Immediate Endoscopy or Initial *Helicobacter pylori* Serological Testing for Suspected Peptic Ulcer Disease: Estimating Cost-Effectiveness Using Decision Analysis

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Objective: To compare the clinical and economic effects of a strategy using immediate endoscopy to a non-invasive strategy utilizing a serologic test for *Helicobacter pylori* infection for individuals with symptoms suggestive of peptic ulcer disease.

Design: Cost-effectiveness analysis evaluating the clinical and economic effects of alternative management strategies of hypothetical patients with suspected peptic ulcer disease in a computer simulation model.

Intervention: Two strategies for hypothetical patients with suspected ulcer disease were evaluated: 1) Immediate endoscopy and biopsy for *H. pylori*, using antisecretory treatment in all patients with documented ulcers and adding antibiotic eradication therapy for those patients with ulcers whose biopsies were positive for *H. pylori*. 2) Empiric treatment with antisecretory therapy and serologic testing for *H. pylori* for all patients, using antibiotic eradication therapy only in patients testing positive for *H. pylori*.

Measurements: Cost per ulcer cured over a one-year study period.

Results: The more cost-effective strategy was the test-and-treat strategy (Strategy 2) with $4481 cost per ulcer cured. The immediate endoscopy strategy resulted in $8045 cost per ulcer cured. The cost-effectiveness advantage of the non-invasive strategy diminished as the cost of endoscopy fell or as the probability of recurrent symptoms rose in patients initially managed without endoscopy.

Conclusion: Endoscopy, though costly, precisely guided diagnosis and treatment and, thus, potentially reduced the number of patients inappropriately treated. However, cost-effectiveness analysis supports the continued practice of initial non-invasive management of patients with symptoms suggestive of peptic ulcer disease, achieving the benefits of *H. pylori* eradication through the use of serologic testing to guide antibiotic use.

INTRODUCTION

Empiric antisecretory therapy has been widely recommended as the initial management for patients presenting with presumed peptic ulcer disease, with endoscopic evaluation reserved for persistent or recurrent symptoms [1]. However, the association between

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dAbbreviations: NSAID, non-steroidal anti-inflammatory drug.

Helicobacter pylori and peptic ulcer disease compels rethinking of the management of this common clinical condition [2-3]. While elimination of the organism slightly improves ulcer healing rates, the principal benefit is the dramatic reduction in ulcer recurrence rates in those patients in whom the infection has been successfully eradicated [4-5]. In order to minimize inappropriate use of antibiotic therapy, guidelines such as those of an NIH Consensus Panel recommend a strategy that requires the objective documentation of an active ulcer and *H. pylori* infection prior to prescription of antibiotic treatment [6].

Such a recommendation makes two assumptions. First, that diagnostic confirmation of both ulcer disease and *H. pylori* infection is the optimal strategy after careful consideration of benefits, risks and costs of available alternatives. Second, that community physicians, who are accustomed to using initial empiric therapy in patients with ulcer-like symptoms, will find this guideline instructive in their clinical practice. Accordingly, the objective of our study was to use decision analytic techniques to assess the impact of a non-invasive approach to patients presenting with symptoms suggestive of peptic ulcer disease.

MATERIALS AND METHODS

Decision analytic model

The details of the decision analytic model used in this study have been published previously elsewhere [7]. Using a decision analysis software program, Decision Maker 7.0 (Pratt Medical Group, Boston, Massachusetts), a simulation was constructed to predict the natural history of peptic ulcer disease, its interaction with *H. pylori* infection and the effects of various diagnostic and therapeutic medical interventions. The analysis started with a cohort of 1000 hypothetical patients presenting to a physician with symptoms suggestive of peptic ulcer disease who were not concurrently taking NSAIDs[d]. On entry to the simulation, all of the hypothetical patients had symptoms of sufficient severity to justify an empiric course of antisecretory agents and no previously documented peptic ulcer disease.

Management strategies evaluated

1)   Immediate endoscopy and biopsy for *H. pylori*: All patients underwent immediate endoscopy and biopsy for *H. pylori*. Patients with an active ulcer detected by endoscopy were prescribed antisecretory therapy. Antibiotic therapy was limited to those individuals with both an ulcer and evidence of *H. pylori* infection found upon biopsy.

2)   Empiric treatment with antisecretory therapy and serologic testing for *H. pylori*: This strategy did not require diagnostic confirmation of an ulcer prior to the initiation of *H. pylori* eradication therapy. Every hypothetical patient was prescribed an empiric course of antisecretory agents, and in the computer simulation, underwent a qualitative *H. pylori* serologic test at the initial medical encounter. Only patients with a positive serologic test received antibiotic therapy.

Resource utilization such as physician visits, pharmaceutical use, procedures and hospitalizations were captured by the model. Each patient was evaluated in the model at six-week intervals for one year for the presence or absence of three clinical conditions on which all further interactions with the medical care system were based: recurrent symptoms, *H. pylori* infection and active ulcer disease. Patients whose symptoms were caused by reasons other than peptic ulcer disease were captured in the simulation up to and including the point at which they were objectively identified as not having an ulcer on endoscopic evaluation.

CLINICAL CONDITIONS AND SUBSEQUENT INTERVENTION

Recurrent Symptoms

After the initial intervention, every simulated patient with persistent or recurrent ulcer-like symptoms was assumed to return for medical evaluation. Those individuals initially managed non-invasively (Strategy 2) underwent endoscopy with biopsy for *H. pylori* infection on the first return visit for recurrent symptoms. All subsequent treatments were based on the endoscopy results and biopsy findings.

H. pylori Infection

Data from epidemiological investigations suggest that *H. pylori* is an infection of childhood to which a lifetime of immunological response is produced. Serological tests are available that qualitatively and quantitatively assess the presence or absence of antibodies to *H. pylori* infection [8]. Although spontaneous elimination of the organism is possible, in most instances the infection is lifelong in the absence of therapy intended to specifically eradicate the organism. In the simulation, *H. pylori* infection affected the likelihood of ulcer recurrence but had no direct effect on the development or resolution of symptoms.

If antibiotic therapy to eradicate *H. pylori* had not been prescribed previously, it was presumed that active infection was present in individuals with the presence of a positive qualitative antibody test. The serologic test was assumed to have 95 percent sensitivity and 95 percent specificity [8]. Although antibody levels fall after eradication of the organism, they remain detectable in the serum in many instances. The persistence of *H. pylori* antibodies after eradication considerably diminishes the value of qualitative serology in assessing whether infection has been cured, in that a positive test can indicate either *past* or *ongoing* infection. Thus, in the simulation, a qualitative serologic test was used only in those patients who had not previously received *H. pylori* eradication therapy.

Once eradication therapy was prescribed, either biopsy for *H. pylori* or a urea breath test was used to confirm cure or establish ongoing *H. pylori* infection. If endoscopy and biopsy were not to be performed for a specific symptomatic encounter, a urea breath test was undertaken to evaluate the effectiveness in eradicating *H. pylori*. Individuals who failed to clear *H. pylori* after three courses of antibiotic therapy were assumed to be infected for the remainder of the study period. Once cleared of *H. pylori*, infection was assumed not to recur [9].

Successful eradication of *H. pylori* in patients with ulcers associated with non-steroidal anti-inflammatory medications or diagnoses other than active ulcer disease (e.g., gastritis) was assumed not to offer any benefit in terms of reducing symptom severity or preventing future ulcer development.

Active ulcer disease

Ulcer status determined the likelihood of symptomatic relief from therapy and, thus, determined the need for future physician visits and related medical interventions. Endoscopy was assumed to be a perfect test to diagnose ulcer disease and was presumed to have no associated adverse events. Ulcer recurrence, not associated with NSAID use, was related to *H. pylori* status and concurrent use of antisecretory therapy [5, 10]. Spontaneous ulcer development was assumed not to occur in patients whose initial symptoms were secondary to non-ulcer causes. Ulcers that failed to heal completely after three courses of antisecretory therapy required maintenance antisecretory therapy for the duration of the study period.

DATA SOURCES

Clinical Probabilities

A Medline search was conducted for English language articles to provide pertinent clinical data for the simulation model. Bibliographies of accepted articles were reviewed and a search of current issues of the peer-reviewed, general medicine, infectious disease and gastroenterology literature was also undertaken to identify additional reports not included in the computerized database. In instances of data unavailability or uncertainty, unpublished data presented at the National Institutes of Health Consensus Development Meeting were used [6]. Clinical input probabilities and ranges used in the simulation are shown in Table 1.

Multiple antibiotic and antisecretory regimens of varying efficacy, cost, and compliance were evaluated. The relatively small differences in ulcer healing and *H. pylori* eradication rates among available regimens were investigated using sensitivity analysis. Compliance and outcomes related to specific medication use, including antibiotic-related adverse events, were incorporated into these analyses.

Table 1: Clinical inputs.

Clinical Probability	Base Case	Range
Active ulcer disease (%)	20	5-30
H. pylori infection ulcer present (%)	95	75-95
H. pylori infection ulcer absent (%)	50	20-60
Ulcer healing rate after antisecretory therapy (%)	75	50-90
H. pylori eradication after antibiotic course		
(%) (includes compliance)	80	50-90
Recurrent symptom rate, active ulcer (%)	90	50-90
Recurrent symptom rate, healed ulcer (%)	10	0-30
Recurrent symptoms, no ulcer (%)/year	30	10-70
Ulcer recurrence, *H. pylori* infection		
(%)/100 patient months	2.7	2.0-6.6
Ulcer recurrence, no infection		
(%)/100 patient months	0.6	0.1-2.0
Serious antibiotic complication per course (%)	0.5	0.1-1.0
Qualitative *H. pylori* serology test sensitivity	0.95	0.50-1.0
Qualitative *H. pylori* serology specificity	0.95	0.50-1.0

Table 2: Cost estimates

Intervention	Base Case ($)	Range ($)
Endoscopy	1180	200-2000
Biopsy for *H. pylori*	210	40-250
Antisecretory therapy (6 week course, full dose)	160	25-250
Maintenance antisecretory therapy (per month)	45	25-75
Antibiotic course (includes adverse events)	30	10-100
Qualitative *H. pylori* serology test	20	10-100
Urea breath test	200	50-200
Physician office visit	39	20-100
Hospitalization for ulcer complication, no surgery	7,095	6,000-12,000
Hospitalization for ulcer complication, surgery	24,081	17,500-38,000

Cost Inputs

The perspective of the economic analysis was from that of the payer. Actual payments, not charges, for ambulatory services, inpatient care and physicians fees were obtained from a large private third-party payer covering approximately three million persons in the Eastern United States (Table 2). Given that variation in actual payments for similar services exist by geographic region, we used the national average of charges allowed by the Health Care Financing Administration for Medicare reimbursement to determine the lower bound of the cost estimates.

SENSITIVITY ANALYSIS

Sensitivity analyses were performed to evaluate the effect of variations in clinical probabilities and cost estimates on the results. These reflect the ranges reported in the published and unpublished literature (Tables 1 and 2). Only those input values whose inclusion into the model would enhance the cost-effectiveness of the immediate endoscopy strategy or diminish cost-effectiveness of initial non-invasive management were investigated.

RESULTS

Cost per ulcer cured

The more cost-effective strategy was the non-invasive strategy incorporating serologic testing (Strategy 2) with $4481 cost per ulcer cured (Figure 1). The immediate endoscopy strategy resulted in $8045 cost per ulcer cured. Given the high rate of symptoms in patients with active ulcer disease, nearly all (over 98 percent) active ulcers and associated *H. pylori* infections were objectively diagnosed and treated by the end of the study period in each strategy. The cost breakdown of various inputs to the cost per ulcer cured is shown in Figure 2. While pharmaceutical costs per ulcer cured were $769 higher for the non-invasive strategy, expenditures for endoscopy were $4606 lower, which more than offset the increased expenditure on drugs.
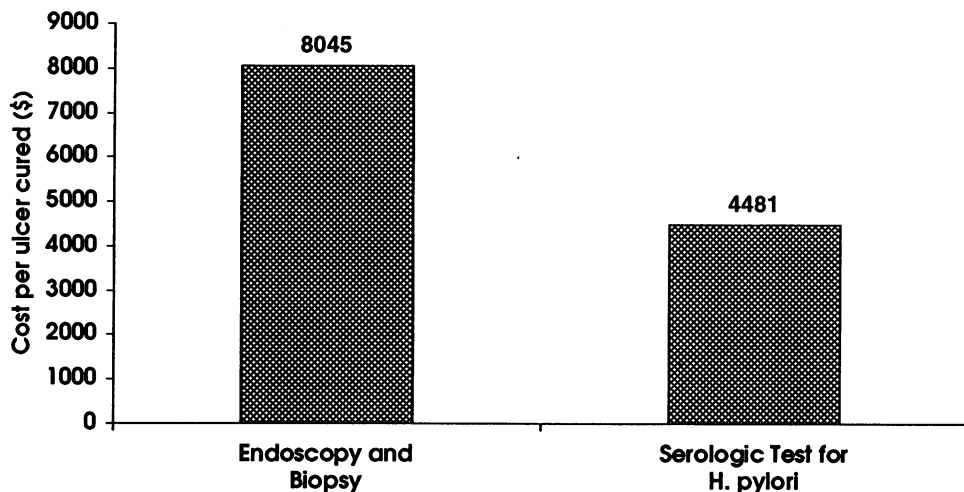

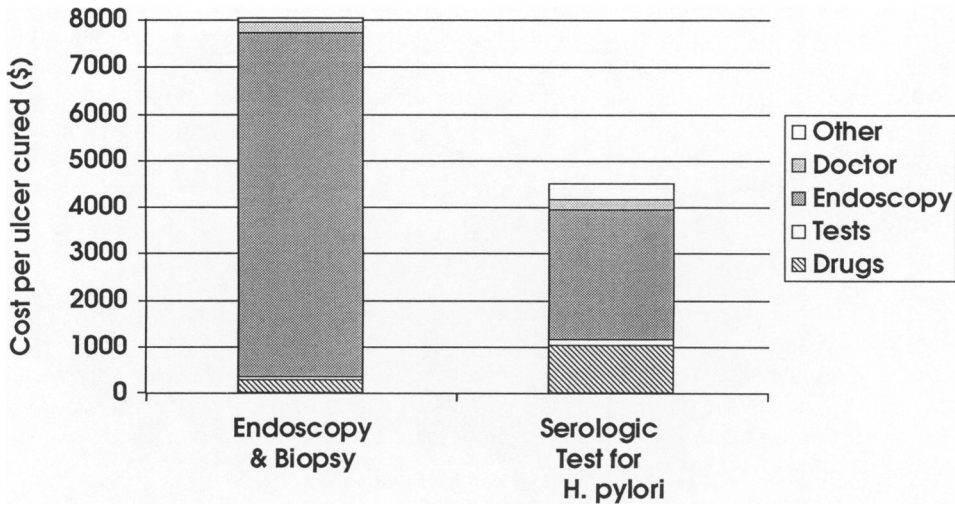**Figure 1. Cost per ulcer cured by management strategy.**

Figure 2. Cost breakdown per ulcer cured.

Sensitivity analysis

Examination of clinical and cost inputs over broad ranges revealed that the cost-effectiveness advantage of non-invasive strategy (Strategy 2) relative to immediate endoscopy (Strategy 1) was sensitive to only two variables: 1) cost of endoscopy and 2) probability of recurrent symptoms in non-invasively treated patients in whom ulcer disease was not the underlying cause of their symptoms.

As the cost of endoscopy fell, the cost per patient treated of strategies using immediate endoscopy approached that of the non-invasive strategies (Figure 3). Endoscopy costs, inclusive of payments for professional fees and suite charges, must fall below $500 for an equivalent cost-effectiveness ratio to result. The cost-effectiveness advantage of non-invasive management was unchanged if biopsy were replaced by a less expensive CLO test.
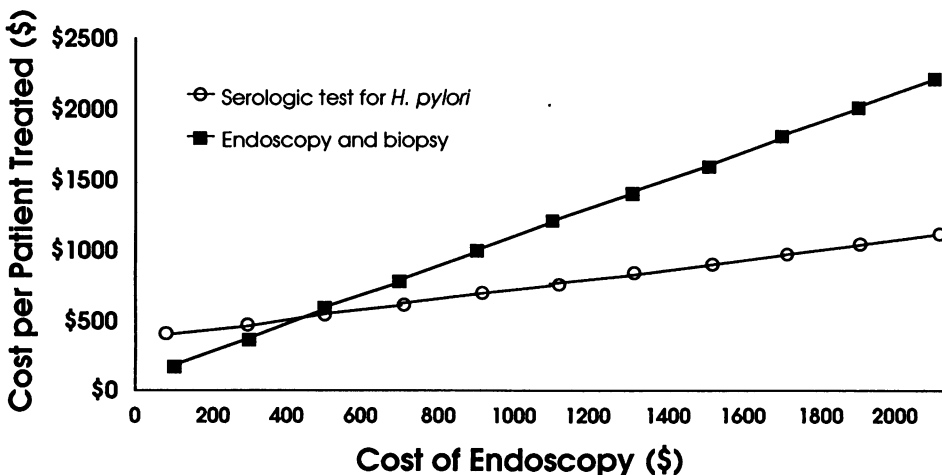

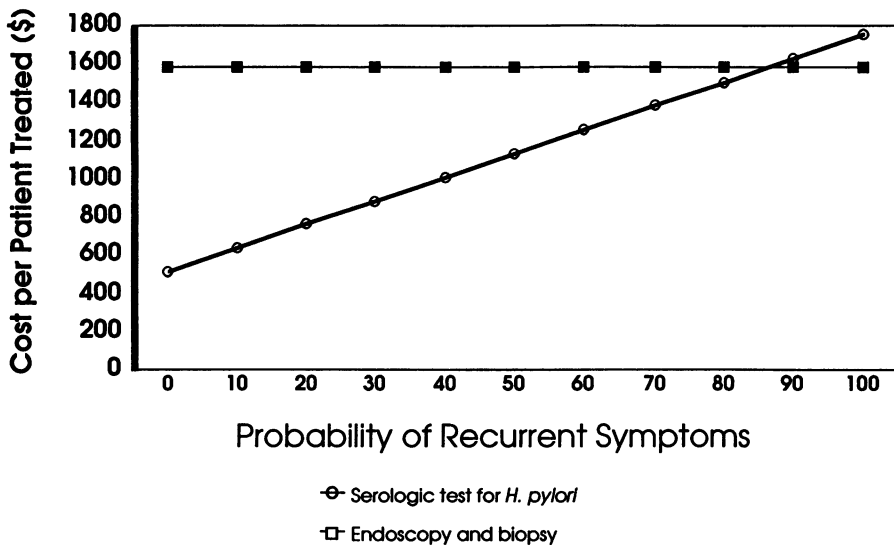**Figure 3. Sensitivity analysis: cost of endoscopy.**

Figure 4. Sensitivity analysis: probability of recurrent symptoms in patients without ulcer disease.

The other input variable found to be important in establishing an advantage for the non-invasive strategies was the probability of recurrent symptoms in patients without ulcer disease. Individuals without ulcer disease with recurrent symptoms after a course of empiric therapy incurred the cost of invasive diagnostic testing (mandatory for recurrent symptoms in all non-invasively treated patients) in addition to the cost of initial therapy. Therefore, as the probability of recurrent symptoms rose in this population, the potential savings of initial non-invasive management diminished as the use of endoscopy increased. As the annual recurrent symptom rate approached 80 percent, the cost per patient treated of the non-invasive strategy approached that of the immediate endoscopy (Figure 4).

Sensitivity analysis which simultaneously varied the cost of endoscopy and the probability of recurrent symptoms in non-ulcer patients was performed. This analysis revealed that the choice of immediate endoscopy and biopsy (Strategy 1) versus test-and-treat (Strategy 2) can be determined at different values of these clinical and economic inputs (Figure 5).

DISCUSSION

In 1985, an American College of Physicians Position Paper supported empiric anti-secretory therapy as the initial management for patients presenting with presumed peptic ulcer disease, recommending endoscopy only in those individuals who failed an appropriate course of therapy [1]. The realization that acid suppression must be accompanied by *H. pylori* eradication to prevent ulcer recurrence, necessitates reevaluating this existing treatment algorithm.

The NIH Consensus Panel Statement implicitly endorsed a strategy to document the presence of both an ulcer and *H. pylori* infection prior to prescribing eradication therapy [6]. The recommendation requiring confirmation of both diagnoses has raised considerable uncertainty among clinicians who have widely accepted an empiric first-line management of patients with presumed peptic ulcer disease. Compliance with the NIH Consensus Panel recommendations would require increased invasive diagnostic testing
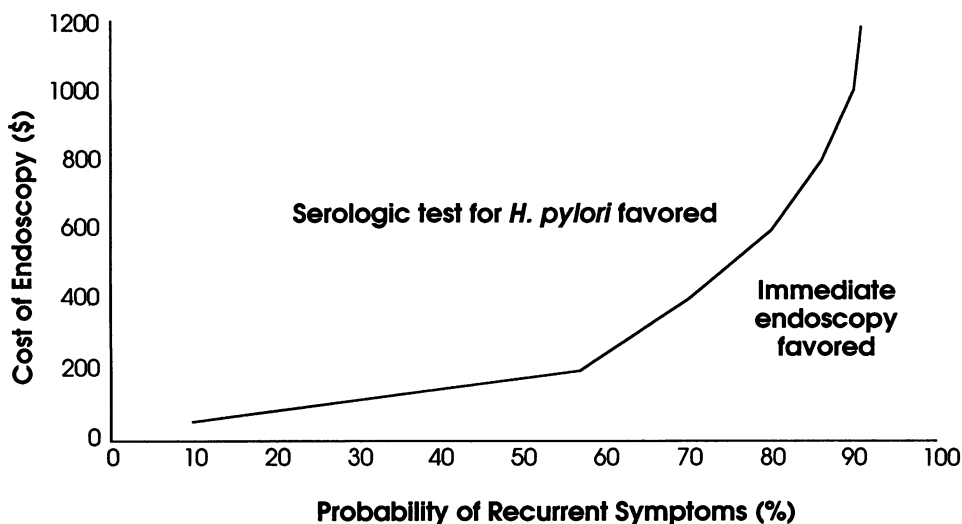
Figure 5. Two variable sensitivity analysis: cost of endoscopy and probability of recurrent symptoms in patients without ulcer disease. Area above solid line favors empiric therapy; area below line favors immediate endoscopy.

prior to treatment, necessitating increased health system and patient-related costs to achieve perfect diagnostic information.

Our cost-effectiveness analysis supports the continued use of a non-invasive treatment strategy incorporating a serologic test for *H. pylori* infection at the first symptomatic episode, changing somewhat the strategy of initial empiric H_2 blocker therapy commonly used in clinical practice. We recommend a single course of empiric therapy guided by a non-invasive serologic test for *H. pylori*. In our simulation, endoscopy was performed on all patients who remained symptomatic or in whom symptoms recurred.

Although the cost-effectiveness ratios included antibiotic-related adverse events, the analysis did not include the non-drug costs of over-prescribing antibiotics which, in theory, increase the likelihood of *H. pylori* resistance [11]. The issue of bacterial resistance is a real one when discussing broad use of antibiotics, especially when an important percentage of patients prescribed these agents may not receive clinical benefit, in that ulcer disease was not the cause of the symptoms. At present, data are being collected to allow quantification of antibiotic resistance. This calculation is complicated by the fact that all of the antibiotic agents currently recommended (but not FDA approved) for treatment of *H. pylori* are prescribed for other clinical indications.

Promotion of antibiotic resistance is not frequently considered in the individual patient-physician episode of care, but is an important societal issue. Nonetheless, the potential to maintain effective treatments in the future is of considerable importance. Interestingly, antibiotic resistance to *H. pylori* may be viewed differently by clinicians, in that when compared to other pathogens (e.g., *S. aureus*) *H. pylori* has a relatively low level of infectiousness, and resultant infection does not cause significant morbidity in a majority of cases.

The cost-effectiveness advantage for the non-invasive strategies over a strategy of immediate endoscopy was sensitive to two inputs: the cost of endoscopy and the probability of recurrent symptoms leading to eventual endoscopy. Lower payments for endoscopy, such as those found in competitive, managed care markets or delivery systems

outside the United States, may lead to a different strategy choice. Independent of endoscopy cost, as the likelihood of eventual endoscopy increased, the savings achieved by initially avoiding this diagnostic test was lost. A recent prospective trial from Denmark comparing empiric H_2 blocker therapy and immediate endoscopy reported that 65 percent of empirically treated patients with dyspepsia eventually underwent endoscopy, although no attempts at *H. pylori* eradication were attempted [12]. At this rate of recurrent symptoms, the cost-effectiveness advantage of the initial non-invasive strategy was minimal (Figure 4).

CONCLUSION

Endoscopy, though costly, precisely guides diagnosis and treatment and, thus, potentially reduces the number of patients treated unnecessarily with antibiotics. However, our cost-effectiveness analysis supports the continued practice of initial non-invasive management of patients with symptoms suggestive of peptic ulcer disease, but achieves the benefits of *H. pylori* eradication through the use of serologic testing to guide antibiotic use.

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