Diagnosis and Eradication of *Helicobacter pylori* in the Management of Peptic Ulcer Disease: A Decision Analysis Model

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Abstract

The goal of this study was to evaluate the costs and outcomes associated with four general approaches to the management of patients with diagnosed peptic ulcer disease: (1) acute-dosage antisecretory therapy, without testing for *Helicobacter pylori*; (2) maintenance-dosage antisecretory therapy, without testing for *H pylori*; (3) immediate noninvasive serologic test for *H pylori*, with combination antimicrobial/antisecretory therapy if patient is *H pylori* positive; and (4) endoscopy with histology for *H pylori*, with combination antimicrobial/antisecretory therapy if patient is *H pylori* positive. We constructed a decision analysis model and simulated the costs and the number of ulcer recurrences for a demographically representative sample of the US population over a 5-year period. A management strategy composed of serologic testing followed by combination antimicrobial/antisecretory therapy for patients who are *H pylori* positive was found to be the least expensive baseline option, with costs of $1,403 per patient treated (about 24% to 40% less than alternative strategies). Two other strategies were associated with fewer recurrences: 9.3% of patients in the maintenance-strategy group had ulcer recurrence, as did 10.3% in the endoscopy-strategy and 10.6% in the serology group. Our results do not include the costs associated with initial diagnosis of peptic ulcer disease, which may include endoscopy or an upper gastrointestinal series evaluation. Serologic testing for *H pylori* in patients with peptic ulcer disease was the lowest-cost option and was always preferred to acute therapy, without testing for *H pylori*. Although better outcomes may be obtained by using diagnostic endoscopy with histology, this strategy is associated with higher costs per patient treated. If physicians are willing to prescribe empiric antimicrobial/antisecretory therapy without testing for *H pylori*, this option is preferred to serology only if the savings generated (ie, $221 per patient treated) are assumed to exceed any cost associated with the possible promotion of antibiotic-resistant bacteria.

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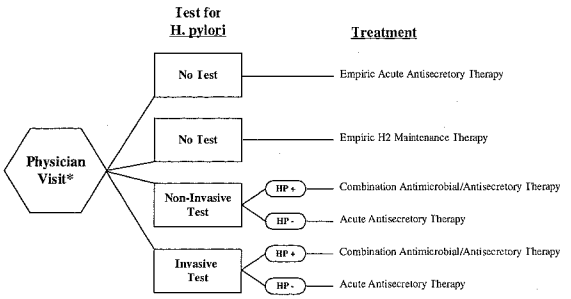
The February 1994 National Institutes of Health (NIH) Consensus Conference on *Helicobacter pylori (H pylori)* concluded that ulcer patients with *H pylori* infection require treatment with antimicrobial agents in addition to antisecretory drugs.[1] However, the NIH conference did not indicate the most cost-effective approach to *H pylori* diagnosis and ulcer treatment. Understanding the clinical economics of alternative management strategies is critical to giving physicians a full picture of the merits of diagnosing and eradicating *H pylori*.

The purpose of this study is to identify the most cost-effective management approach to peptic ulcer disease (PUD). We use a decision analysis model to project likely costs for a representative sample of the US population, evaluating the four management alternatives shown in Figure 1: (1) acute antisecretory therapy, without testing for *H pylori*; (2) acute antisecretory therapy, without testing for *H pylori*, followed by maintenance therapy; (3) invasive diagnosis of *H pylori*, followed by combination antimicrobial/antisecretory therapy if *H pylori* is present, and followed by antisecretory therapy alone if *H pylori* is absent; and (4) noninvasive diagnosis of *H pylori*, followed by combination antimicrobial/antisecretory therapy if *H pylori* is present, and followed by antisecretory therapy alone if *H pylori* is absent.

The analysis uses a seven-state decision analysis model to assess the four alternative management options for patients with an established diagnosis of PUD. In addition, we have evaluated a fifth manage-

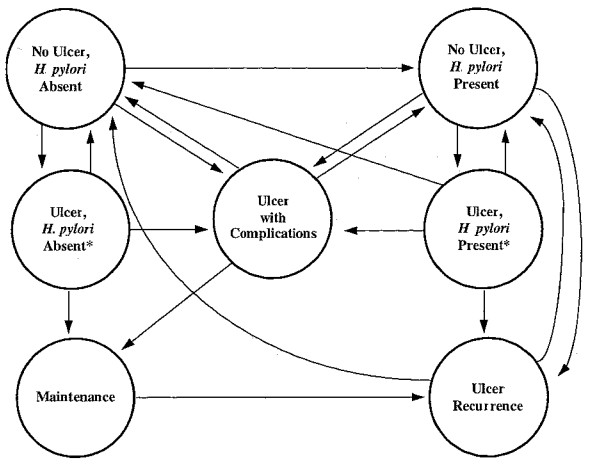
ment option, empiric antimicrobial/antisecretory therapy, as a sensitivity analysis. We have included both gastric ulcers and duodenal ulcers and hve allowed for the possibility of recurrences, bleeding ulcers, patients with chronic disease, and misdiagnoses. We report simulated costs and outcomes for our baseline case, and sensitivity analyses with respect to *H pylori* prevalence, type of costs (direct/indirect), eradication rate, and pharmaceutical prices.

Figure 1. Overview of Management Strategies



HP+ = *H pylori* positive; HP- = *H pylori* negative
*The model assumes patient has a diagnosed ulcer before the initial physician visit.

Figure 2. Health States in Model



*The costs of any initial studies necessary to diagnose ulcer are not included in this model

Our model of PUD is the first to evaluate both costs and outcomes across a variety of management strategies. Although Unge and coworkers[2] evaluated both costs and outcomes, they considered management strategies postendoscopy only and did not evaluate the empiric antisecretory or serology approaches. Sonnenberg and Townsend[3] also evaluated both costs and outcomes but did not examine the same range of management options as was analyzed in our study. Three other recently published studies, by O'Brien et al,[4] Fendrick et al,[5] and Imperiale et al,[6] investigated a range of management approaches similar to those examined in our study but focused solely on costs. Our analysis also improves on those studies[4-6] by considering a longer time frame (ie, 5 years). Despite the differences in management approach and time frame, our main conclusion is consistent with the conclusion in some of the studies: eradication of *H pylori* is a cost-effective strategy in the management of PUD.

··· METHODS ···

Through a MEDLINE search, we identified 260 abstracts of review articles published after 1990 pertaining to *H pylori* in the context of PUD. After excluding letters, editorials, and non-English publications, we collected and categorized approximately 80 articles into three subject groups: (1) diagnosis of *H pylori*; (2) treatment of *H pylori*; and (3) epidemiology of PUD. Data from these articles were incorporated as assumptions into a clinical model built using *i think* software (High Performance Systems, Hanover, NH). Because the software is flexible, we are able to alter the baseline assumptions easily and thus test the robustness of the results from our analysis through a variety of sensitivity analyses, some of which are presented in this paper.

The clinical model allows for patients in seven states of health (Figure 2): (1) no ulcer, *H pylori* absent; (2) no ulcer, *H pylori* present; (3) active ulcer, *H pylori* absent; (4) active ulcer, *H pylori* present; (5) ulcer with complications; (6) ulcer recurrence; and (7) maintenance state. The model begins with ulcer-free patients distributed between state 1 (no ulcer, *H pylori* absent) and state 2 (no ulcer, *H pylori* present) according to the prevalence of *H pylori* in the US population. Every month, patients move through the various health states according to the key model parameters (eg, incidence of ulcers, incidence of *H pylori* infec-

tion, and probability of recurrence after treatment), which are detailed in Table 1. We run the model for a 5-year time period to reflect the time frame typically reported in studies of long-term maintenance therapy. We assume that patients without ulcers accrue no costs, and that patients who develop ulcers accrue costs according to the assumptions in Table 2. While the majority of health states are defined by the key parameters presented in Table 1, three of the states merit further discussion.

Table 1. Key Parameters (%)

Incidence of Ulcers and *H pylori*	
Annual incidence of *H pylori* infection[7]	1
Dyspepsia caused by peptic ulcer disease*	17
H pylori status of peptic ulcers[9,10]	
H pylori positive	79.7
H pylori negative	20.3
Diagnosis and Treatment of *H pylori*	
Diagnostic approach (sensitivity, specificity)[11]	
Endoscopy with histology	96, 97
Serology	93.5, 90.5
Ulcer healing rates (with and without antimicrobial agents)	
After 8 wk H2-receptor antagonist therapy	92
After 12 wk H2-receptor antagonist therapy	100
Eradication rate[12]	84
Recurrence After Treatment	
Recurrence after acute H2-receptor antagonist therapy (cumulative)[13-15]	
0-3 mo	50
3-6 mo	65
6-9 mo	75
9-12 mo	80
Recurrence during H2-receptor antagonist maintenance therapy (cumulative)[16-18]	
Year 1	8
Year 2	13
Year 3	17
Year 4	21
Year 5	22
Long-Term Management	
H pylori-negative ulcer patients requiring long-term therapy	20
H pylori-negative bleeding ulcer patients requiring long-term therapy	100
Ulcer Complications	
Annual incidence of bleeding ulcer in general population[19]	0.07
Clinical characteristics of GI bleeds[19]	
Clean base	48
Flat spot	23
Adherent clot	13
Active bleed or visible vessel	15
Patients requiring therapeutic endoscopy[19]	
Flat spot or adherent clot ulcers	10
Active bleed or visible vessel	100
Active bleed patients requiring surgery[19]	10

GI = gastrointestinal.
*Lewin-VHI, Inc. calculation, based on Heikkinen et al.[8]

Ulcer with Complications. Patients may flow into this state through any of the nonactive ulcer states (no ulcer, *H pylori* absent; no ulcer, *H pylori* present; or maintenance). We have assumed that all patients with a complication (ie, gastrointestinal bleeding) present to the emergency department for treatment and receive a diagnostic endoscopy to determine the clinical characteristics of the ulcer. Depending on the results of the endoscopy, a patient is released (in the case of a clean base), admitted for observation (if a flat spot or adherent clot is found), or given a therapeutic endoscopy (the patient has a flat-spot or adherent-clot ulcer with recurrent bleeding and active bleeding/visible vessel).[19] If the therapeutic endoscopy cannot control the gastrointestinal bleeding, patients undergo surgery.

We have assumed that, during the endoscopic diagnosis of the clinical characteristics of the bleeding ulcer, physicians collect a tissue specimen to test for *H pylori*. Depending on the results of the test, patients receive either acute antisecretory therapy or combination antimicrobial/antisecretory therapy on release from the hospital. After completion of acute therapy, *H pylori*-negative patients receive maintenance therapy.[19]

Ulcer Recurrence. The majority of patients who are *H pylori* positive after acute treatment and who do not receive maintenance therapy will have an ulcer recurrence within 1 year. Regardless of the initial approach to diagnosis and treatment, the model assumes that all patients with an ulcer recurrence will be given an endoscopy with histology for diagnosis of *H pylori*. If the histology indicates that *H pylori* is present, a patient receives combination antimicrobial/antisecretory therapy. If *H pylori* is not present, the patient receives an acute course of antisecretory treatment.

Maintenance. In this health state, both *H pylori*-positive patients and *H pylori*-negative patients receive maintenance therapy. The model assumes that *H pylori*-positive patients will experience ulcer recurrence at a cumulative rate of 22% over 5 years, and that *H pylori*-negative patients will not experience ulcer recurrence. Patients receiving maintenance therapy are assumed to visit the physician twice annually, and to visit the pharmacy four times per year, to purchase antisecretory medication.

Patients initiate maintenance therapy for one of three reasons. First, they might be treated according

Table 2. Direct and Indirect Costs ($)

Code	Item	Medicare Payment
Endoscopic Diagnosis of *H pylori*		
CPT43239	Upper GI endoscopy with biopsy	623*
CPT88305	Surgical pathology, Level IV	62*
CPT88312	Special stains; Group I	27*
Ulcer Recurrence		
CPT99214	Physician visit, established patient; 25 min	23
CPT43239	Upper GI endoscopy with biopsy	623*
CPT88305	Surgical pathology, Level IV	62*
CPT88312	Special stains; Group I	27*
Clean-Base Ulcer with Complications		
CPT99285	Emergency department visit	406†
CPT43239	Upper GI endoscopy with biopsy	623*
CPT88305	Surgical pathology, Level IV	62*
CPT88312	Special stains; Group I	27*
Spot or Clot Ulcer with Complications		
CPT99285	Emergency department visit	131‡
CPT43239	Upper GI endoscopy with biopsy	228‡
CPT88305	Surgical pathology, Level IV	44‡
CPT88312	Special stains; Group I	23‡
CPT99231	Subsequent hospital care, 3 days	93‡
DRG 175	GI hemorrhage without control of bleeding	2,034
Nonsurgical Treatment of Active Bleed		
CPT99285	Emergency department visit	131‡
CPT43255	Upper GI endoscopy with control of bleeding	346‡
CPT88305	Surgical pathology, Level IV	44‡
CPT88312	Special stains; Group I	23‡
CPT99231	Subsequent hospital care, 3 days	93‡
DRG 175	GI hemorrhage without control of bleeding	2,034
Active Bleed Requiring Surgery		
CPT99285	Emergency department visit	131‡
CPT43255	Upper GI endoscopy with control of bleeding	346‡
CPT88305	Surgical pathology, Level IV	44‡
CPT88312	Special stains; Group I	23‡
CPT43640	Vagotomy	918‡
CPT00790	Anesthesia for upper abdominal procedures	252‡
DRG 155	Stomach, esophageal, and duodenal procedures, age >17 yr	5,274
Miscellaneous Costs		
CPT99203	Initial physician visit, new patient; 30 min	59
CPT99212	Follow-up physician visit, established patient; 10 min	51
	Serology test for *H pylori*	80§
	Acute antisecretory therapy (4 wk)	70§
	Maintenance antisecretory therapy (3 mo)	120**
	Combination antimicrobial/antisecretory therapy (4 wk)	90¶

CPT = current procedure terminology; GI = gastrointestinal; DRG = diagnosis-related group.
*Assumption based on expert clinical opinion; includes both professional component and facility or technical.
†Includes professional fee of $131 and average emergency department costs from Health and Hospitals Corporation of $275.
‡Professional fee only; facility fee is included in DRG.
§SmithKline Beecham Clinical Laboratories.
**Average wholesale price (AWP).
¶AWP for 4 weeks of treatment; the model then assumes patients continue acute antisecretory therapy for an additional 4 to 8 weeks, depending on the rate of ulcer healing. Our baseline figures assume triple therapy and the use of generic products. See sensitivity analyses for tests of this assumption.

to the strategy of *empiric* maintenance therapy management (described in the Maintenance Strategies section). Second, patients will flow into the maintenance state if they develop an ulcer with complications and are *H pylori* negative. Third, the model assumes that 20% of high-risk ulcer patients diagnosed as *H pylori* negative receive maintenance therapy after acute treatment for the active ulcer.

Management Strategies

Management of PUD begins when a patient moves into an active-ulcer health state (with or without *H pylori*). We assume that PUD already has been diagnosed, and that the episode begins with an initial visit to the physician, who has several management options. First, the physician has a choice of three approaches to diagnosis: (1) an invasive test for *H pylori* (ie, endoscopy with histology); (2) a noninvasive test for *H pylori* (ie, serology); or (3) no test for *H pylori*. Next, the physician has three pharmacologic treatment options: (1) acute antisecretory treatment; (2) acute antisecretory treatment followed by H2-receptor antagonist maintenance therapy; and (3) combination antimicrobial/antisecretory therapy.

Recommended therapies for the diagnosis and eradication of *H pylori* are changing rapidly. Therefore, although the decision analysis model is flexible and can analyze numerous diagnosis and treatment scenarios with varying sensitivities, specificities, and costs, we have not reported results for specific pharmaceutical regimens. We have evaluated the following four management alternatives (shown in Figure 1):

- ***Acute Antisecretory Therapy, Without Testing for* H pylori.** Patients present to the physician with a diagnosed ulcer and begin acute antisecretory therapy, without being tested for *H pylori*.
- ***H2-Receptor Antagonist Maintenance Therapy, Without Testing for* H pylori.** Patients with a diagnosed ulcer visit the physician and

begin treatment with acute antisecretory therapy, without being tested for *H pylori*. After completing acute therapy, patients receive long-term maintenance therapy (ie, for 5 years).

- ***Noninvasive Diagnosis.*** Patients with a diagnosed ulcer visit the physician and are given a serologic test for *H pylori*. If *H pylori* is present, they receive combination antimicrobial/antisecretory therapy. If *H pylori* is not present, they receive an acute course of antisecretory treatment.
- ***Invasive Diagnosis.*** Patients with a diagnosed ulcer present to the physician and are scheduled for an endoscopy with histology. If *H pylori* is present, they receive combination antisecretory/antimicrobial therapy. If *H pylori* is not present, they receive an acute course of antisecretory treatment.

Costs and Effectiveness

For each of the four management alternatives, we estimated direct medical costs and indirect costs (lost wages) per patient treated. We also estimated the percentage of patients who will have a recurrence over a 5-year period. Direct and indirect costs were inflated annually to reflect real growth rates of 5% for physician and hospital costs, 4% for pharmaceutical costs, and 2% for wages. All costs were discounted to 1994 dollars, assuming a 5% real discount rate.

Table 2 presents the direct and indirect cost inputs to the model. Direct costs for physician procedures and facility costs were estimated on the basis of 1994 Medicare payment amounts (ie, relative value units (RVUs) for physician costs, ambulatory surgical center rates for outpatient facility costs, and diagnosis-related groups for inpatient facility costs). Two direct cost figures were not available from Medicare date: (1) the facility cost of an outpatient emergency visit; and (2) the cost of the serology test. We used data from Health and Hospitals Corporation (New York, NY) to estimate the former, and the cost of the serology test from SmithKline Beecham Clinical Laboratories (San Jose, CA) to estimate the latter.

Direct costs for pharmaceutical agents were assigned on the basis of the lowest average wholesale price (AWP) as reported in the August 1994 *Red Book Update*.[20] In cases in which the AWP was not available in the August *Update*, we abstracted pricing information from the 1994 *Red Book*.[21] In addition, a $5 dispensing fee was included in the cost of each prescription. For patients receiving maintenance therapy, we have assume that four prescriptions are filled each year (ie, a total of $20 in dispensing fees).

Indirect costs were measured in terms of productivity lost as a result of morbidity. The model assumes that patients lose 8 hours of productivity when they experience an ulcer flare-up. Additionally, we assigned a productivity loss of 2 hours to a physician visit and 8 hours to an outpatient endoscopy. If a patient develops a gastrointestinal complication associated with a spot or clot ulcer or receives a therapeutic endoscopy, we assumed a 1-week loss in productivity (40 hours). If the patient requires surgery, we assumed a 3-week productivity loss (120 hours). We used the 1994 minimum hourly wage in the United States of $4.25 to estimate the cost of productivity loss in the model.

Side effects associated with the eradication of *H pylori* can influence economic costs in two ways: (1) directly, through expenditures on drugs and medical care to treat the side effects themselves; and (2) indirectly, by reducing patient compliance with *H pylori* treatment regimens. We have assumed that the direct costs attributable to common adverse reactions, such as diarrhea, nausea/vomiting, and rashes, are not significant enough to merit inclusion in the model. We adjust the published antimicrobial/antisecretory therapy eradication rates to account for treatment failures by including individuals who have discontinued treatment because of side effects in the eradication rate.

The model does not include costs that may accrue from rare side effects, such as pseudomembranous colitis, as the incidence of such side effects is low. We also did not include any costs associated with complications from endoscopy (eg, perforation, infection, or cardiopulmonary incidents).

··· RESULTS ···

The 5-year cost per patient treated varies by management alternative. As shown in Figure 3, noninvasive diagnosis of *H pylori*, at $1,403 per patient treated, is the least costly management strategy, whereas a strategy of maintenance therapy without diagnosis is the highest-cost alternative ($2,341 per patient treated. In Figure 4, we translate cost per patient treated into a cost per covered life. As seen in the figure, health plans could save $0.13 per member per month by switching from a maintenance strategy to a serology strategy.

We also calculated the percentage of patients experiencing an ulcer recurrence (Figure 5). The model shows that similar percentages of patients treated with serology and with endoscopy will have recurrences (10.6% and 10.3%, respectively). Acute antise-

Figure 3. Cost of PUD Management Alternatives (Cost per Patient Treated over 5 Years)

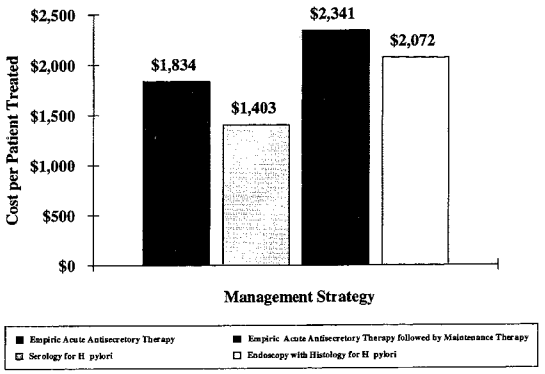


Figure 4. Cost of PUD Management Alternatives (Cost per Member per Month)

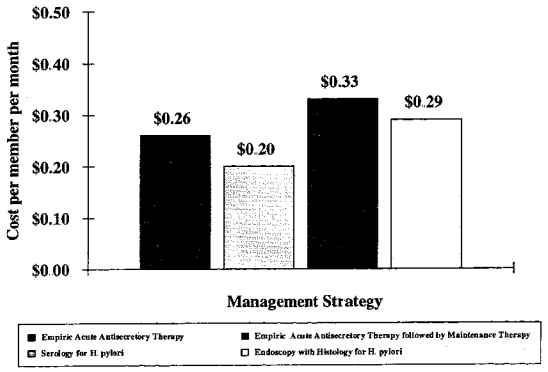
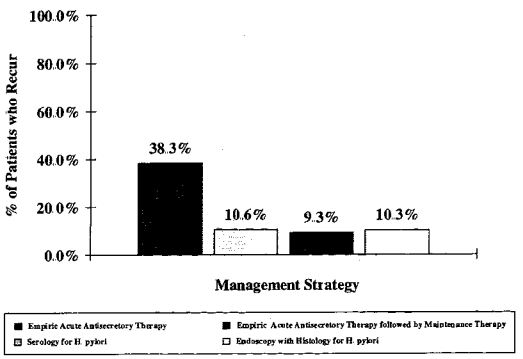


Figure 5. Effectiveness of PUD Management Alternatives (for 100,000 Nationally Representative Patients Over 5 Years)



PUD = peptic ulcer disease

cretory treatment, without testing for *H pylori*, is associated with the largest percentage of patients with recurrence (38.3%); maintenance treatment, without testing for *H pylori*, is associated with the lowest percentage (9.3%).

On the basis of both costs and recurrences, noninvasive diagnosis is always preferable to acute antisecretory therapy without testing for *H pylori* (ie, the former strategy is lower cost and has better outcomes). By contrast, invasive diagnosis and maintenance therapy are associated with higher costs but fewer recurrences than is serology. Because preferences would depend on the value associated with avoiding recurrence, we calculate the incremental cost per recurrence avoided for endoscopy and maintenance therapy compared with that for a serology baseline. The model predicts that the cost of avoiding a recurrence is high: invasive diagnosis results in an additional cost of $268,594 per recurrence avoided and maintenance therapy, without testing for *H pylori*, costs an additional $72,119 per recurrence avoided.

Sensitivity Analyses

To verify the results of our simulation, we tested the sensitivity of our model to reasonable variation in key parameters. Although costs per patient treated varied, our sensitivity analyses confirmed that serologic testing followed by appropriate drug therapy is, in most cases, the least costly management option.

Vary Epidemiologic Parameters. Because few epidemiologic studies on the prevalence of *H pylori* have been conducted, we tested variation by increasing and decreasing the prevalence of *H pylori* by 10 percentage points. We found that costs and recurrences varied, whereas the relationship between those results remained constant: serology continued to be the lowest-cost strategy, and cost per recurrence avoided remained high (ie, $219,296 to $375,717 for immediate endoscopy and $61,420 to $93,601 for empiric maintenance therapy).

Disregard Indirect Costs. To simulate the perspective of a healthcare payer responsible for direct medical costs but not for lost wages, we eliminated indirect costs from the model. Costs decreased by approximately 6.3%. Serologic testing continued to be the most favorable management strategy, with a cost of $1,306 per patient treated. Costs were greater for endoscopy ($1,944 per patient treated); acute therapy, without testing for *H pylori* ($1,708 per patient treated); and maintenance therapy, without testing for *H pylori* ($2,214 per patient treated).

Vary the Eradication Rate. Standard estimates of *H pylori* eradication are likely to change with an individ-

ual's compliance with the antimicrobial regimen, the development of new antimicrobial regimens, and the availability of new data from large, population-based clinical trials. We therefore decreased and increased eradication rates by 10 percentage points. Although costs varied, the relationship between cost and recurrence remained constant. Costs of serology varied from $1,325 to $1,495 per patient treated, compared with costs of $1,777 to $2,372 per patient treated for other management strategies. Similar to the baseline case, noninvasive diagnosis with serologic testing always was preferable to acute therapy, without testing for *H pylori*.

Unlike the case with our other sensitivity analyses, an alteration in the eradication rate changed the percentage of patients who experienced an ulcer recurrence, as well as the relationship between the results. When the eradication rate increased by 10 percentage points, invasive diagnosis became the most effective strategy, with 4.5% percent of patients experiencing a recurrence. Thus, at that high eradication rate, endoscopy and serology are always preferable to maintenance therapy.

Vary Pharmaceutical Costs. As detailed in Table 2, we used the least expensive pharmaceutical regimen possible, by assuming that generic products are used. However, the costs shown in the table clearly are subject to change, as recommended therapies and their costs vary over time. We therefore tested the sensitivity of the model to a 25% increase and a 25% decrease in the cost of pharmaceutical agents. We found that, whereas the overall costs of treatment will vary, the choice of management strategy holds.

Although the model is capable of generating results while varying the full range of parameters, including the sensitivity and specificity of the diagnostic tests, the costs of procedures and pharmaceutical products, and the demographic characteristics of the population, space limitations preclude us from representing further results here.

Prescription of Antibiotics Without Testing for *H pylori*

We followed an approach similar to that in other studies on the most appropriate approach to ulcer treatment by modeling the costs and recurrences associated with empiric antimicrobial/antisecretory therapy. Under this management strategy, patients with an ulcer visit the physician and are prescribed combination antimicrobial/antisecretory therapy without being tested for *H pylori*. The model predicts costs of $1,182 per patient treated over the 5-year period, with 8.7% of patients experiencing recurrence. Although these costs and recurrence rates are lower than those reported for all the other management strategies considered, the approach is associated with the risk that the population's resistance to antibiotic therapy will increase over time. Because quantifying the costs of resistance to antibiotic therapy is beyond the scope of our analysis, we offer this strategy only for sensitivity analysis.

··· DISCUSSION ···

The least expensive PUD management option is a serologic test for *H pylori*, followed by an antisecretory/antibiotic regimen if the patient is *H pylori* positive. The costs of this management strategy are 24% to 40% less than those of the three alternatives examined. Although more recurrences can be avoided by using more expensive management options, the costs per recurrence avoided are high relative to those associated with serology: $72,119 for maintenance therapy, without testing for *H pylori*, and $268,594 for *H pylori* testing using endoscopy with histology. Treatment with antisecretory drugs alone without considering whether *H pylori* is present is associated with the highest percentage of patients experiencing ulcer recurrence.

Gastroenterologists can use other techniques to detect *H pylori*, including endoscopy with urease (ie, CLO [campylobacter like organisms] test) and the urease breath test. We chose to model endoscopy with histology rather than with endoscopy with urease because the sensitivity of the histology test is the best available.[11] Modeling the endoscopy-with-urease approach would be expected to decrease both costs and outcomes somewhat. Because the cost difference between the histology and the urease test is small ($64) compared with the cost difference between endoscopy with histology and serology ($632), serology would remain the lowest-cost management approach. We chose not to model the breath test because it has not yet been approved by the Food and Drug Administration; when information becomes available on the cost and sensitivity of the test, the model would be capable of evaluating that approach.

As demonstrated by the four sensitivity analyses presented in our paper, the model is robust to reasonable variation in many of our clinical assumptions. For example, if clinical evidence suggests that eradication rates are actually 10 percentage points lower than the 84% used in the model, the serology management strategy continues to be preferable to empiric antisecretory therapy in terms of both costs ($1,495 vs $1,900 per patient treated) and recurrences (occurring

in 17% vs 43% of patients). Similarly, the serology management strategy remains preferable to acute antisecretory therapy when we increase or decrease the prevalence of *H pylori* in the population by 10 percentage points, disregard indirect costs, vary pharmaceutical costs by 25%, or vary the cost of endoscopy.

Our fundamental conclusions change if physicians are willing to use antibiotics without testing for *H pylori*. Both costs and recurrences are lower in this scenario than in other management scenarios. As discussed, however, our model does not attempt to assess the costs that might be generated by contributing to the presence of antibiotic-resistant bacteria.

Although no previous study has examined costs and outcomes associated with endoscopy, serology, empiric antisecretory, maintenance, and empiric antimicrobial/antisecretory management strategies, the findings in three previously published studies[4-6] are consistent with our fundamental conclusion that antimicrobial/antisecretory therapy is the least costly approach to management of PUD. Differences in methodology distinguish our study from previously published work. The model described by Fendrick et al[5] estimates the cost per ulcer cured beginning with the patient's presentation to the physician with symptoms of dyspepsia. In contrast, our model focuses solely on estimating costs for patients diagnosed with PUD.

The time frame investigated in our study (5 years) also differs from the time frames in the studies by O'Brien and colleagues,[4] Fendrick et al,[5] and Imperiale and coworkers[6] (1-year time frames). A 5-year time frame provides two advantages. First, we are able to model more accurately ulcer recurrence after acute antisecretory therapy in *H pylori*-positive patients (ie, clinical evidence suggests that patients will continue to experience a recurrence approximately 1 year after acute antisecretory therapy). Second, the 5-year time frame is necessary to evaluate a maintenance therapy scenario that appropriately models clinical evidence suggesting that patients experience recurrence over a 5-year period.[13]

It is important to note that our study does not consider the costs associated with initial diagnosis of PUD. Moreover, this study assumes that no test for *H pylori* is available from any studies that may have been conducted to diagnose PUD. For example, if an initial diagnosis were made through endoscopy, and if histology identified the presence of *H pylori*, the payer would be presented only with the incremental cost of performing the histology ($89), rather than with the cost of an additional endoscopy with histology ($712). Research should focus on studying the more general question of the costs associated with the management of dyspepsia, thereby including the costs of initial studies necessary to diagnose PUD.

Our study reports only one outcome measure—ulcer recurrences. Although this measure is important if physicians are to understand patient outcomes, other measures, such as symptom-free days,[2] also may be important in fully characterizing the benefits of *H pylori* eradication. For example, recent research[22] suggests that the presence of *H pylori* may be an independent factor in the achievement of symptomatic relief. Additional research on which outcome measures (eg, ulcer recurrences, symptom-free days) influence a physician's approach to the diagnosis and treatment of PUD is necessary to better describe the physician decision-making process.

··· CONCLUSION ···

Our results show that the United States can achieve significant cost savings by adopting new PUD management strategies that include eradication of *H pylori*. Substituting serology followed by appropriate drug treatment for acute antisecretory therapy, without testing for *H pylori*, would reduce the costs of treating PUD by 24%—savings that might be realized by health plans, the Medicare program, or patients. Moreover, adapting this strategy would reduce ulcer recurrences by 72% over 5 years.

Identifying and eradicating *H pylori* in patients with PUD can reduce US healthcare costs and result in significant improvements in patient care. On the basis of these findings, we conclude that diagnosis and eradication of *H pylori* should be considered standard treatment for patients with diagnosed PUD.

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··· REFERENCES ···

1. Helicobacter pylori in Peptic Ulcer Disease. NIH Consensus Statement. 1994 Feb 7-9;12(1):1-15.
2. Unge P, Jonsson B, Stalhammar N. The cost-effectiveness of *Helicobacter pylori* eradication versus maintenance

and episodic treatment in duodenal ulcer patients in Sweden. *PharmacoEconomics* 1995;8:410-427.
3. Sonnenberg A, Townsend WF. Costs of duodenal ulcer with antibiotics. *Arch Intern Med* 1995;155:922-928.
4. O'Brien B, Goeree R, Mohamed AH, et al. Cost-effectiveness of *Helicobacter pylori* eradication for the long-term management of duodenal ulcer in Canada. *Arch Intern Med* 1995;155:1958-1964.
5. Fendrick AM, Chernew ME, Hirth RA, et al. Alternative management strategies for patients with suspected peptic ulcer disease. *Ann Intern Med* 1995;123:260-268.
6. Imperiale TF, Speroff T, Cebul RD, et al. A cost analysis of alternative treatments for duodenal ulcer. *Ann Intern Med* 1995;123:665-672.
7. Talley NJ. Epidemiology of *Helicobacter pylori* infection. NIH Consensus Statement. 1994 Feb 7-9;12(1):1-15.
8. Heikkinen M, Pikkarainen p, Takala J, et al. Etiology of dyspepsia: Four hundred unselected consecutive patients in general practice. *Scand J Gastroenterol* 1995;30:519-523.
9. Rabeneck L, Ransohoff DF. Is *Helicobacter pylori* a cause of duodena ulcer? A methodologic critique of current evidence. *Am J Med* 1991;91:566-572.
10. Isselbacher KJ, Braunwald E, Wilson JD, et al. *Harrison's Principles of Internal Medicine*. 13th ed. New York: McGraw-Hill, Inc.; 1994:1367.
11. Brown KE, Peura DA. Diagnosis of *Helicobacter pylori* infection. *Gastroenterol Clin North Am* 1993;22:105-115.
12. Chiba N, Rao BV, Rademaker JW, et al. Meta-analysis of the efficacy of antibiotic therapy in eradicating *Helicobacter pylori*. *Am J Gastroenterol* 1992;87:1716-1727.
13. Penston JG, Wormsley KG. Review article: Maintenance treatment with H2-receptor antagonists for peptic ulcer disease. *Aliment Pharmacol Ther* 1992;6:3-29
14. Walan A. Chronically recurring ulcer. *Scand J Gastroenterol* 1987;22:18-20.
15. Graham DX, Lew GM, Klein PD, et al. Effect of treatment of *Helicobacter pylori* infection on the long-term recurrence of gastric or duodenal ulcer. *Ann Intern Med* 1992;116:705-708.
16. Penston JG, Wormsley KG. Efficacy and safety of long-term maintenance therapy of duodenal ulcers. *Scand J Gastroenterol* 1989;24:1145-1152.
17. Penston JG, Wormsley KG. Long-term maintenance treatment of gastric ulcers with ranitidine. *Aliment Pharmacol Ther* 1990;4;339-355.
18. Bardhan KD, Hinchliffe RFC, Bose K, et al. Six years of continuous cimetidine treatment in peptic ulcer disease: Efficacy and safety. *Aliment Pharmacol Ther* 1988;2: 395-405.
19. Laine L, Peterson WL. Bleeding peptic ulcer. *N Engl J Med* 1994;331:717-727.
20. *Red Book Update 1994*. Montvale, NJ: Medical Economics Data Production Co; 1994.
21. *Red Book*. Montvale, NJ: Medical Economics Co; 1994.
22. Velanovich V. The spectrum of *Helicobacter pylori* in upper gastrointestinal disease. *Am Surg* 1996;62:60-63.