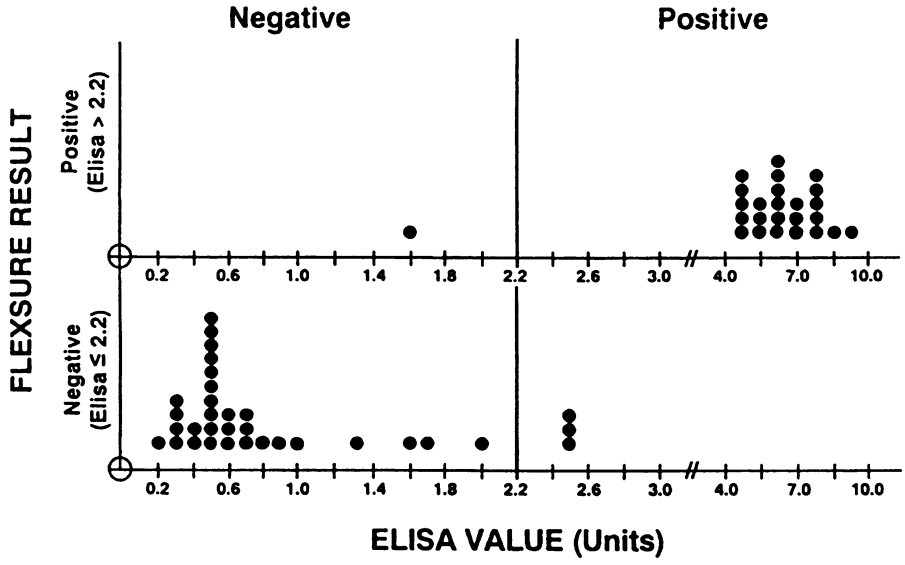

Figure 1. Correlation between office-based rapid serum antibody testing and laboratory-based formal Elisa antibody testing for *H. pylori* diagnosis in 58 patients not previously treated for *H. pylori* infection. Elisa test results are shown along the x-axis (an Elisa value of > 2. 2 units corresponds with a positive result). Rapid serum antibody test results are shown along the y-axis. There was a 93 percent agreement between the two *H. pylori* antibody test methods (Kappa = 0.78).

Of 74 patients evaluated with all non-invasive diagnostic tests, five were excluded because they had indeterminate gold standard results. Fifty-four of the remaining patients had not previously been treated for *H. pylori* infection, and 15 were post therapy. Twenty-three of the 54 untreated patients were *H. pylori* positive by the gold standard, and one of the 15 post-therapy patients was still infected. The sensitivity and specificity of each diagnostic test in the diagnosis of *H. pylori* infection both pre- and post-therapy are shown in Table 4. In untreated patients, invasive thiazine staining (the currently accepted gold standard for diagnosis) had a sensitivity of 83 percent and a specificity of 97 percent. By comparison, the sensitivity and specificity of urea breath testing in this population was 100 percent. In evaluating *H. pylori* status post-therapy, the sensitivity and specificity of invasive testing with thiazine (for organisms) or hematoxyllin and eosin staining (for chronic inflammation), or rapid urease testing (for urease detection) was 100 percent. Urea breath testing had a sensitivity of 100 percent, but its specificity was only 86 percent.

Figure 1 illustrates the agreement between the two serologic tests in patients not previously treated for *H. pylori* infection, including four additional patients with indeterminate gold standard results. Test results agreed in 54 of 58 patients (93 percent) with a Kappa statistic of 0.78. Test results disagreed in four patients (7 percent), three with negative rapid antibody results and positive Elisa tests and one with a positive rapid antibody test and a negative Elisa test. The discordant antibody test results are shown in more detail in Table 5. In three of the four disagreements, the rapid antibody test was the correct test when compared with other diagnostic modalities including rapid urease testing, thiazine testing and urea breath testing.

DISCUSSION

The current study makes clear a number of realities regarding *H. pylori* diagnosis. First, there is no true diagnostic gold standard in general clinical practice. This is brought out by the fact that the correlation between standard thiazine staining for *H. pylori* diagnosis and other non-invasive diagnostic methods (urea breath testing or rapid urease testing) is closer when interpreted by an expert gastrointestinal pathologist as opposed to rotating pathology faculty in a large teaching hospital. The major shortcoming appears to be one of overdiagnosis since specificity is unacceptably low when slides are interpreted by rotating pathology faculty. In keeping with our previous report [6], the initial specificity of *in situ* hybridization relative to thiazine staining suggested that the tendency for over-diagnosis exists with expert pathologists as well. However, the current ROC analysis suggested that this was not the case.

The ROC analyses of the pathologists in training suggest that the learning curve for diagnosing *H. pylori* infection both by thiazine stain and by *in situ* hybridization is short. ROC values for the trainees were all acceptable, but their diagnostic performance was more favorable with the *in situ* method (area under the ROC curve of 0.94) than with standard thiazine staining (0. 88). We interpret this data to suggest that a trained gastrointestinal pathologist accurately diagnoses *H. pylori* infection using standard special stains most of the time. In comparison, trainee pathologists are less accurate with standard stains, but their accuracy approaches that of an expert if specialized methods such as *in situ* hybridization are utilized. However, such methods are not routinely available and are, thus, clearly beyond the scope of routine clinical practice. The results of the current study do suggest that *in situ* hybridization may be useful for training pathologists in interpreting *H. pylori* slides. Thus, the second reality of the current study regarding *H. pylori* diagnosis is that accurate interpretation of thiazine-stained slides is a learned activity.

The current study did not directly address the potential effect of sampling error on invasive diagnostic results. Other investigators have suggested that this is a real consideration affecting diagnostic yield [4]. In this regard, it is interesting to note that in the current study, urea breath testing (which samples a much larger area of the gastric mucosa than any of the biopsy-based tests) detected more potential infections than either rapid urease testing or histology (thiazine staining and *in situ* hybridization). Thus, sampling error may be a factor affecting test accuracy with diagnostic methods that depend upon small pinch biopsies of the gastric mucosa.

Given the limitations of invasive testing in clinical practice, we chose to evaluate the diagnostic performance of non-invasive diagnostic methods in previously untreated and post therapy patients as possible clinical practice alternatives. The gold standard for comparison in these studies was devised using a combination of tests in order to limit the likelihood that the test under consideration appeared less accurate than it actually was because of a gold standard inaccuracy. The limitations of this approach have been described above. This methodology was chosen over a concordance method using invasive testing because we feel that invasive testing has limitations even in the best hands. For diagnosis in patients not previously treated for *H. pylori* infection, urea breath testing appears to be the most accurate (i.e., the gold standard for clinical practice). While the current study addresses only carbon 14 urea breath testing, it is likely that results with carbon 13 urea breath testing would be similar. Previous studies on the diagnostic accuracy of urea breath testing have shown it to be an excellent test [6, 9, 11]. For post-therapy *H. pylori* diagnosis, the current data would suggest that invasive testing is most accurate. However, in evaluating patients post-therapy in general clinical practice, it is most important that the test under consideration always correctly identify non-cured patients. Urea breath testing was positive in all the non-cured patients in the current study. Its apparent shortcoming, in

keeping with other investigators [11], was that it was occasionally positive in post-therapy patients who appeared to be cured by all other testing methods. This data could also be interpreted to suggest that urea breath testing is the most sensitive of all methods for determining failure to eradicate an infection. In order to determine which of these two possibilities is true, patients with apparent false-positive urea breath tests will need to be re-evaluated on a second occasion some time later to see whether the breath test becomes negative (i.e., a false-positive initial breath test) or the other tests became positive (i.e., a true-positive initial breath test). Further studies will be required to address this issue. Thus the third reality of the current study regarding *H. pylori* diagnosis is that urea breath testing is likely to be the diagnostic method of choice in general clinical practice for previously untreated patients. For post-therapy confirmation of *H. pylori* eradication, urea breath testing is accurate, although there is a question regarding false-positive testing in some patients.

In the absence of urea breath testing, the next best diagnostic modalities in untreated patients appear to be rapid antibody testing or rapid urease testing. Both these modalities have specificities of 100 percent and sensitivities of 91 percent, but the rapid antibody test is likely to be more useful in routine clinical practice because it is non-invasive and less costly. Rapid antibody testing is at least as accurate as formal Elisa testing [10, 17]. In the current study, rapid antibody testing had similar sensitivity (91 percent) but a better specificity (100 percent versus 94 percent). In three of the four cases in which there was discordance between rapid antibody testing and formal Elisa testing, the rapid test was the correct test. Thus, the fourth diagnostic reality of the current study is the fact that rapid antibody testing is at least as accurate as formal Elisa testing and almost as accurate as breath testing. There is no longer a need to send blood to a reference laboratory in order to test for *H. pylori* antibodies, and antibody testing should remain the screening method of choice for *H. pylori* diagnosis because of ease of performance and low cost. Whole blood antibody testing is now being developed for routine office use, and it is likely that whole blood antibody testing will ultimately replace serum antibody testing because of ease of use, providing that it can be shown to be as accurate [18].

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