Evaluation of the Dyspeptic Patient: A Cost-Utility Study

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BACKGROUND. Traditionally, patients presenting with uncomplicated dyspepsia have been managed using empiric antisecretory therapy, followed by endoscopy in the event of persistent symptoms or complication. Since *Helicobacter pylori* is now accepted as an important and potentially reversible cause of ulcer disease, it is important to reevaluate the management of dyspepsia. The goal of this study is to evaluate seven outpatient strategies for the management of dyspeptic patients using a cost-utility analysis.

METHODS. The study design was that of a cost-utility analysis. The model assumes that an adult patient with signs of dyspepsia but no signs of complication presents to the outpatient office of a primary care physician. Seven strategies are modeled: empiric antisecretory therapy; empiric *H pylori* eradication using oral omeprazole (500 mg twice daily), clarithromycin (500 mg twice daily), and amoxicillin (1000 mg twice daily); use of either upper endoscopy, an upper gastrointestinal barium study (an upper GI), or the serum titer for *H pylori* as a diagnostic test to identify patients for *H pylori* eradication; or use of an initial diagnostic test followed by the serum titer for *H pylori*. The primary outcome was the cost per quality-adjusted life year (QALY) for each strategy for a 1-year period from presentation; secondary outcomes included the probability of symptomatic ulcer recurrence, cost per ulcer cure, and mortality.

RESULTS. Three strategies were similarly cost-effective: empiric *H pylori* eradication ($1198 per QALY), use of a serum *H pylori* titer as an initial diagnostic test ($1214 per QALY), and empiric antisecretory therapy ($1288 per QALY). Empiric antisecretory therapy, however, was associated with significantly more symptomatic ulcer recurrences and deaths than any other strategy.

CONCLUSIONS. This cost-utility analysis suggests that two strategies are reasonable for patients presenting with dyspepsia: (1) empiric *H pylori* eradication and (2) use of a serum *H pylori* titer to identify patients who might benefit from *H pylori* eradication. The latter strategy may be preferable because it is less likely to lead to antibiotic resistance. Strategies utilizing an upper GI or upper endoscopy (either with or without serum *H pylori* titer) or empiric antisecretory therapy do not improve outcomes and are associated with greater cost, morbidity, and/or mortality.

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Dyspepsia is a common reason for visiting the primary care physician, representing 1% to 2% of all visits,[1,2] or approximately 2 million outpatient consultations annually in the United States.[1] It is also an extremely common complaint in population-based surveys, with a period prevalence of approximately 30% per year[3,4] and an annual incidence of 10%.[5] Traditional management recommendations have emphasized lifestyle changes such as weight loss, tobacco avoidance, and dietary manipulation, empiric use of antacids and histamine$_2$ receptor antagonists, and judicious use of imaging and endoscopic procedures for diagnosis.[6]

Recent studies have confirmed the role of *Helicobacter pylori* in the pathogenesis of gastric ulcer, duodenal ulcer, and gastric cancer,[7] and that eradication of *H pylori* greatly reduces the rate of ulcer recurrence.[8-11] This new information about the role of *H pylori* ulcer disease puts the previous approach to management of dyspepsia in question, and suggests that accurate diagnosis of ulcer disease may be more important in guiding therapy than previously thought. Thus, greater use of upper endoscopy or an upper gastrointestinal barium study (an upper GI) to accurately identify patients with peptic ulcer disease (ie, those who

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will benefit most from *H pylori* eradication) may be appropriate. On the other hand, because of its safety and potential benefit, empiric *H pylori* eradication either of all patients or of only *H pylori* –positive patients may be more cost-effective than other strategies, despite lack of evidence for the efficacy of *H pylori* eradication in patients with non-ulcer dyspepsia.

Two previous economic analyses of upper gastrointestinal disease either have been too old to include consideration of *H pylori* infection[9] or began with the assumption that the index patient had a duodenal ulcer diagnosed by endoscopy rather than dyspepsia.[10] A recent cost-effectiveness analysis considered evaluation of the dyspeptic patient, and, using the outcomes of cost per ulcer cured and cost per ulcer treated, found that empiric eradication of *H pylori* in all dyspeptic patients was the most cost-effective strategy.[11] These investigators, however, did not consider strategies involving an upper GI as the diagnostic test, or strategies in which an upper GI was followed by use of a serologic test for *H pylori* to determine which patients are treated for *H pylori* eradication. They also did not measure the utility of each strategy in quality-adjusted life years (QALYs), and did not consider mortality as an outcome.

This study modeled seven strategies to identify the most cost-effective strategy (in dollars per QALY) for the management of dyspepsia in the primary care setting. The baseline analysis uses the combination of omeprazole 20 mg, clarithromycin 500 mg, and either amoxicillin 1 g or metronidazole 500 mg (for amoxicillin-allergic patients), each twice daily for 1 week to eradicate *H pylori*. This regimen has been recommended by the Practice Parameters Committee of the American College of Gastroenterology, and has been shown to be 86% to 91% effective in eradicating *H pylori*.[12] Strategies considered include the following: empiric antisecretory therapy for 1 month with omeprazole; empiric *H pylori* eradication; use of either upper endoscopy, an upper GI, or the serum titer for *H pylori* as a diagnostic test to identify patients for *H pylori* eradication; and use of upper endoscopy or an upper GI followed by the serum titer for *H pylori* if positive for ulcer

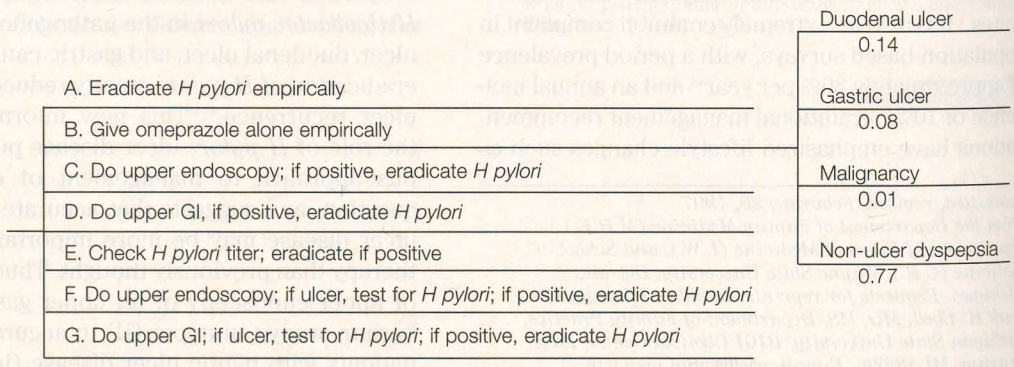
METHODS

Index Patient

The index patient is an adult presenting to a primary care physician in the outpatient setting with a chief complaint of dyspepsia. Dyspepsia is defined as intermittent pain in the upper abdomen caused by disease of the esophagus, stomach and/or duodenum of at least 2 weeks' duration, typically associated with gas, eructations, bloating, and nausea. The patient was assumed not to have signs of serious complication such as gastrointestinal bleeding, obstruction, or perforation at the initial presentation, although complications were a possibility if a patient with an ulcer suffered a recurrence during the year following his or her initial presentation. A 1-year time horizon was used because the literature does not support reliable estimates for important variables beyond that point.

FIGURE 1

Strategies considered in the cost-utility analysis of the management of dyspepsia. Also shown is the initial arborization of Strategy B, with the probability that a dyspeptic patient has each of the diagnoses shown.



Cost-Utility Model

Seven possible strategies for the management of dyspepsia were identified and modeled for the cost-utility analysis (Figure 1). The decision analytic model was created using DATA version 2.6.6 for Windows (TreeAge Software, Inc, Williamstown, Mass); the final cost-utility model had 1078 nodes. While it is not possible to display or describe in detail every strategy modeled in the decision tree, it is available for downloading through File Transfer Protocol from the Internet at ftp://users.aol.com/mhebell/dyspep.tre.

The primary outcome was cost per quality-adjusted life year ($/QALY). Secondary outcomes include cost per ulcer cure (cure defined as a patient with ulcer not experiencing a recurrence for 1 year), cost per dyspeptic patient, utility per dyspeptic patient in QALYs, and the rates of symptomatic ulcer recurrence and death associated with each strategy.

Determination of Probabilities

The MEDLARS database of the National Library of Medicine from 1980 to 1995 was searched for relevant abstracts using a strategy involving the key words "Helicobacter pylori," "peptic ulcer disease," "triple therapy," and "antibiotic treatment." The resulting list of approximately 700 abstracts was reviewed by the investigators (M.H.E. and L.W.), and 250 articles were selected for closer review. Articles that described nonclinical research were not further reviewed. An explicit quality review was not attempted.

The investigators created a list of variables needed for the cost-utility model, such as the probability that a dyspeptic patient has a duodenal ulcer and the probability that triple therapy will eradicate *H pylori*. Each paper was pre-reviewed by the research assistant, who identified which variables were contained in each article. Then, each of the investigators (M.H.E. and L.W.) reviewed each article and abstracted data about relevant variables and recorded them in a spreadsheet. This spreadsheet was then sorted to group articles addressing a given variable together, and this information was used to determine a summary value for the cost-utility analysis. While a weighted average was the starting point for determining the summary value, the population studied in an article and the quality of the study's methodology were also considered by the investigators in determining the final value used as the point estimate in the cost-utility model. The same data were used to determine the range for the sensitivity analyses.

The following probabilities were identified for the cost-effectiveness analysis (Table 1): the probability of *H pylori* infection for patients with duodenal ulcer,[16-21] gastric ulcer,[17,19-21] and non-ulcer dyspepsia[18,20-23]; the probability of duodenal ulcer, gastric ulcer, gastric cancer, and non-ulcer dyspepsia among dyspeptic patients[18,20,21,24-29] before testing; the probability that a recurrence of duodenal or gastric ulcer is complicated and requires hospitalization[30-33]; that a complicated duodenal or gastric ulcer recurrence leads to death,[33] that a duodenal[9-12] or gastric[34] ulcer will recur in an *H pylori*–negative patient; that a duodenal[30,35] or gastric[30,35] ulcer will recur in an *H pylori*–positive patient receiving maintenance therapy; that an ulcer recurrence is symptomatic[36]; that *H pylori* is eradicated by the baseline regimen of omeprazole 20 mg twice daily, clarithromycin 500 mg twice daily, and amoxicillin 1000 mg twice daily for 1 week[15]; and that *H pylori* is eradicated by an alternative regimen of bismuth subsalicylate 2 tablets four times daily, tetracycline 500 mg four times daily, and metronidazole 250 mg four times daily for 2 weeks.[15,37] The probability of a minor adverse drug reaction to *H pylori* eradication was estimated by the authors to be 10% for the baseline regimen, and the probability of *H pylori* infection in patients with gastric cancer was assumed to be the same as that in patients with gastric ulcer; reliable data could not be found in the literature for these variables. Sensitivity analyses for these assumptions were performed and did not affect the ranking of preferred strategies. The value of 0.45 for *H pylori* infection in patients with non-ulcer dyspepsia reflects an estimate for patients in the United States, which is somewhat lower than estimates reported in some Asian and European studies.[7]

The sensitivity and specificity of the following tests were identified from the literature: a urease test of the endoscopic biopsy specimen for *H pylori*[38,39]; a serum IgG titer for *H pylori*[40,41]; upper endoscopy[42-44]; and an upper GI.[45,46] These results are summarized in Table 2.

Determination of Cost

A payer perspective was used to determine the cost of each strategy. Five pharmacies were surveyed to

obtain the cost of omeprazole, clarithromycin, tetracycline, metronidazole, and amoxicillin, and the average charge was used as a proxy for cost. Medicare reimbursement at a local community hospital, a university hospital, and a large community teaching hospital, as well as the reimbursement level of a large health maintenance organization, were used as a proxy for the cost of upper endoscopy, an office visit, serum IgG for *H pylori*, an upper GI, hospitalization for gastrointestinal bleeding, and hospitalization for ulcer surgery. These data are summarized in Table 3.

Calculation of Quality-Adjusted Life Years

The disutility (a measure of morbidity) of individual events such as experiencing endoscopy or experiencing an ulcer recurrence were measured using the Index of Well-Being (IWB), a well-validated multiattribute measure of general health status.[47] The IWB takes into account patient mobility, physical activity, social activity, and symptoms. To calculate the disutility of an event for the cost-utility model, the following formula was used:

$$\text{Disutility in QALYs} = \frac{(1-\text{utility of health state}) \times (\text{duration of health state in days})}{365}$$

For example, a utility of 0.7433 for a 6-week delay in diagnosing cancer would result in a total disutility of $[(1-0.7433) \times 42] / 365 = (0.2567 \times 42) / 365 = 10.8/365 = 0.03$ QALYs. Patients began the model with an optimal quality of life (QALY = 1.0) when they entered the model, which was decremented by the number of QALYs associated with each adverse event. For example, a patient experiencing an upper endoscopy and a minor side effect of antibiotic therapy would have a total QALY for the year of the study of $1.0 - 0.001 - 0.005 = 0.994$. The disutilities are summarized in Table 4.

Assumptions

Any cost-utility analysis makes assumptions about the process of care, patient behavior, and physician decision-making in order to simplify the model while maintaining believability. The model assumed an initial cost of $0 and an initial QALY of 1.0; costs were then added and disutilities subtracted as they were experienced by patients in each diagnostic strategy. In the decision model, a patient was assumed to have either duodenal ulcer, gastric ulcer, gastric cancer, or non-ulcer dyspepsia. A patient with gastric or duodenal ulcer could either experience a recurrence or remain disease-free. Recurrences included those that took place both early and late within 1 year following initial therapy, and it was assumed that 60% of these would be symptomatic.[36] Patients remaining completely disease-free did not require maintenance therapy, while those suffering an asymptomatic ulcer recurrence were assumed to take a maintenance dose of an H_2 antagonist every other day. While asymptomatic in terms of presenting to a physician for care, these patients were assumed to have some dyspeptic symptoms requiring use of an antisecretory agent.

Symptomatic ulcer recurrences resulted in reevaluation and upper endoscopy, and could be simple (outpatient treatment with omeprazole and *H pylori* eradication, followed by maintenance therapy with an H_2 antagonist) or complicated (hospitalization with a 20% chance of surgery for bleeding, obstruction, or perforation, followed by omeprazole and *H pylori* eradication, and finally maintenance therapy with an H_2 antagonist). Patients with gastric ulcer always underwent repeat endoscopy, regardless of whether they experienced a recurrence.

In the strategy of initial empiric *H pylori* eradication, the probability of recurrence depended on the initial rate of *H pylori* infection for each diagnosis and the success rate for *H pylori* eradication. Our baseline assumption used oral omeprazole 20 mg twice daily, clarithromycin 500 mg twice daily, and amoxicillin 1000 mg twice daily for 1 week to eradicate *H pylori*, followed by 3 weeks of only omeprazole 20 mg four times a day. This has been associated with a rate of *H pylori* eradication in previous studies of 86% to 91%.[15] If a diagnostic test such as endoscopy, upper GI, or serum titer for *H pylori* was used to identify patients for *H pylori* eradication, patients with ulcer ran the risk of being misclassified as ulcer-free and not receiving needed therapy to eradicate *H pylori*. On the other hand, patients treated empirically ran the risk of having a diagnosis of cancer delayed by 6 weeks; it was assumed, however, that patients with cancer would have persistent symptoms, and would therefore undergo endoscopic diagnosis after 6 weeks of unsuccessful empiric therapy.

Patients with non-ulcer dyspepsia are not "cured" by either antisecretory therapy or *H pylori* eradication, and are assumed to have persistent symptoms

TABLE 1

Probability of Events in the Cost-Utility Model

Event	Probability	Range of Sensitivity Analyses
Probability that patients with the following are *H pylori* infected:		
Duodenal ulcer	0.95	0.8 - 1.0
Gastric ulcer	0.85	0.8 - 1.0
Gastric cancer	0.9	0.8 - 1.0
Non-ulcer dyspepsia	0.45	0.3 - 0.6
Probability that dyspepsia represents:		
Duodenal ulcer	0.14	0.05 - 0.25
Gastric ulcer	0.08	0.03 - 0.10
Gastric cancer	0.01	0.01 - 0.03
Non-ulcer dyspepsia	0.77	0.62 - 0.91
Probability that:		
A recurrence of duodenal or gastric ulcer is complicated (bleeding, obstruction, perforation) and requires hospitalization	0.2	0.05 - 0.3
A complicated duodenal or gastric ulcer recurrence leads to death	0.01	0.0 - 0.10
A duodenal ulcer will recur in an *H pylori*-negative patient	0.08	0.04 - 0.20
A gastric ulcer will recur in an *H pylori*-negative patient	0.05	0.02 - 0.15
A duodenal ulcer will recur in an *H pylori*-positive patient on maintenance therapy	0.3	0.1 - 0.6
A gastric ulcer will recur in an *H pylori*-positive patient on maintenance therapy	0.25	0.1 - 0.5
A duodenal or gastric ulcer recurrence is symptomatic	0.6	0.3 - 0.9
H pylori is eradicated by 1 week of omeprazole 20 mg po bid + clarithromycin 500 mg po bid + amoxicillin 1000 mg bid	0.85	0.5 - 0.95
H pylori is eradicated by 2 weeks of bismuth subsalicylate 2 tablets po qid + tetracycline 500 mg po qid + metronidazole 250 mg po qid	0.85	0.5 - 0.95
A patient has a minor reaction to *H pylori* eradication	0.1	0.05 - 0.3

following the initial evaluation, which are generally controlled by maintenance antisecretory therapy. (It was conservatively assumed that *H pylori* eradication had no effect on the course of non-ulcer dyspepsia, and that successful maintenance treatment of non-ulcer dyspepsia does not change a patient's quality of life.) Whether a patient with non-ulcer dyspepsia eventually underwent endoscopy depended on the initial management strategy. If patients had an initial endoscopy or upper GI that was falsely positive for ulcer, it was assumed that 2 of 3 patients would undergo endoscopy in follow-up; if their initial endoscopy or upper GI was negative for ulcer, only 1 of 3 patients underwent endoscopy in follow-up. Among patients with non-ulcer dyspepsia who did not have an initial endoscopy or upper GI, one half were assumed to have persistent symptoms severe enough to require endoscopy eventually. Since evidence is not available in the literature for the above variables concerning non-ulcer dyspepsia, these estimates are based on the clinical experience of the authors and discussions with colleagues.

Analysis

One-way sensitivity analysis was performed for each probability, cost, and utility in the cost-utility model. In a one-way sensitivity analysis, a variable is varied over a broad but realistic range of values to see if a point can be identified at which a competing strategy becomes more cost-effective than the preferred strategy in the baseline model. Clinically important pairs of variables were also evaluated using a two-way sensitivity analysis, in which two variables are simultaneously varied, again to determine whether any strategy becomes more cost-effective at a particular combination of values for these variables than the preferred strategy in the baseline model.

RESULTS

The cost, QALYs, marginal cost, and cost per QALY for each strategy are shown in Table 5.

TABLE 2

Test Characteristics (sensitivity and specificity) for the Cost-Utility Analysis

Test and Condition Being Evaluated	Sensitivity	Range for Sensitivity Analysis	Specificity	Range for Specificity Analysis
Urease test of biopsy specimen for *H pylori*	0.9	0.8 - 1.0	0.95	0.8 - 1.0
Serum IgG titer for *H pylori*	0.9	0.75 - 1.0	0.9	0.75 - 1.0
Upper endoscopy:				
Gastric cancer	0.95	0.9 - 1.0	0.98	0.95 - 1.0
Duodenal ulcer	0.9	0.8 - 1.0	0.98	0.95 - 1.0
Gastric ulcer	0.95	0.9 - 1.0	0.98	0.95 - 1.0
Upper gastrointestinal barium study:				
Gastric cancer	0.9	0.7 - 1.0	0.93	0.8 - 1.0
Duodenal ulcer	0.75	0.7 - 1.0	0.93	0.8 - 1.0
Gastric ulcer	0.9	0.7 - 1.0	0.93	0.8 - 1.0

Because the difference in effectiveness (QALYs) of the different strategies was not felt to be clinically significant, the marginal cost-effectiveness was not calculated. The cost-effectiveness data are shown graphically in Figure 2. Three strategies (A, B, and E) were roughly equal in cost per dyspeptic patient and cost-effectiveness: empiric *H pylori* eradication for all patients ($1198/QALY), *H pylori* eradication if a serum *H pylori* titer was positive ($1214/QALY), and empiric antisecretory therapy ($1288/QALY).

Secondary outcomes for each strategy are shown in Table 6. Empiric *H pylori* eradication (strategy A) was associated with the lowest probability of symptomatic ulcer recurrence (1.3% of all dyspeptic patients) and death (2.6 deaths per 100,000 dyspeptic patients). Empiric antisecretory therapy (strategy B) had a considerably greater rate of symptomatic recurrence (3.5% of all dyspeptic patients) and death (7.0 deaths per 100,000 dyspeptic patients) than any other strategy. The greatest utility in QALYs was associated with a strategy of empiric antisecretory therapy (strategy B). Because of the rarity and short duration of bad or unpleasant outcomes in dyspepsia, however, there was very little difference in utility between the seven strategies, with a total range from the highest utility strategy (B) to the lowest utility strategy (D) of only 0.001 QALY.

One-way sensitivity analysis of each probability, cost, and utility over the range shown in Tables 1 through 3 found that several variables affected the determination of which strategy was the most cost-effective. Eradicating *H pylori* in patients with a positive upper GI and positive serum *H pylori* titer (strategy G) became roughly equivalent to the three top strategies in the baseline analysis (A, B, and E) when the cost of an upper GI was less than $50. Relying on the results of the serum *H pylori* titer (strategy E) became more cost-effective than empiric *H pylori* eradication (strategy A) when the cost of a serum *H pylori* titer dropped from $60 to below $44 or the cost of *H pylori* eradication rose from $128 to above $162. Empiric antisecretory therapy became the most cost-effective strategy when the cost of *H pylori* eradication rose from $128 to above $273.

Two-way sensitivity analysis of the sensitivity and specificity of each test in Table 2 did not affect the choice of the optimal strategy. Two-way sensitivity analyses were also performed for several combinations of variables of potential clinical interest: cost of *H pylori* eradication and probability of side effects of therapy; probability of gastric and duodenal ulcer; and probability of complicated recurrence and death. The combination of lower cost ($60 rather than $128) and more side effects (40% rather than 10%) simulates the use of 2 weeks of traditional triple therapy to eradicate *H pylori*, ie, tetracycline 500 mg four times daily, metronidazole 250 mg four times daily, and bismuth subsalicylate 2 tablets four times daily. Using this strategy, empiric *H pylori* eradication remained the most cost-effective strategy ($1138/QALY), still followed by treatment

based on the serum *H pylori* titer ($1182/QALY) and empiric antisecretory therapy ($1285/QALY).

The remaining two-way sensitivity analysis found that the optimal strategy was sensitive to the probabilities of duodenal and gastric ulcer. At a low probability of duodenal or gastric ulcer (combined probability less than ~12%), empiric antisecretory therapy was the preferred strategy; at higher probabilities of ulcer, empiric *H pylori* eradication was preferred. The probability of death or complicated ulcer recurrence did not affect the choice of the optimal strategy.

TABLE 3

Cost of Events Experienced by Patients with Dyspepsia

Clinical Event	Value Used in Cost-Utility Analysis,$	Range for Sensitivity Analysis,$
Minor reaction to *H pylori* eradication therapy	15	5 - 30
Cost of inpatient therapy for complicated ulcer	6000	4000 - 10,000
Cost of inpatient therapy for complicated ulcer including surgery	15,000	10,000 - 20,000
Urease test for *H pylori* on biopsy specimen (not including the cost of endoscopy)	60	10 - 150
Omeprazole 20 mg po qd for 4 weeks	108	50 - 200
H pylori eradication: omeprazole 20 mg po bid + amoxicillin 1000 mg po bid + clarithromycin 500 mg po bid for 1 week	126	150 - 350
H pylori eradication: bismuth subsalicylate 2 tablets po qid + tetracycline 500 mg po qid + metronidazole 250 mg po qid for 2 weeks	40	20 - 60
Serum IgG titer for *H pylori*	60	25 - 150
Maintenance H_2 antagonist therapy for 1 year	600	300 - 1500
Office visit to a physician	45	30 - 70
Upper gastrointestinal barium study	300	50 - 500
Upper endoscopy (both hospital and physician fees)	1000	200 - 1500

DISCUSSION

Three strategies for the management of dyspepsia in the primary care setting were roughly equal in cost-effectiveness in the baseline model: empiric *H pylori* eradication, *H pylori* eradication if the serum *H pylori* titer was positive, and empiric antisecretory therapy. The latter strategy, however, was associated with a significantly greater probability of symptomatic ulcer recurrence (3.5% vs 1.3%) and death (7 deaths vs 2.6 deaths per 100,000 dyspeptic patients) than the other two; for this reason, we feel that it cannot be recommended unless the probability of ulcer, and therefore risk of ulcer recurrence or death, is very low. It is important to note that some of the model's assumptions were quite conservative: we assumed no benefit of *H pylori* eradication for patients with non-ulcer dyspepsia, and thus may have underestimated the benefit of *H pylori* eradication in dyspeptic patients; and we also assumed a lower rate of *H pylori* eradication than that noted in the literature (85% vs 86% to 91%).

Why was *H pylori* eradication, either empirically or only for patients with a positive serum *H pylori* titer, the most cost-effective strategy? Several factors can be identified: the low incremental cost of *H pylori* eradication compared with antisecretory therapy alone ($99), the safety of *H pylori* eradication, avoidance of other diagnostic procedures such as endoscopy or upper GI with their attendant cost and discomfort, and a much lower ulcer recurrence rate for *H pylori*–negative patients. Using a diagnostic test for ulcers to guide *H pylori* eradication ran the risk of misclassifying patients with duodenal or gastric ulcer as ulcer-free (a false-negative result), resulting in some patients not receiving needed *H pylori* eradication. Empiric antisecretory therapy essentially uses symptomatic recurrence to identify patients with ulcer who will benefit from *H pylori* eradication, explaining the higher rates of morbidity and mortality associated with that strategy. Not surprisingly, it is only the most cost-effective strategy if

TABLE 4

Utility, Duration, and Total Disutility of Events Experienced by Patients with Dyspepsia

Clinical Event	Utility of Health State (0 - 1.0)	Duration of Health State (days)	Disutility of Health State (QALYs)	Range for Sensitivity Analysis
Delaying diagnosis of cancer by 6 weeks	0.7433	42	0.030	0.01 - 0.1
Experiencing upper endoscopy	0.5675	1	0.001	0 - 0.1
Inpatient treatment of a complicated ulcer (7 days)	0.4902	7	0.010	0.005 - 0.1
Inpatient treatment of a complicated ulcer with surgery (4 days ICU, 10 days hospital)	0.4642	14	0.021	0.01 - 0.1
Drug rash or diarrhea (7 days)	0.7604	7	0.005	0.001 - 0.1
Experiencing an upper gastrointestinal barium study	0.6301	1	0.001	0 - 0.1

QUALYs denotes quality-adjusted life years; ICU, intensive care unit.

ulcer is uncommon (combined rate of duodenal and gastric ulcer less than 12%).

The findings of this cost-utility analysis have important implications for health policy. Using empiric *H pylori* eradication or basing treatment on the serum *H pylori* titer saves from $73 to $929 per episode of dyspepsia when compared with the other five strategies studied. If one conservatively assumes that the 2 million outpatient consultations per year for dyspepsia represent 500,000 episodes of dyspepsia, using one of the preferred strategies results in a cost savings of $36.5 million to $464.5 million, from 1 to 22 fewer deaths, and from 500 to 11,000 fewer symptomatic ulcer recurrences compared with the other five strategies. Empiric *H pylori* eradication is

TABLE 5

Results of the Cost-Utility Analysis

Strategy	Cost ($)	Marginal Cost ($) *	Utility (QALYs)	Cost-Utility ($/QALY)
A—Eradicate *H pylori* empirically	1,196.74		0.9987	1,198.25
E—Check *H pylori* titer; if positive, eradicate *H pylori*	1,213.14	16.40	0.9990	1,214.41
B—Give omeprazole alone empirically	1,286.39	73.25	0.9991	1,287.53
G—Do UGI; if ulcer, do *H pylori* titer; if positive, eradicate *H pylori*	1,452.39	166.00	0.9981	1,455.08
D—Do UGI; if ulcer, eradicate *H pylori*	1,509.50	57.11	0.9981	1,512.44
C—Do EGD; if ulcer, eradicate *H pylori*	2,109.92	600.42	0.9982	2,113.79
F—Do EGD; if ulcer, do *H pylori* titer; if positive, eradicate *H pylori*	2,125.99	16.07	0.9982	2,129.87

* Additional cost for this strategy when compared with the next less expensive one above it.
QALY denotes quality-adjusted life year; UGI, upper gastrointestinal barium study; EGD, esophagogastroduodenoscopy.
NOTE: Marginal cost is the difference between a strategy and the one immediately preceding it; marginal cost-utility is not reported because the difference in utility between strategies was not clinically significant.

TABLE 6

Probability of Ulcer Cure, Cost per Episode of Dyspepsia, Cost per Ulcer Cure, and Mortality Rate for Each Strategy, Sorted in Ascending Order of Probability of Recurrence

Strategy	Probability of a Symptomatic Ulcer Recurrence (%)	Cost per Episode of Dyspepsia ($)	Cost per Ulcer Cure ($/cure) *	Deaths / 100,000 Dyspeptic Patients
A—Eradicate *H pylori* empirically	1.3	1,196.74	5,780.70	2.6
E—Check *H pylori* titer; if positive, eradicate *H pylori*	1.4	1,213.14	5,891.03	2.8
C—Do upper endoscopy; if ulcer, eradicate *H pylori*	1.5	2,109.92	10,283.04	3
F—Do upper endoscopy; if ulcer, do *H pylori* titer; if positive, eradicate *H pylori*	1.7	2,125.99	10,463.48	3.4
D—Do upper GI; if ulcer, eradicate *H pylori*	1.7	1,509.50	7,450.72	3.5
G—Do upper GI; if ulcer, do *H pylori* titer; if positive, eradicate *H pylori*	1.8	1,452.39	7,199.77	3.7
B—Give omeprazole alone empirically	3.5	1,286.39	6,947.30	7

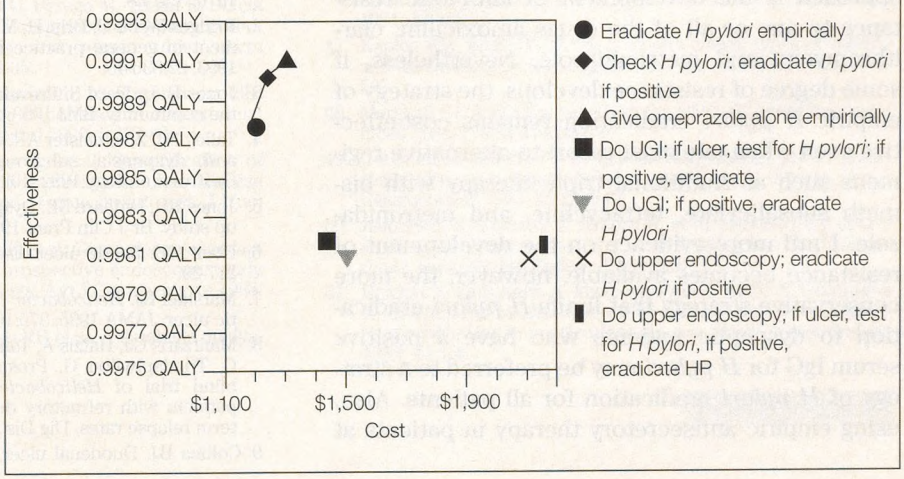
* The probability of cure is the probability that a patient has gastric or duodenal ulcer (22%) minus the probability of symptomatic recurrence within the first year. The "cost per ulcer cure" is calculated by dividing the cost per episode of dyspepsia by this probability (expressed as a percentage).

also an attractive strategy for clinicians, because it does not require that the patient be contacted with results of a upper GI or serum *H pylori* titer before initiating *H pylori* eradication.

This analysis is limited by the 1-year time horizon. Studies have shown, however, that protection from ulcer recurrence by *H pylori* eradication may extend to at least 2 years, and that reinfection only occurs at a rate of 1% per year.[48,49] Also, strategies that do not eradicate *H pylori* in some ulcer atients (empiric antisecretory therapy and strategies based on the results of upper GI and endoscopy) would become more expensive as the time horizon increased, because more patients would accrue the costs associated with continued maintenance antisecretory therapy. Thus, use of a 1-year time horizon is probably conservative, and underestimates the benefits of *H pylori* eradication. Another limitation is that of any cost-utility analysis: the probabilities, costs, and utilities in the model may be inaccurate or may not reflect a particular patient population. Although the analysis may not

FIGURE 2

Cost versus effectiveness. Preferred strategies A, B, and E (the most cost-effective) are in the upper left corner of the graph.



have modeled all risks or disadvantages of empiric *H pylori* eradication, the assumptions regarding *H pylori* eradication, benefit, and recurrence rates were conservative, and the model did not include possible benefits of *H pylori* eradication such as a reduction in rebleeding rates.[50,51] While indirect costs were not included in the model, their inclusion would be expected to make the two preferred strategies (which had the lowest rates of symptomatic recurrence) even more attractive. Finally, the preferred strategies were robust to a wide variety of sensitivity analyses.

Another possible criticism of this study is that some other regimen will be shown to be more effective in eradicating *H pylori* than the baseline treatment regimen of omeprazole, clarithromycin, and amoxicillin for 1 week. Altering the baseline assumptions, however, to reflect traditional triple therapy (by lowering the cost of therapy and increasing the probability of side effects to 40%) did not alter the optimal strategy, and actually made empiric *H pylori* eradication more attractive. Also, the sensitivity analysis for the cost of *H pylori* eradication showed that a strategy would have to be $150 more expensive than the baseline regimen (omeprazole, clarithromycin, and amoxicillin for 1 week) before empiric antisecretory therapy became the most cost-effective strategy. Even if that were true, empiric antisecretory therapy would have the liability of greater morbidity and mortality, making it difficult to recommend at any cost.

Adoption of the results of this analysis would result in more widespread use of regimens to eradicate *H pylori*. A possible disadvantage of such an approach is the development of antibiotic resistance to any or all of the drugs amoxicillin, clarithromycin, and metronidazole. Nevertheless, if some degree of resistance develops, the strategy of empiric *H pylori* eradication remains cost-effective even when one must resort to alternative regimens such as traditional triple therapy with bismuth subsalicylate, tetracycline, and metronidazole. Until more evidence on the development of resistance becomes available, however, the more conservative strategy that limits *H pylori* eradication to dyspeptic patients who have a positive serum IgG for *H pylori* may be preferred to a strategy of *H pylori* eradication for all patients. Also, using empiric antisecretory therapy in patients at low risk of ulcer is supported by this analysis, which would further reduce the number unnecessarily receiving *H pylori* eradication.

RECOMMENDATIONS

Given the safety of *H pylori* eradication and likely benefits in reducing ulcer recurrence and death, primary care physicians should consider a strategy of eradication of *H pylori* in all dyspeptic patients with a positive serum *H pylori* titer. Of course, physicians should continue to exercise good clinical judgment. Patients at low risk for ulcer may benefit from a trial of empiric antisecretory therapy, while patients at a higher than average risk for malignancy (age over 50, history of tobacco or alcohol use, or symptoms suspect for malignancy) should be considered for upper endoscopy. Because of the similarity in cost-effectiveness of empiric *H pylori* eradication, treatment based on the serum *H pylori* titer, and empiric antisecretory therapy for dyspepsia, it is important that a randomized controlled clinical trial comparing these strategies be performed in the primary care setting to confirm the findings of this analysis. Such a study should follow patients for at least 1 year, and measure the impact of each strategy on important patient-oriented outcomes such as ulcer recurrence, symptoms, quality of life, and resource utilization.

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