Noninvasive *Helicobacter pylori* Testing for the “Test-and-Treat” Strategy

*An Decision Analysis to Assess the Effect of Past Infection on Test Choice*

William D. Chey, MD, FACP, FACG; A. Mark Fendrick, MD

**Background:** Clinical guidelines support a noninvasive *Helicobacter pylori* “test-and-treat” strategy for individuals with uncomplicated dyspepsia. However, consensus is lacking regarding the preferred noninvasive testing method.

**Objective:** To use decision analytic modeling to estimate the clinical and economic outcomes associated with noninvasive tests designed to detect either *H pylori* antibody or active *H pylori* infection.

**Design:** Decision analytic model.

**Patients:** A simulated patient cohort with uncomplicated dyspepsia.

**Interventions:** The simulated dyspepsia cohort underwent antibody testing or testing to detect active *H pylori* infection (active testing). Individuals testing positive received eradication therapy.

**Main Outcome Measures:** Appropriate and inappropriate treatment prescribed, cost per patient treated, incremental cost per unnecessary treatment avoided.

**Results:** Active testing led to a substantial reduction in unnecessary treatment for patients without active infection (antibody, 23.7; active, 1.4 per 100 patients) at an incremental cost of $37 per patient. The clinical advantage and cost-effectiveness of active testing was enhanced as the percentage of individuals with a positive antibody test result from past, but not current, infection increased.

**Conclusions:** Active testing for *H pylori* infection significantly decreases the inappropriate use of antimicrobial therapy when compared with antibody testing. The advantages of active testing should be enhanced as the widespread use of antimicrobial agents increases the proportion of patients with antibody to *H pylori*, but without active infection.

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**THE AMERICAN Gastroenterological Association and other professional organizations endorse a “test-and-treat” strategy for Helicobacter pylori for patients with previously unevaluated, uncomplicated dyspepsia.**

The driving forces behind the adoption of this strategy include the desire to decrease the use of expensive, endoscopic procedures and to use *H pylori* eradication therapy only in infected patients. While there is little controversy that nonendoscopic *H pylori* tests should be the initial test performed in this patient group, consensus is lacking regarding the preferred testing method.

Noninvasive tests for *H pylori* can be distinguished by their ability to detect either active infection or a systemic antibody response to the organism. Both office-based, qualitative antibody tests and quantitative enzyme-linked immunosorbent assays are available. Though antibody tests offer reasonable sensitivity to detect IgG against *H pylori*, a positive antibody test result cannot distinguish between individuals with active infection and those previously, but not currently, infected. Thus, positive antibody test results can occur in 3 distinct patient groups: (1) those with detectable antibody and active *H pylori* infection (true-positive antibody, infected); (2) those with detectable antibody, but not actively infected (true-positive antibody, not infected [TPNI]); and (3) those never infected and no antibody detectable (false-positive [FP] result). This distinction is important because the use of eradication therapy is of no clinical value in groups 2 and 3.

While clinical investigators may have included patients having TPNI results in the specificity calculation of certain anti-
PATIENTS AND METHODS

A cohort of patients with uncomplicated, ulcer-like dyspepsia who had not been previously tested for 
*Helicobacter pylori* was entered into the decision analytic model. Noninvasive 
*Helicobacter pylori* diagnostic tests including antibody (sensitivity, 89%; specificity, 79%) and active tests (sensitivity, 93%; specificity, 98%) were evaluated. Principal case inputs for the antibody test were obtained from a meta-analysis that evaluated 21 studies comparing different commercially available serologic kits.

Published studies consistently report a sensitivity and specificity exceeding 90% for the urea breath and stool antigen tests. Cost inputs were based on 1999 Medicare reimbursements for serologic testing ($25, Current Procedural Terminology code 86677) and the urea breath test ($100, Current Procedural Terminology codes 83013 and 83014).

In the principal analysis, active *Helicobacter pylori* infection was estimated to be present in 30% of the individuals undergoing testing. Of the 70% of individuals not infected, 20% were assumed to be infected at some time in the past, yielding a TPNI rate of 14%. All patients who tested positive were treated with a 14-day course of a combination of lansoprazole, clarithromycin, and amoxicillin at a cost of $20. This cost input was chosen after making the assumption that most prescription medication plans acquire this therapy for less than the average wholesale price (Prevpac; TAP Pharmaceuticals Inc, Lake Forest, Ill; average wholesale price, $252).

Outcomes estimated by the model were based on the presence or absence of active *Helicobacter pylori* infection and the appropriateness of eradication therapy given a patient’s active infection status. In the antibody strategy, patients who did not benefit from prescribed therapy: those with TPNI, and those who were never infected (FP result). Individuals with TPNI and no antibody detectable (false-positive results). Patients with TPNI and active infection (true-positive antibody) were assumed to be infected at some time in the past, yielding a TPNI rate of 14%. All patients who tested positive were treated with a 14-day course of a combination of lansoprazole, clarithromycin, and amoxicillin at a cost of $20. This cost input was chosen after making the assumption that most prescription medication plans acquire this therapy for less than the average wholesale price (Prevpac; TAP Pharmaceuticals Inc, Lake Forest, Ill; average wholesale price, $252).

Economic outcomes and incremental cost-effectiveness were also estimated by the model. The average cost per patient tested in each strategy was derived using the cost of the test (incurred by all patients) summed with the cost of *H pylori* eradication therapy (incurred only by patients with a positive test result). For example, in the active testing strategy, the average cost per patient tested was calculated using the following formula:

\[
\text{Test Cost} = \text{Cost Treatment} \times [\text{(Active Hp %} \times \text{Sensitivity}) + (1 - \text{Active Hp %} \times (1 - \text{Specificity}))],
\]

Where Hp % is percentage of *H pylori*. If a situation arose where a superior clinical outcome resulted at a higher cost, an incremental cost per appropriate treatment prescribed or incremental cost per inappropriate treatment avoided was calculated.

.body tests, this convention is incorrect. Technically, only individuals without detectable antibody, but with a positive antibody test result are, in fact, true-negative positives in that these patients do not have the entity that the test was designed to measure.

Tests that detect active *Helicobacter pylori* infection (“active testing”) include the urea breath test (ie, urea tagged with nonradioactive carbon 13 or radioactive carbon 14) and the stool antigen test. Unlike antibody tests, active tests produce a positive result in only 2 circumstances: (1) those with active *Helicobacter pylori* infection (true-positive result), and (2) those never infected (FP result). Individuals with TPNI are not identified because active infection with *Helicobacter pylori* organisms is necessary to produce a positive urea breath test or stool antigen test result.

Owing largely to issues of availability, convenience, and cost, antibody tests are the most widely used noninvasive tests for *Helicobacter pylori*. However, choosing the appropriate noninvasive *Helicobacter pylori* test requires an explicit understanding of the tradeoffs between the lower acquisition costs of antibody testing and the superior accuracy of active testing. Accordingly, a decision analytic model was constructed to measure the clinical benefits of active testing and quantify the costs necessary to obtain them.

RESULTS

CLINICAL OUTCOMES

Using a TPNI rate of 14%, the active testing strategy led to a substantial reduction in unnecessary treatment for patients without active *Helicobacter pylori* infection (antibody test, 23.7 per 100 patients [TPNI and FP groups]; active test, 1.4 per 100 patients [FP group]). In addition, when compared with the antibody strategy, active testing identified 3 additional patients with current infection per 100 patients tested (Table).

ECONOMIC OUTCOMES

Average Cost per Patient

To achieve these clinical advantages, active testing costs an additional $37 per patient tested compared with antibody testing (active test, $160 per patient; antibody test, $123 per patient). The contribution of testing and the

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**Table**

<table>
<thead>
<tr>
<th>Patient Result†</th>
<th>Antibody Test Result</th>
<th>Active Test Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active <em>H pylori</em> infection</td>
<td>25.5</td>
<td>28.5</td>
</tr>
<tr>
<td>Untreated</td>
<td>4.5</td>
<td>1.5</td>
</tr>
<tr>
<td>No active <em>H pylori</em> infection</td>
<td>23.7‡</td>
<td>1.4§</td>
</tr>
<tr>
<td>Untreated</td>
<td>46.3</td>
<td>68.6</td>
</tr>
</tbody>
</table>

*Assumes that 20% of the patients without active *H pylori* infection have positive antibody.

†Value based on number of patients per 100 tested.

‡Value includes patients with true-positive antibody, but not actively infected with *H pylori* and those never infected with *H pylori* and no antibody detectable (false-positive results).

§Value includes only those patients who were never infected with *H pylori* and have no antibody detectable (false-positive results).
use of appropriate and inappropriate eradication therapy to the costs for 100 patients in each strategy are shown in Figure 1. The figure demonstrates the tradeoff between testing costs ($7500 higher per 100 patients tested in the active testing strategy) and expenditures on inappropriate treatment of patients without active infection ($4460 less per 100 patients tested with active testing).

Cost-effectiveness Analysis

In the base-case analysis, an additional investment of $164 in active testing was necessary to avoid 1 unnecessary course of eradication therapy. Although an incremental $1233 must be spent on active testing to identify each additional infected individual whose condition was not diagnosed using antibody testing, at least part of this cost increase would be offset by expenditures associated with the management of patients with active infection who test false negative using the antibody test.

SENSITIVITY ANALYSIS

Sensitivity analysis was performed to evaluate the effect of altering individual input variables on the clinical and economic results. The incremental cost per unnecessary treatment avoided decreased significantly as the proportion of individuals who were TPNI increased (Figure 2). Active testing decreased the inappropriate use of eradication therapy under all circumstances evaluated, including when the prevalence of active *H pylori* infection in the model cohort ranged from 10% to 50%. The incremental cost per unnecessary treatment avoided did not change significantly when the sensitivity and specificity of the *H pylori* tests were evaluated over their published ranges. Using a TPNI rate of 14%, the cost per patient tested with the active strategy became equivalent to antibody testing ($123 per patient) when the test cost differential was reduced to $37.

The cost of therapy influenced the results of the analysis. Sensitivity analysis revealed that when the average wholesale price of $252 for the combination therapy of lansoprazole, clarithromycin, and amoxicillin (Prevac; TAP Pharmaceuticals Inc), was used the model calculated the following results: (1) cost per patient treated using antibody testing = $149, using active testing = $175.30; (2) incremental cost per correct diagnosis = $876; and (3) incremental cost to avoid 1 unnecessary course of eradication therapy = $118.

A decision analytic model estimated that active testing dramatically reduced the number of patients inappropriately treated for presumed *H pylori* infection when compared with antibody testing. Active testing also marginally increased the number of patients correctly identified with active *H pylori* infection. This decrease in unnecessary therapy is important from multiple perspectives. For the patient, it makes no sense to ingest multiple medications, each with associated inconvenience, adverse effects, and out-of-pocket expense without an expectation of clinical benefit. For the payer, the cost associated with the prescribing of therapy in uninfected patients can be substantial.

From a societal perspective, targeted diagnosis is an essential weapon against the development of antimicrobial resistance—a significant and growing problem worldwide. The emergence of antimicrobial resistance is not only an issue for *H pylori* but also for virtually all pathogens previously considered easily treatable.

Recent studies by Whitney et al and Donskey et al highlight the emergence of multidrug-resistant *Streptococcus pneumoniae* and *Enterococcus* species. In an editorial accompanying those studies, Wenzel and Edmund state: “the inappropriate use of these drugs (antibiotics) threatens our ability to cope with infections.” While the model demonstrates that the adoption of testing strategies that decrease the unnecessary use of antimicrobial agents require incremental expenditures in the short-term, it is important to consider the long-term benefits of slowing the emergence of resistant organisms. Although these future benefits are difficult to quantify, a substantial amount of resources continue to be devoted to the growing problem of antimicrobial resistance.

When interpreting the principal analysis, it is important to consider how expected changes in *H pylori* epidemiology will further strengthen the clinical and cost-effectiveness argument for active testing. The percentage
of patients with TPNI is likely to increase as antimicrobial therapy becomes more widespread. Commonly used antimicrobial agents, such as clarithromycin or amoxicillin, can result in an H pylori cure rate of 20% to 40% when used alone.13 This “incidental” eradication, when combined with successful H pylori eradication with approved regimens, will lead to an even larger TPNI population. In addition, as the background prevalence of active H pylori infection decreases, one can expect a correlative decrease in the accuracy and cost-effectiveness of antibody testing. At the current cost differential between antibody and active tests used in the principal analysis, the incremental investment in active testing necessary to avoid 1 inappropriate course of eradication therapy fell to approximately $100 when the TPNI rate associated with antibody testing exceeded 30% (Figure 2).

Our findings suggest that active testing will markedly reduce the number of patients inappropriately treated for H pylori infection. Thus, the cost consequences of initial H pylori test choice depend not only on differences in acquisition costs but also on the treatment costs for individuals without infection. The $37-per-patient difference between the strategies demonstrates that half of the $75 difference in test cost is recovered through appropriate use of eradication therapy. Cost neutrality should not be a requirement for the adoption of active testing. The benefits for reducing unnecessary and potentially harmful therapy for patients and society must be acknowledged.

CONCLUSIONS

Active testing for H pylori achieves measurable clinical benefits over antibody testing at an incremental cost. The advantages associated with active testing should be enhanced as the widespread use of antimicrobial agents increases the proportion of individuals with TPNI. In addition, the decreasing background prevalence of H pylori should serve to strengthen the argument for active testing on clinical and economic grounds. The ability to better direct therapy to patients with active H pylori infection will also improve patient satisfaction and prove advantageous in an environment increasingly concerned with antimicrobial resistance.

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Corresponding author: William D. Chey, MD, FACP, FACG, 3912 Taubman Center, Ann Arbor, MI 48109-0362 (e-mail: wchey@umich.edu).

REFERENCES