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Accuracy and Economics of *Helicobacter pylori* Diagnosis

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Many diagnostic tests are available to establish *Helicobacter pylori* infection status. Most of the tests are accurate though none works perfectly, and no gold standard for diagnosis exists. Newly developed serum immunoassay kits can substitute for laboratory-based enzyme-linked immunosorbent assays, but whole blood immunoassays do not yet demonstrate adequate performance characteristics.

Serologic diagnosis of *H. pylori* remains the most cost-effective option and should be utilized to establish initial infection in the majority of cases. If rapid urease testing is performed at endoscopy, negative results can be confirmed with a subsequent serologic test in those patients with a high probability of infection. Obtaining additional gastric tissue at endoscopy to evaluate for bacterial infection is reasonable if specimens are being taken for a mucosal defect. Confirmation of bacterial eradication cannot be justified for all post-treatment patients at present due to the expense. It is important to test for cure in those patients with complicated ulcer disease and those with recurrent symptoms after therapy.

Multiple diagnostic methods have been developed for the identification of *Helicobacter pylori* infection. Such tests are generally divided into those that require endoscopy, called invasive tests, such as rapid urease tests or histology, and those that do not require endoscopy, or noninvasive tests, such as serology or urea breath tests. In 1995, we evaluated all of the diagnostic modalities then available to us in a cohort of 268 previously untreated Detroit patients undergoing esophagogastroduodenoscopy [1]. For this study, *H. pylori* infection was defined by the majority of test results for each patient rather than by a predefined gold standard. We found that all of the diagnostic tests worked but none worked perfectly (Table 1). There was complete concordance among all the results in 134 of 268 patients (50 percent) and near complete agreement, that is at most one test in variance, in 81 percent. No single test was found to be the statistically superior in the identification of bacterial infection. That is, endoscopic rapid urease tests and antral histology with staining were as effective in determining *H. pylori* status as the noninvasive tests of serology and urea breath test. Endoscopic diagnosis of infection could thus be supplanted by office-based tests.

Culture of gastric tissue specimens was not performed as part of the above study, though such testing is not required to diagnose *H. pylori*, and culture has not gained broad acceptance in the United States. Immunoassay detection of anti-*H. pylori* antibodies utilizing either separated serum or whole blood was also not available and hence not included in the aforementioned study. Access to office-based serologic tests has improved, and utilization has increased in the last year. Serum immunoassay tests are comparable to enzyme-linked immunosorbent assays (ELISA)[b] in performance and can readily substitute for the laboratory-based assay [2, 3]. Whole blood immunoassays do not function

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[b]*Abbreviations:* ELISA, enzyme linked immunosorbent assays.

Table 1. Accuracy of diagnostic tests for *H. pylori* performed in a cohort of 268 patients undergoing esophagogastroduodenoscopy.

Diagnostic test	Sensitivity (percent)	Specificity (percent)
Invasive		
Histology with staining	93	99
Rapid urease test	90	100
Noninvasive		
[^{13}C]urea breath test	90	96
IgG serology	91	92

with the same accuracy as the serum tests and should not be utilized until improvements in clinical results are demonstrated (Table 2).

There has been an decline in the specificity of all serologic tests in last two to three years. While the specificity for ELISA among a group of patients in Detroit in 1992-1993 was 92 percent [1], analysis of a similar Detroit cohort in 1994-1995 utilizing a commercial serum immunoassay kit yielded a specificity of 77 percent [4]. A multicenter center study from five centers in the U.S. and Canada presented in 1996 demonstrated a similar decline in serologic test specificity [2]. Identical results have been reported from other U.S. sites using various antibody detection kits [5]. The explanation for the decline in specificity of serologic tests is probably related to unintentional *H. pylori* eradication with clarithromycin. It is unlikely that there has been a change in the antigenic profile of the bacterium. Additionally, the consistent change in specificity across study centers makes under-diagnosis of the infection a less plausible explanation. It is most probable that utilization of clarithromycin for unrelated non-gastrointestinal infections has resulted in unintended bacterial eradication in a significant proportion of patients. Monotherapy with clarithromycin has been shown to cure *H. pylori* infection in up to 30 to 40 percent of infected patients [6].

The accuracy of diagnostic tests for *H. pylori* following therapy should be similar to pretest values, assuming that sufficient time has passed from the eradication attempt to the follow-up evaluation. Qualitative immunoassays remain positive following cure of the bacterial infection and should not be used to confirm eradication. Urea breath tests are the test of choice to confirm *H. pylori* cure. In an evaluation of the utility of the [^{13}C]urea breath test to establish eradication of bacterial infection, Slomianski et al. calculated the sensitivity and specificity at 88 percent and 94 percent, respectively [7]. Similar results were obtained in a study from Baylor [8]. The [^{13}C]urea breath test was recently approved by the U.S. Food and Drug Administration. Its broad implementation has been delayed by

Table 2. Accuracy of office-based antibody for *H. pylori* against antral histology evaluated in five centers across North America [2].

Antibody test	Sensitivity (percent)	Specificity (percent)
Serum ELISA	94	78
Serum immunoassay	89	74
Venipuncture whole blood immunoassay	90	67
Fingerstick whole blood immunoassay	83	75

issues of cost and reimbursement.

In the approach to patients with suspected ulcer disease or *H. pylori* infection, it is better to test for the bacterial infection and selectively treat those who are seropositive than to empirically treat all patients. The work by Fendrick et al. published in 1995 evaluated the cost per ulcer cured as well as the cost per ulcer treated for five alternative management strategies [9]. The authors demonstrated that the addition of a serologic test to establish *H. pylori* infection prior to the initiation of eradication therapy resulted in approximately the same costs as empiric therapy without testing. Work presented by Dr. Vakil in abstract form in 1996 directly compared the three management strategies of empiric *H. pylori* therapy, serology followed by treatment and urea breath test followed by treatment [10]. It was shown that the lowest cost per patient cured of symptoms occurred with serology followed by treatment ($720) as compared with empiric therapy ($1280) or urea breath test plus treatment ($1257). Most recently, Sonnenberg generated a decision analytic approach to examine the cost-benefit relationships of various options in dyspepsia and *H. pylori* infection [11]. He demonstrated that it was less expensive to test for *H. pylori* and selectively treat those found to be infected than to empirically treat all dyspeptic patients. Since testing for bacterial infection prior to treatment reduces overtreatment of noninfected patients and results in costs similar to or probably less than empiric therapy without testing, the next question to address is which test modality is most appropriate for the initial diagnosis of *H. pylori*.

Recent work to be published later this year modeled the cost-effectiveness of the available noninvasive testing strategies for *H. pylori* in dyspeptic office patients [12]. A decision tree analysis was developed comparing FlexSure HP, HM-CAP ELISA and [^{13}C]urea breath test utilizing established clinical accuracy and costs. It was concluded that office based serology is the optimal strategy for the noninvasive diagnosis of *H. pylori* infection in dyspeptic patients, that whole blood tests are too inaccurate to be cost-effective at present and that laboratory-based ELISA may not be cost-effective where office-serology is available. The urea breath test became the initial test of choice when its cost decreased to below $53.

Diagnosis of *H. pylori* infection by invasive techniques at esophagogastroduodenoscopy is appropriate in certain situations and does offer some advantages in improved specificity to noninvasive test methods. When gastric tissue specimens are to be taken for histopathologic evaluation of a mucosal abnormality, biopsing areas away from the mucosal defect for the presence of the bacterial infection is reasonable and adds little if any cost. Rapid urease tests remain the test of choice to diagnose *H. pylori* at endoscopy. Previously, experts in the field suggested that samples for histology be obtained at the time of endoscopy and then stored until rapid urease test results were complete. Positive urease results could be accepted and the histologic specimen discarded. Negative urease results would be followed by submission of the stored specimen to further evaluate for *H. pylori*. Evaluation of this approach was recently undertaken [13]. A cost-analysis for diagnosis of the bacterial infection at initial endoscopy was undertaken. The rapid urease test was assumed to be the initial test of choice and secondary test strategies to follow negative urease test results were evaluated. It was determined that given a reasonable suspicion for the presence of *H. pylori* infection, a negative rapid urease test should be complimented by a confirmatory antibody test. Secondary histology or breath tests were not found to be cost-effective strategies.

Confirmation of *H. pylori* eradication is not required for most patients who have received therapy. Patients with complicated ulcer disease, such as bleeding, obstruction or perforation, and patients with recurrent symptoms after treatment, will need to be evaluated for cure of the infection after antibiotic therapy. At present, this is best performed with repeat esophagogastroduodenoscopy with biopsies or a urea breath test.

Patients found to have a gastric ulcer at initial endoscopy typically undergo repeat visualization to confirm ulcer healing and evaluate for malignancy. If therapy for *H. pylori* is accomplished prior to such follow-up, then histologic specimens may be taken at the second endoscopy to evaluate the ulcer and to confirm bacterial eradication.

Performance of urea breath tests in all post-treatment patients cannot be justified from an economic point of view [14]. Given an estimated rebleed risk per year for all ulcers of less than two percent and an *H. pylori* treatment regimen with 70 percent efficacy, urea breath tests would need to be performed in 200 patients to prevent one bleed per year. At a cost of $300 per breath test, $60,000 would be spent per bleed prevented. The cost per bleed prevented is directly affected by several factors including the rebleed risk per year and the cost of the test. As the rebleed risk increases and test costs decrease, the cost per bleed prevented declines. However, as therapies for *H. pylori* improve and exceed 70 percent efficacy, the number of patients that would need to be tested to prevent one bleed would rapidly rise. At present, the best follow up after treatment for *H. pylori* is selective retesting.

In summary, initial diagnosis of *H. pylori* infection in the dyspeptic patient or in the patient for whom antimicrobial therapy may be warranted should be accomplished with serology, either laboratory-based ELISA or office-based serum immunoassay. If gastric tissue of a mucosal defect is to be obtained, additional biopsies may be collected to evaluate the infection status. Rapid urease tests may be performed at endoscopy with negative results confirmed by serology in those patients with a high likelihood for infection. Confirmation of bacterial eradication is required in those with complicated ulcers or recurrent symptoms after therapy. Confirming successful treatment in all patients is not presently cost-effective.

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