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Dyspepsia Management in Primary Care: A Decision Analysis of Competing Strategies

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See editorial on page 1521.

One-third of adults experience pain or discomfort in the upper abdomen during a given year.[1] Of these, 1/4 seek treatment, making dyspepsia the presenting complaint of 4% of patients visiting primary care physicians.[2,3] The optimal approach to uncomplicated dyspepsia in this setting remains controversial. Previous guidelines recommended initial antisecretory therapy, while reserving additional interventions for nonresponders.[4] However, as evidence mounts to suggest that *Helicobacter pylori* eradication may relieve symptoms in many patients,[5] several consensus statements have suggested a "test and treat" approach for patients with simple uninvestigated dyspepsia.[6–9] Specifically, patients younger than 45 with dyspepsia[6,8] and without "alarm" symptoms (bleeding, weight loss, dysphagia, anorexia, vomiting) should be tested for *H. pylori* and, if positive, receive a 10- to 14-day course of eradication therapy. If symptoms fail to improve with treatment, then diagnostic upper endoscopy should be performed.

Despite evidence in support of this approach,[5] several prospective trials have cast uncertainty regarding the effectiveness of "test-and-treat" for dyspepsia.[10–13] For example, 1 recent high-quality randomized control trial suggested that the test and treat strategy applied to the general population may provide symptomatic relief for only 5% of patients and makes no appreciable impact on quality of life.[10] These results may be explained in part by 4 advances in our understanding of *H. pylori* eradication:

1. Prospective clinical trials and several meta-analyses suggest that *H. pylori* eradication may play only a modest role at best in relieving the symptoms of patients with nonulcer dyspepsia (NUD),[14–19] a group that represents up to 2/3 of those with uninvestigated dyspepsia and thus plays a substantial role in dictating the cost-effectiveness of competing strategies.[5,20]
2. *H. pylori* eradication does not improve the symptoms of gastroesophageal reflux disease (GERD),[21] which may be the underlying cause of dyspepsia in up to one fourth of patients.[5,20]
3. Despite the fact that *H. pylori* eradication heals most infected peptic ulcers,[22,23] nearly one half of ulcer patients continue to experience dyspeptic symptoms after successful cure.[24]
4. *H. pylori* eradication rates are decreasing as a consequence of unfavorable resistance patterns[25,26] combined with limited success in promoting patient compliance with prescribed therapies.[27]

In contrast to test and treat, emerging data now support the use of empiric proton pump inhibitor (PPI) therapy in dyspepsia management. In particular, 3 factors promote a consideration of PPI-based strategies:

1. PPI therapy improves symptoms for patients with NUD,[28–33] because it is now evident that many of these subjects may have underlying nonerosive reflux disease.[34–36]
2. Empiric PPI therapy may accurately diagnose[37–40] and effectively treat[41–43] most patients with GERD.
3. PPI therapy may induce symptomatic remission[44–49] and provide sustained relief[50–57] for most patients with peptic ulcer disease (PUD).

In light of these new data and conflicting trends, we sought to reappraise the endorsement of current guidelines for uninvestigated dyspepsia and to consider alternative approaches based on a trial of PPIs. We proposed that strategies incorporating a 6-week trial of once-daily PPIs before endoscopy may relieve dyspepsia in more patients at a lower cost than current guidelines. Our objective was to use a decision analytic model reflecting

Abbreviations used in this paper: AGA, American Gastroenterological Association; ELISA, enzyme-linked immunosorbent assay; GERD, gastroesophageal reflux disease; NUD, nonulcer dyspepsia; PPI, proton pump inhibitor; PUD, peptic ulcer disease; QALY, quality-adjusted life-year.

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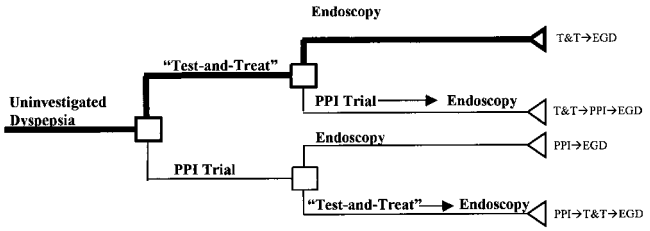

Figure 1. Truncated diagnostic flowchart of 4 empiric strategies for the management of simple uninvestigated dyspepsia. Square nodes denote decision points where the clinician may choose between alternative paths. Patients progress through each strategy only if persistently symptomatic. Two strategies (T&T→EGD and T&T→PPI→EGD) begin with the test and treat approach for *H. pylori,* and 2 others (PPI→EGD and PPI→T&T→EGD) begin with a 6-week trial of PPI. All strategies progress to upper endoscopy for patients with refractory symptoms. The strategy supported by current guidelines is marked in *bold lines*. See text for details on the individual strategies.

these new data to estimate the cost-effectiveness of 4 competing empiric strategies available to clinicians in the outpatient setting (Figure 1): (1) initial test and treat, followed by endoscopy for nonresponders (T&T→EGD); (2) initial test and treat, followed by a PPI trial for nonresponders, followed by endoscopy for persistently symptomatic patients (T&T→PPI→EGD); (3) initial PPI trial, followed by endoscopy for nonresponders (PPI→EGD); and (4) initial PPI trial, followed by test and treat for nonresponders, followed by endoscopy for persistently symptomatic patients (PPI→T&T→EGD).

Materials and Methods

Decision analysis is a quantitative method for estimating the financial costs and clinical outcomes of alternative management strategies under conditions of uncertainty. Using decision analysis software,[58] we evaluated the cost-effectiveness of 4 sequential empiric strategies for patients with dyspepsia (Figure 1). One pair of strategies begins with *H. pylori* testing, followed by either endoscopy or a PPI trial for nonresponders, whereas the other pair begins with a PPI trial, followed by either endoscopy or *H. pylori* testing for nonresponders. Each strategy progresses to upper endoscopy for persistently symptomatic patients. Our analysis considered a hypothetical cohort of patients younger than 45 presenting to their primary care provider for the first time with a complaint of recurrent upper abdominal pain or discomfort. Patients with "alarm" symptoms (e.g., bleeding, weight loss, dysphagia, anorexia, vomiting) were excluded from this analysis, as were patients with a predominant symptom of acid reflux or regurgitation. Additionally, patients taking long-term nonsteroidal anti-inflammatory drugs (NSAIDs) were not considered part of the cohort. Patients were considered to have NUD, PUD, esophagitis, or gastric carcinoma as the underlying cause of their symptoms. To make the model clinically realistic, we assumed that the patients had not been previously investigated. Therefore, the patients progressed through the evaluation without the primary care physician knowing the underlying cause of their symptoms.

Our model incorporated base-case estimates derived from a systematic review of published reports from the MEDLINE and HealthSTAR bibliographic databases and the Cochrane Library of Systematic Reviews. We reviewed English-language articles from 1985 to 2001 and articles identified by reviewing bibliographies of key references, and relied most heavily on the highest-quality studies to derive our probability estimates. Where the literature offered a range of possibilities, we chose estimates that would tend to favor the current guidelines. We then used sensitivity analysis to evaluate a wide range of cost and probability estimates over a 1-year period.

Decision Model

Current guidelines (T&T→EGD). This strategy, which serves as the referent case for our analysis, begins with the administration of a serum enzyme-linked immunosorbent assay (ELISA) for *H. pylori.* Patients who test positive receive a 14-day course of antibiotic therapy for *H. pylori* eradication, whereas those who test negative receive a 6-week trial of once-daily PPI. Although the American Gastroenterological Association (AGA) guidelines suggest 1 month of empiric antisecretory therapy,[6] we have adopted a 6-week duration based on the average treatment course from published studies, which ranges from 2 to 8 weeks. Patients rendered asymptomatic by the PPI trial continue once-daily maintenance PPI therapy, whereas those with persistent or relapsing symptoms despite the PPI trial are referred for upper endoscopy. Patients who receive antibiotic therapy and are rendered asymptomatic receive no further treatment or interventions, whereas those with persistent or relapsing symptoms despite antibiotic therapy undergo a carbon-14 urea breath test to establish cure. Although the AGA guidelines do not include urea breath test confirmation, a recent dyspepsia guideline endorses this practice with the aim to detect unsuccessful *H. pylori* eradication before endoscopic evaluation.[7] If the urea breath test reveals a persistent infection, then a second therapeutic course with an alternative anti–*H. pylori* regimen is administered; those with a negative urea breath test are referred for upper endoscopy. Patients with persistent or relapsing symptoms despite a second course of antibiotic therapy are likewise referred for endoscopic evaluation.

Because there is no consensus regarding whether to perform confirmatory *H. pylori* testing in patients with persistent symptoms, we also constructed an additional model in which this practice was not performed. In this model, patients with persistent symptoms despite anti–*H. pylori* therapy proceed directly to endoscopy rather than to confirmatory testing.

If a peptic ulcer is discovered by endoscopy, then a rapid urease test is performed during the procedure. Patients with a positive rapid urease test undergo culture and sensitivity of the *H. pylori* strain and receive a third round of eradication therapy based on the results. Those with a negative rapid urease test receive 6 weeks of once-daily PPI therapy to heal the ulcer,

reflecting the average treatment course in published studies, followed by once-daily maintenance PPI therapy.

Patients diagnosed with NUD by endoscopy receive a 4-week trial of once-daily PPI. Those with improved symptoms after this trial are placed on once-daily maintenance PPI therapy, whereas those with persistent symptoms receive a 4-week trial of a prokinetic agent. Patients who are persistently symptomatic despite prokinetic therapy are placed on low-dose amitriptyline therapy.

Patients with endoscopic evidence of esophagitis receive an 8-week course of once-daily PPI therapy to heal the lesion, followed by once-daily maintenance PPI therapy. Patients found to have gastric cancer are treated surgically.

Interposed PPI trial (T&T→PPI→EGD). Patients entering this strategy begin by receiving a serum ELISA for *H. pylori.* Management then proceeds as specified in the current guidelines. Unlike the current guidelines, however, patients who are persistently symptomatic or who relapse after up-front test and treat receive a 6-week course of once-daily PPI therapy rather than immediately progressing to upper endoscopy. Therefore, in this strategy a PPI trial is interposed between test and treat and endoscopy. Patients with improved symptoms after the PPI trial are placed on once-daily maintenance PPI therapy, whereas those with persistent dyspepsia are referred for endoscopic evaluation. Management decisions then proceed according to endoscopic findings following the current guidelines.

Initial PPI trial (PPI→EGD). In this empiric strategy, patients initially receive a 6-week trial of once-daily PPIs. Those with improved symptoms are placed on once-daily maintenance PPI therapy, whereas those with persistent or relapsing symptoms are immediately referred for upper endoscopy. Management then proceeds according to endoscopic findings, following the current guidelines. Therefore, in this strategy, empiric PPI therapy is administered in favor of test and treat, and *H. pylori* eradication is reserved only for endoscopically confirmed rapid urease-positive ulcers.

Interposed test and treat (PPI→T&T→EGD). Patients entering this strategy receive a 6-week trial of twice-daily PPIs and subsequent once-daily PPI therapy if rendered asymptomatic. Those with persistent or relapsing symptoms undergo an *H. pylori* ELISA and are then managed following the current guidelines. Therefore, in this strategy, test and treat is interposed between an up-front PPI trial and endoscopy.

General Model Assumptions

1. All assumptions regarding therapeutic responses were based on symptomatic response rates as reported in the medical literature rather than on endoscopic healing rates.
2. We assumed that primary care physicians provided all patient care and referred to gastroenterologists only when upper endoscopy was indicated, and that the primary care physicians performed subsequent follow-up.
3. Patients who responded to a PPI trial were continued on once-daily maintenance PPI therapy. We made no assumptions regarding "step-down" or "on-demand" therapy because this would economically favor the PPI-based strategies, which rely more heavily on long-term antisecretory therapy than do the current guidelines.
4. We assumed that symptom relapse during antisecretory therapy developed within 8 weeks of initiating therapy.
5. Because there are little data regarding the efficacy of sequential therapeutic trials, symptom response rates in this model were not adjusted based on previous treatment failures.
6. Although there are several causes of uncomplicated dyspepsia, we assumed that patients had only 1 of 4 underlying etiologies: NUD, PUD, esophagitis, or gastric carcinoma. We assumed that a careful history and physical examination excluded additional etiologies, such as biliary tract disease or pancreatitis.
7. Patients with predominant symptoms of acid reflux or regurgitation were considered to have underlying GERD and were not included in this analysis.

Clinical Inputs and Probability Estimates Derived From Systematic Review

Disease prevalence and *H. pylori* status (Table 1).

Nonulcer dyspepsia. Most patients with uncomplicated dyspepsia have no findings on endoscopy.[5,20] These patients are considered to have NUD, which includes functional bowel disorders and nonerosive reflux disease. Because most dyspeptic

Table 1. Probability Estimates of Disease Prevalence and *H. pylori* Status of Dyspeptic Cohort

Probability	Base-case estimate	Range in literature	Range tested	References
Probability that the cause of dyspepsia is NUD	66%	27%–83%	0–100%	5, 20
Probability that NUD is *H. pylori* positive	48%	9%–88%	0–100%	19, 59, 60
Probability that the cause of dyspepsia is PUD	23%	2%–34%	0–100%	5, 20
Probability that PUD is *H. pylori* positive	90%	60%–95%	0–100%	63
Probability that the cause of dyspepsia is esophagitis	10%	0–29%	0–100%	5, 20
Probability that esophagitis is *H. pylori* positive	40%	8%–76%	0–100%	64, 65
Probability that the cause of dyspepsia is gastric cancer	.5%	0–3%	0–100%	5, 20
Probability that gastric cancer is *H. pylori* positive	85%	65%–95%	0–100%	66

NUD, nonulcer dyspepsia; PUD, peptic ulcer disease.

patients have 1 of these conditions, the exact proportion of patients with NUD selected in a decision model plays a large role in dictating the relative cost-effectiveness of competing strategies. Based on 2 previously published systematic reviews, we assumed that 66% of the cohort had underlying NUD,[5,20] and this estimate varied from 0% to 100% in sensitivity analysis. Although up to 40% of asymptomatic patients are *H. pylori* positive, it has been suggested that significantly more patients with NUD are colonized.[19,59,60] Although this contention is controversial, we nonetheless assumed that 48% of our NUD cohort tested positive for *H. pylori* to bias the model in favor of the current test and treat guidelines.[19,59,60]

Peptic ulcer disease. Up to one half of *H. pylori*–positive patients with dyspepsia have underlying PUD,[61,62] including both gastric and duodenal ulcers. However, no more than one third of uninvestigated dyspepsia patients not taking NSAIDs have PUD.[5,20] We assumed that 23% of our uninvestigated cohort had underlying PUD as the cause of their symptoms,[5,20] and further assumed that 90% of these patients were *H. pylori* positive.[63]

Esophagitis. The reported prevalence of esophagitis in dyspeptic subjects ranges from 0% to 29%.[5,20] This includes a spectrum of endoscopic findings ranging from minimal esophageal erythema to mucosal breaks and erosions. We assumed that in 10% of the cohort, underlying esophagitis was the cause of symptoms.[5,20] The prevalence of *H. pylori* colonization in patients with esophagitis is no different from that in asymptomatic subjects,[64,65] and thus we estimated that 40% were *H. pylori* positive.[64,65]

Gastric cancer. Gastric cancer is a rare and serious cause of dyspepsia. Between 0% and 3% of patients under 50 years old without "alarm" symptoms have underlying cancer.[5,20] Because the upper estimate is derived from studies based on tertiary center referral populations, we assumed that 0.5% of our young outpatient cohort had cancer; 85% of these tested positive for *H. pylori*.[66,67]

Effectiveness of anti–*H. pylori* therapy. *Eradication rate.* Anti–*H. pylori* therapy cures between 29% and 98% of infections, depending on patient compliance, length of treatment, and the specific regimen used (Table 2).[68–74] We estimated that 85% of patients who received a 14-day course of omeprazole 20 mg twice daily, metronidazole 500 mg twice daily, and clarithromycin 250 mg twice daily achieved successful *H. pylori* eradication.[68–74] We further estimated that the eradication rate from a second round of alternative therapy was 80%.[68–74]

Nonulcer dyspepsia symptoms. The effectiveness of *H. pylori* eradication on symptoms of NUD is controversial. Although several meta-analyses have arrived at disparate results,[16–19] the weight of the evidence suggests that only a modest improvement may be achieved in many patients treated for *H. pylori* infection. Based on our review of the literature,[14–19,75,76] we estimated that 48% of successfully eradicated patients had initial symptom improvement. Although several high-quality randomized controlled trials have detected much lower response rates for NUD (20% to 30%), we explicitly chose this potentially inflated estimate to bias the model in favor of the current test and treat guidelines. The long-term benefits of anti–*H. pylori* therapy for NUD are not as robust, however.[16,75,76] We therefore assumed that only one third of the NUD cohort remained in complete symptomatic remission 12 months after receiving treatment.[16,75,76]

Table 2. Probability Estimates for Effectiveness of Anti–*H. pylori* Therapy on Dyspeptic Symptoms

Probability	Base-case estimate	Range in literature	Range tested	References
Probability that HP is successfully eradicated by the first round of antibiotic therapy[a]	85%	29%–98%	0–100%	67–74
Probability that HP is successfully eradicated by the second round of antibiotic therapy	80%	20%–95%	0–100%	67–74
Probability that patient with NUD has initial symptom improvement with anti-HP therapy	48%	21%–89%	0–100%	14–19, 75, 76
Probability that a patient with NUD has sustained symptom improvement 1 year after anti-HP therapy	33%	21%–73%	0–100%	75, 76
Probability that a patient with PUD has initial symptom improvement with anti-HP therapy	85%	60%–96%	0–100%	77–84
Probability that a patient with PUD has sustained symptom improvement 1 year after anti-HP therapy	70%	38%–95%	0–100%	24, 77, 79, 82, 83, 85–91
Probability that a patient with esophagitis has initial symptom improvement with anti-HP therapy	25%	7%–43%	0–100%	92, 93
Probability that patient with esophagitis has sustained symptom improvement 1 year after anti-HP therapy	15%	No data found	0–100%	Assumption
Probability that a patient with gastric cancer has initial symptom improvement with anti-HP therapy	10%	No data found	0–100%	Assumption
Probability that a patient with gastric cancer has sustained symptom improvement 1 year after anti-HP therapy	2%	No data found	0–100%	Assumption

NUD, nonulcer dyspepsia; PUD, peptic ulcer disease; HP, *H. pylori*.
[a]Includes a 14-day course of omeprazole 20 mg twice daily, metronidazole 500 mg twice daily, and clarithromycin 250 mg twice daily.

Peptic ulcer symptoms. Antibiotic therapy heals more than 95% of *H. pylori*–positive ulcers and dramatically reduces the rate of ulcer recurrence.[22,23] However, despite the extensive literature relating to ulcer healing, few studies have specifically addressed the effect of *H. pylori* eradication on symptoms. Existing data indicate that between 60% and 90% of PUD patients achieve initial symptomatic relief after successful eradication therapy.[77–84] We estimated that 85% of our PUD cohort obtained initial relief.[77–84] Nonetheless, clinical data indicate that the durability of this response may not be as robust. The high incidence of concurrent GERD in patients with PUD may explain why up to one half of successfully cured patients with PUD develop recurrent dyspepsia within 1 year of treatment.[37] Based on our review,[24,77,79,82,83,85–91] we estimated that 70% of the PUD cohort remained in symptomatic remission at the end of 1 year.

Esophagitis symptoms. Because *H. pylori* has not been shown to cause esophagitis,[21,64] we assumed that patients with esophagitis treated for *H. pylori* responded no differently than those treated with placebo. We estimated that 25% of treated patients experienced symptomatic improvement, which is equivalent to the reported rate of spontaneous symptom resolution in patients with esophagitis.[92,93] We found no data on the long-term effects of antibiotic therapy for esophagitis, and thus assumed that 15% of the esophagitis cohort remained in symptomatic remission 1 year after *H. pylori* eradication.

Gastric cancer symptoms. Although most gastric carcinomas are associated with *H. pylori*,[94] dyspeptic patients with cancer are unlikely to achieve symptomatic improvement with eradication therapy. Because there are limited data on the effects of therapy on symptoms in these patients, we assumed that only 10% improved with anti–*H. pylori* therapy alone. We further assumed that 2% of the gastric cancer cohort remained in symptomatic remission 1 year after eradication.

Effectiveness of the PPI trial. *Nonulcer dyspepsia symptoms.* Between 35% and 65% of patients with NUD experience initial symptom relief with a 6-week trial of once-daily PPI (Table 3).[28–36] Although the subset of NUD patients with nonerosive reflux achieved the most durable response,[28,30–32,34–36] all subgroups experience significant improvement versus placebo. The crude average symptom response rate of NUD among 8 randomized controlled studies of varying size, design, patient population, and quality was 46%.[28–31,34,46] Because the study by Talley et al.[28] is significantly larger than the other studies combined and is of high methodologic quality, we adopted this report's response rate of 38% as our base-case estimate. This value, representing the proportion of patients with NUD that achieved complete symptom relief with a 4-week course of omeprazole, 20 mg daily, was significantly higher than the 28% response rate to placebo. There are limited data on the effects of long-term maintenance therapy on symptomatic remission in NUD. A recent study found that 86% of patients with nonerosive reflux remained symptom-free after 6 months of "on-demand" PPI therapy.[32] To bias the model against the PPI-based strategies, we conservatively assumed that only 28% of our NUD cohort remained in symptomatic remission after 1 year of maintenance PPI therapy, a percentage equal to the placebo response from the large trial of Talley et al.[28]

Peptic ulcer symptoms. Although a 6-week PPI trial may heal up to 98% of peptic ulcers,[44–49] a smaller proportion of patients obtain initial symptomatic relief.[44–49] We assumed that 80% of our PUD cohort achieved this outcome.[37,39–49] We further assumed that 75% of the cohort remained in symptomatic remission after 1 year of maintenance PPI therapy.[50–57]

Esophagitis symptoms. Endoscopic and clinical outcomes are disparate for patients with esophagitis. Up to 93% of lesions are healed with a PPI trial,[41–43] but fewer patients have

Table 3. Probability Estimates for Effectiveness of PPI Therapy on Dyspeptic Symptoms

Probability	Base-case estimate	Range in literature	Range tested	References
Probability that a patient with NUD has initial symptom improvement with PPI trial	38%	36%–65%	0–100%	16–19, 28–36
Probability that a patient with NUD has sustained symptom improvement after 1 year of continuous PPI therapy	28%	No data found	0–100%	Assumption
Probability that a patient with PUD has initial symptom improvement with PPI trial	80%	55%–98%	0–100%	44–49
Probability that a patient with PUD has sustained symptom improvement after 1 year of continuous PPI therapy	75%	50%–100%	0–100%	50–57
Probability that a patient with esophagitis has initial symptom improvement with PPI trial	80%	70%–96%	0–100%	41–43
Probability that a patient with esophagitis has sustained symptom improvement after 1 year of continuous PPI therapy	70%	32%–91%	0–100%	42, 43
Probability that a patient with gastric cancer has initial symptom improvement with PPI trial	33%	44% (1 study identified)	0–100%	96
Probability that a patient with gastric cancer has sustained symptom improvement after 1 year of continuous PPI therapy	2%	No data found	0–100%	Assumption

NUD, nonulcer dyspepsia; PUD, peptic ulcer disease.

concurrently improved symptoms. We therefore assumed that 80% of our esophagitis cohort obtained initial symptom relief.[41–43] We estimated that 70% remained in symptomatic remission after 1 year of maintenance PPI therapy.[42,43]

Gastric cancer symptoms. There are limited data on the effects of PPI therapy on symptoms of gastric cancer. One case report suggests that PPI therapy may delay the diagnosis of gastric cancer,[95] and 1 retrospective series has indicated that up to 44% of cancer patients may achieve temporary symptom improvement with PPI.[96] We assumed that one third of our cancer cohort obtained initial relief from a PPI trial and also assumed that only 2% remained in symptomatic remission after 1 year of maintenance PPI therapy.

Complications of endoscopy. The most common complications of endoscopy are cardiorespiratory and generally require only additional observation. Our model assumed a 0.02% probability of severe endoscopic complications requiring hospitalization and surgery.[97–99] The costs of severe endoscopic complications were modeled after the surgical repair of a perforation.

Complications of antibiotics. The most common side effects of oral antibiotics include mild abdominal discomfort and nausea. We assumed that no additional costs were incurred unless mild side effects resulted in the discontinuation of therapy and retreatment. Our model estimated that 5% of patients discontinued therapy on the basis of mild side effects.[100,101] We assumed that 0.5% of patients developed moderate side effects, including pseudomembranous colitis treated on an outpatient basis.[23,102] Finally, we assumed that .001% of patients developed a "worst-case" scenario for complications of antibiotic therapy, including pseudomembranous colitis requiring hospitalization and surgery.[102–105]

Utilities. In economic analyses, a utility is an objective value placed on a subjective preference for a heath state. Utilities are traditionally reported on a scale of 0 to 1, with 0 representing death and 1 representing perfect health. To accurately determine the utility of a given disease state, patients with the disease in question are interviewed in a standardized manner. Once utilities are established, they can be applied to a decision analysis to calculate quality-adjusted life-years (QALYs), which in turn are used as a primary outcome measure to compare the effectiveness of competing strategies. As the name implies, a QALY is a year of life adjusted for the quality in which it is lived. For example, 1 year of life lived with a condition imparting a utility of 0.66 is equivalent to 2/3 of a year lived in perfect health. A recent study of 73 patients with dyspepsia used the time trade-off method to derive utilities of mild (0.93), moderate (0.89), and severe (0.87) dyspepsia symptoms.[106] To calculate base-case QALYs, we assumed that 50% of our cohort had severe dyspepsia, 25% had moderate dyspepsia, and 25% had mild dyspepsia. To account for alternative case-mixes, we used sensitivity analysis to vary the proportion with severe dyspepsia from 0% to 100%, with the remaining proportion composed of moderate and mild dyspeptics maintained at a 1:1 ratio. Because these utilities are based on a limited sample size from 1 study, in sensitivity analyses we varied the value for each between 0 and 1.0.

Cost estimates. Cost estimates were obtained from the perspective of a third-party payer, considering only direct health care costs (Table 4). Drug costs were obtained from the 2000 Red Book of average wholesale prices for pharmaceuticals. Costs for endoscopic and diagnostic procedures and physician services were obtained from the 2000 American Medical Association Current Procedural Terminology Code Book and the 2000 Medicare Fee Schedule (Table 2).

Table 4. Current Procedural Terminology and Costs to Medicare

Variable	Base-case cost estimate ($)	Range tested ($)
Cost of PPI trial (6 weeks of pantoprazole, 40 mg once daily)	126	20–500
Cost of 1 month of PPI therapy (pantoprazole 40 mg once daily)	90	20–500
Cost of 1 month of prokinetic therapy (metoclopramide 10 mg 3 times daily)	70	5–100
Cost of 1 month of amitriptyline therapy (10 mg once daily)	4	5–100
Cost of 14-day course of anti–*H. pylori* therapy[a]	304	20–600
Cost of mild side effects of antibiotic therapy	115	20–200
Cost of pseudomembranous colitis treated on an outpatient basis	270	50–500
Cost of severe complication of antibiotic therapy[b]	25,000	1000–30,000
Cost of *H. pylori* serum ELISA	10	5–300
Cost of *H. pylori* urea breath test	80	10–300
Cost of general medicine office visit	99	10–150
Cost of gastrointestinal office visit	232	50–250
Cost of upper endoscopy without rapid urease test[c]	544	100–1500
Cost of upper endoscopy with rapid urease test[d]	694	100–1500
Cost of severe complications of endoscopy[e]	27,000	1000–30,000
Cost of surgery for gastric cancer	28,000	1000–40,000

[a]Includes omeprazole 20 mg twice daily, metronidazole 500 mg twice daily, and clarithromycin 250 mg twice daily.
[b]Includes cost of major small and large bowel procedure, cost of anesthesia, and cost of inpatient hospital care for a 10-day stay.
[c]Includes facility charge and drug costs.
[d]Includes facility charge and drug costs, cost of biopsy, and cost of rapid urease test.
[e]Includes cost of surgical procedure for single bowel perforation, cost of anesthesia, and cost of inpatient hospital care for a 10-day stay.

Table 5. Results of Base-Case Cost-Effectiveness Analysis

Strategy	Cost/ patient treated	Marginal cost[a]	Effectiveness (% symptom-free at 1 year)	Marginal effectiveness[b]	Average cost-effectiveness ($/symptom-free at 1 year)	Marginal cost-effectiveness[c]
T&T→EGD (current guidelines)	$1902	—	75%	—	$2535	—
T&T→PPI→EGD	$1680	−$222	84%	+9%	$1996	Negative value
PPI→EGD	$1628	−$274	78%	+3%	$2078	Negative value
PPI→T&T→EGD	$1788	−$114	84%	+9%	$2124	Negative value

[a]Cost per patient treated versus current guidelines.
[b]Proportion of symptom-free patients at 1 year versus current guidelines.
[c]Cost per additional symptom-free patient at 1 year versus current guidelines.

Outcomes

The clinical outcome most relevant to patients with dyspepsia is unknown. Although guidelines on economic analyses suggest that QALYs are the most appropriate unit for cost-effectiveness analysis,[107] others contend that symptom-relief most closely mirrors clinical reality for patients with dyspepsia.[20,108,109] Therefore, we evaluated 2 types of effectiveness outcomes: (1) the proportion of patients rendered symptom-free at 1 year and (2) QALYs. We report both the average and incremental cost-effectiveness ratios compared with the current guidelines.

Sensitivity Analysis

We performed one-way sensitivity analysis to evaluate the effect on our results of varying individual cost and probability estimates over ranges in excess of the degree of uncertainty expected based on the medical literature. We then performed 2-way sensitivity analyses on the most clinically significant and potentially influential variables. Finally, we conducted a Monte Carlo simulation to evaluate the second-order uncertainty around our base-case estimates. We report the mean cost and effectiveness for each strategy from 1000 trials using random samples of variable estimates.

Results

We estimated the potential clinical and economic impact of implementing the 4 alternative strategies in separate cost-effectiveness and cost-utility analyses (Tables 5 and 6). The PPI→EGD strategy generated the lowest cost per patient, $1628, compared with $1902 for the strategy supported by current guidelines (T&T→EGD). The T&T→PPI→EGD strategy cost $1680 per patient, and the PPI→T&T→EGD strategy cost $1788 per patient. The T&T→PPI→EGD and PPI→T&T→EGD strategies were most effective in both analyses, with 84% of patients rendered symptom-free and 0.98 QALY, compared with 75% of patients and 0.92 QALY by current guidelines. The PPI→EGD strategy rendered 78% of patients asymptomatic and provided 0.97 QALY. Therefore, of the 4 competing strategies, the approach supported by current guidelines was both the least effective and the most expensive in both analyses. The T&T→PPI→EGD strategy had the lowest cost per symptom-free patient at 1 year (Table 5), whereas the PPI→EGD strategy had the lowest cost per QALY (Table 6). Of these 2 latter strategies, the incremental cost-effectiveness of T&T→PPI→EGD over PPI→EGD was $866 per additional symptom-free patient at 1 year and $5200 per additional QALY gained.

The cost-effectiveness of competing strategies depends partly on the use of resources, including diagnostic tests and prescription medications (Table 7). Compared with current guidelines, the T&T→PPI→EGD strategy required only a 5% increase in the use of long-term PPIs

Table 6. Results of Base-Case Cost-Utility Analysis

Strategy	Cost/ patient treated	Marginal cost[a]	Effectiveness (QALY)	Marginal effectiveness[b] (QALY gained)	Average cost-effectiveness ($/QALY gained)	Marginal cost-effectiveness[c]
T&T→EGD (current guidelines)	$1902	—	.92	—	$2067	—
T&T→PPI→EGD	$1680	−$222	.98	+.06	$1714	Negative value
PPI→EGD	$1628	−$274	.97	+.05	$1678	Negative value
PPI→T&T→EGD	$1788	−$114	.98	+.06	$1824	Negative value

[a]Cost per patient treated versus current guidelines.
[b]QALY gained versus current guidelines.
[c]Cost per QALY gained versus current guidelines.

Table 7. Therapeutic and Diagnostic Utilization at 1 Year per 1000 Patients

Utilization parameter	T&T→EGD	T&T→PPI→EGD	PPI→EGD	PPI→T&T→EGD
Upper endoscopic procedures/subspecialist office visits	741	520	634	520
Courses of anti–*H. pylori* therapy	1270	1270	207	672
Years of PPI use	443	465	682	682
Primary care office visits	2212	2650	1820	2593
Urea breath tests	590	590	79	309

and a 15% increase in primary care office visits. However, this was financially offset by a 30% reduction in both endoscopic procedures and subspecialty office visits versus current guidelines. Whereas the PPI→EGD strategy required a 35% increase in the use of long-term PPI over current guidelines, it resulted in an 85% reduction in the use of antibiotics and thus lower cost per average patient treated compared with current guidelines.

We performed one-way sensitivity analysis using cost per symptom-free patient as the outcome to determine whether our findings were robust to changes in the clinical probability estimates (Table 8). The effectiveness of anti–*H. pylori* therapy, which varies widely in clinical practice, impacted the model results. When the rate of first-round *H. pylori* eradication decreased below 60% the PPI→EGD strategy became the most cost-effective approach, reflecting its minimal reliance on antibiotic therapy.

Because most patients with dyspepsia have underlying NUD, the response rate of NUD to *H. pylori* eradication plays a pivotal role in determining the effectiveness of test and treat strategies. We found that the PPI→EGD strategy, in which *H. pylori* eradication is bypassed in favor of empiric PPIs, became most cost-effective when fewer than 15% of the NUD cohort responded to anti–*H. pylori* therapy. Because the proportion of patients with NUD largely dictates the cost-effectiveness of competing strategies, we further tested our conclusions by varying the probability of underlying NUD. The T&T→PPI→EGD strategy remained most cost-effective when more than 25% of the cohort had NUD, whereas the PPI→EGD strategy was preferred for values below this threshold, reflecting the incremental effectiveness of up-front test and treat for NUD versus initial PPI therapy. Although the current guidelines gained cost-effectiveness as the proportion of NUD increased, they remained less cost-effective than T&T→PPI→EGD, even when the proportion of NUD was 100%.

Antibiotic therapy is most effective for *H. pylori*–positive ulcers. Therefore, the probability of underlying PUD impacted the model results. The PPI→EGD strategy became most cost-effective when <8% of the cohort had PUD, because the test and treat strategies were less effective when the probability of ulcer disease was low.

Table 8. Results of Threshold Analysis Applied to Cost per Average Symptom-Free Patient Dataset

Variable	Base-case estimate	Threshold value	Comment
Cost of upper endoscopy without rapid urease test	$544	$152	If less than the threshold value, then PPI→EGD is the most cost-effective.
Cost of a 14-day course of anti–*H. pylori* therapy	$304	$450	If more than the threshold value, then PPI→EGD is the most cost-effective.
Cost of 1 month of PPI therapy (pantoprazole 40 mg once daily)	$90	$45	If less than the threshold value, then PPI→EGD is the most cost-effective.
Probability that *H. pylori* is eradicated by the first round of antibiotic therapy	85%	60%	If less than the threshold value, then PPI→EGD is the most cost-effective
Probability that symptoms of NUD initially improve with anti–*H. pylori* therapy	48%	15%	If less than the threshold value, then PPI→EGD is the most cost-effective
Probability that esophagitis is the cause of dyspepsia	13%	70%	If more than the threshold value, then PPI→EGD is the most cost-effective
Probability that PUD is the cause of dyspepsia	20%	8%	If less than the threshold value, then PPI→EGD is the most cost-effective.
Probability that NUD is the cause of dyspepsia	64%	25%	If less than the threshold value, then PPI→EGD is the most cost-effective.
Probability that PUD is *H. pylori* positive	90%	50%	If less than the threshold value, then PPI→EGD is the most cost-effective.
Probability that NUD is *H. pylori* positive	48%	12%	If less than the threshold value, then PPI→EGD is the most cost-effective.

NUD, nonulcer dyspepsia; PUD, peptic ulcer disease.

The prevalence of *H. pylori* affected the model results. The PPI→EGD strategy became most cost-effective when <12% of NUD and <50% of PUD was *H. pylori* positive. Therefore, the T&T→PPI→EGD strategy was preferred when the 2 most common conditions had a high prevalence of *H. pylori*, reflecting the greater incremental effectiveness of *H. pylori* eradication for PUD and NUD versus PPI therapy alone. The prevalence of *H. pylori* in gastric cancer or erosive esophagitis did not impact the model results. The current guidelines were not preferred under any combination of *H. pylori* prevalence among the conditions studied.

We used one-way sensitivity analysis to examine whether altering the cost estimates affected our results. When the cost of upper endoscopy was reduced by 72% (from $544 to $152), the PPI→EGD strategy became most cost-effective, reflecting its heavy reliance on invasive procedures (Table 7). Likewise, when the cost of anti–*H. pylori* therapy was increased by 48% (from $304 to $450), the PPI→EGD strategy was again preferred, as a result of its restrained use of antibiotic therapy (Table 7). The PPI→EGD strategy was also most cost-effective when the cost of 1 month of PPI therapy was reduced by 50% (from $90 to $45). The model was robust to changes in the costs of other diagnostic tests, referral costs, and surgical costs.

Threshold analysis revealed that the cost of 1 month of PPI therapy had to increase 30-fold (from $90 to $2700) before the current guidelines became the most cost-effective. Therefore, 29 years of continuous PPI therapy would be needed for the current guidelines to realize a cost-effectiveness advantage over the T&T→PPI→EGD strategy, reflecting the nearly equivalent use of PPI between these strategies.

We performed sensitivity analysis on the QALY-gained outcome by varying the utility for dyspepsia symptoms from 0 to 1 (base-case≃0.87). When the utility value decreased below 0.5, the T&T→PPI→EGD strategy cost the least per QALY gained, whereas for values above this estimate, the PPI→EGD approach cost the least per QALY gained. Therefore, as the severity of dyspepsia symptoms decreased (i.e., as the utility for symptoms approached 1), the PPI→EGD approach gained a cost-utility advantage over the alternative strategies, whereas the T&T→PPI→EGD strategy was preferred as the severity increased. We performed further sensitivity analysis by varying the proportion of patients with "severe" dyspepsia from 0% to 100%, and found that this did not affect the model results.

Because the practice of routinely confirming *H. pylori* cure in patients with persistent symptoms is controversial, we constructed an additional model in which this practice was avoided. Despite lowering average costs for the strategies incorporating test and treat, this model yielded results similar to those for the base-case model.

We performed 2-way sensitivity analysis on combinations of key variables. The current guidelines did not gain a cost-effectiveness advantage under any combination of cost or probability estimates. However, the 2-way analyses delineated circumstances under which 1 PPI-based approach may be preferred over another. For example, the T&T→PPI→EGD strategy remained the most cost-effective overall as long as the cost of endoscopy remained above $250 and the probability of NUD symptom improvement with *H. pylori* eradication remained above 36%, whereas the PPI→EGD strategy gained cost-effectiveness as these 2 values decreased below their respective thresholds (Figure 2). Likewise, the T&T→PPI→EGD strategy was preferred as long as the probability of underlying esophagitis was less than 55% and the cost of anti–*H. pylori* therapy was less than $360, whereas the PPI→EGD strategy gained cost-effectiveness as the 2 values increased above these thresholds (Figure 3).

We performed Monte Carlo simulation to evaluate the second-order uncertainty around our base-case estimates. The mean cost-effectiveness from 1000 trials using random combinations of variable estimates was similar to the data derived from our base-case analysis (Table 9). The data were comparable when 100, 500, and 2000 trials were simulated.

Discussion

This analysis of alternative management strategies for uninvestigated dyspepsia suggests that the current guidelines may not be the most cost-effective approach. Compared with the current guidelines, interposing a 6-week PPI trial between test and treat and upper endos-

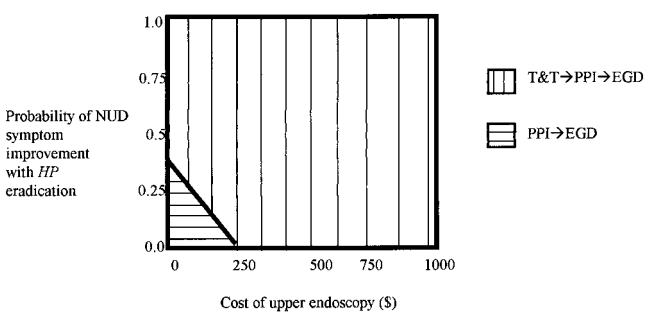

Figure 2. Two-way sensitivity analysis comparing the cost of upper endoscopy with the probability of initial symptom improvement of NUD with *H. pylori* eradication. The T&T→PPI→EGD strategy remains the most cost-effective as long as the cost of endoscopy remains above $250 and the probability of NUD symptom improvement with *H. pylori* eradication remains above 36%.

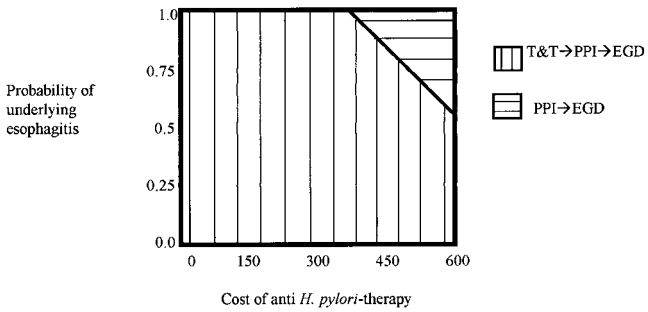

Figure 3. Two-way sensitivity analysis comparing the cost of anti–*H. pylori* therapy with the probability of underlying erosive esophagitis. The T&T→PPI→EGD strategy remains the most cost-effective as long as the cost of antibiotic therapy remains below $365 and the probability of esophagitis remains below 55%.

copy may improve symptomatic relief at 1 year while reducing costs by substantially minimizing the endoscopic burden. Our analysis reveals that the use of PPI therapy before endoscopy may serve as a filter to identify patients who can be rendered asymptomatic without the use of invasive procedures. This finding reflects the clinical reality that most patients undergoing endoscopy by current guidelines are eventually placed on antisecretory therapy despite the intervention.[110,111] The additional cost generated by committing patients to long-term PPI therapy before endoscopy appears to be offset by the improved effectiveness and 30% reduction in invasive procedures provided by this approach. In short, our model reveals that the T&T→PPI→EGD strategy may achieve improved patient outcomes at a lower overall cost than current guidelines.

Our analysis further suggests that the previous recommendation to use initial antisecretory therapy for dyspepsia, published more than 15 years ago,[4] may now be more relevant with the advent of potent antisecretory agents. The PPI→EGD strategy, in which *H. pylori* eradication is performed only after an infected ulcer is confirmed by endoscopy, cost the least per QALY and was only marginally less effective than the T&T→PPI→EGD approach. Moreover, our analysis indicates that the PPI→EGD strategy may be most cost-effective overall if the likelihood of underlying PUD or NUD is low or the likelihood of underlying esophagitis is high. Initial PPIs may also be preferred if the rate of effective *H. pylori* eradication decreases below 60% or if less than 15% of NUD patients achieve symptom relief with *H. pylori* eradication; both of these values lie within the reported range in the literature. Therefore, despite the overwhelming data in support of antibiotic therapy for *H. pylori*–positive PUD, the initial use of PPI therapy for uninvestigated dyspepsia may be clinically and economically feasible in some circumstances.

Because most patients with dyspepsia have underlying NUD, the cost-effectiveness of competing strategies depends heavily on the ability of each to improve the symptoms of NUD. Delaney et al.,[112] in an extensive meta-analysis of randomized controlled trials for NUD treatment, found a modest but statistically significant improvement in symptoms with *H. pylori* eradication and a modest but statistically insignificant improvement in symptoms with PPI therapy. These authors applied these data to a decision analysis for NUD treatment and concluded that the high cost of PPI cannot offset its benefits, and thus PPI is not cost-effective in NUD.[112] Although our model is designed to evaluate uninvestigated dyspepsia rather than NUD alone, our findings are consistent with these previous studies. For example, the PPI→EGD strategy is preferred in our model only when the prevalence of NUD is low or when the effect of *H. pylori* eradication on symptoms of NUD decreases below the placebo rate; both conditions suppress the established effectiveness of test and treat in NUD. Conversely, the combination of *H. pylori* eradication and PPI therapy gains incremental effectiveness compared with PPI therapy alone as the prevalence of NUD increases. Therefore, our analysis is consistent with the findings of Delaney et al.[112] that PPI therapy alone is not cost-effective in NUD and further suggests that the sequential use of test and treat and PPI therapy may be significantly more cost-effective than either strategy alone.

Table 9. Results of Monte Carlo Simulation Using 1000 Trials

Strategy	Mean cost/patient treated	Mean marginal cost[a]	Mean effectiveness (% symptom-free at 1 year)	Mean marginal effectiveness[b]	Mean cost-effectiveness ($/symptom-free at 1 year)	Mean marginal cost-effectiveness[c]
T&T→EGD (current guidelines)	$1930	—	76%	—	$2539	—
T&T→PPI→EGD	$1726	−$204	86%	+10%	$2007	Negative value
PPI→EGD	$1548	−$382	82%	+6%	$1888	Negative value
PPI→T&T→EGD	$1795	−$135	84%	+8%	$2137	Negative value

[a]Mean cost per patient treated versus current guidelines.
[b]Mean proportion of symptom-free patients at 1 year versus current guidelines.
[c]Mean cost per additional symptom-free patient at 1 year versus current guidelines.

Our study has several unique features compared with previous economic analyses for dyspepsia management. First, whereas most published reports focus on selected subgroups of dyspepsia patients, including those with documented PUD,[113] "suspected" PUD,[114,115] resistant dyspepsia,[116] and *H. pylori*–positive dyspepsia,[117] we evaluate patients with uninvestigated and undifferentiated dyspepsia presenting to the primary care provider for the first time. Second, whereas most analyses that evaluate uninvestigated dyspepsia compare initial endoscopy versus 1 noninvasive approach,[118,119] we focus on competing noninvasive strategies to address the options available in the primary care setting. Third, the few analyses that compare more than 1 noninvasive strategy evaluate *H. pylori* eradication versus empiric antisecretory therapy,[120] whereas we investigate hybrid strategies that allow the clinician to alternate between noninvasive therapies in response to persistent symptoms rather than mandate the continuation of an otherwise failing approach. Fourth, whereas previous decision analyses evaluated 1 primary outcome (e.g., cost per ulcer cured,[114,115] cost per average patient treated,[117] or time spent with ulcer disease[113]), we report 2 outcomes relevant to the outpatient setting: (1) cost per QALY and (2) cost per asymptomatic patient. Finally, most of these economic models were published before the recent accumulation of data regarding the efficacy of *H. pylori* eradication and PPI therapy in NUD; we attempt to incorporate these new data into our analysis.

A recent elegant model reported by Delaney et al.[112] uses discrete event simulation to estimate the cost-effectiveness of 2 invasive strategies with 3 empiric strategies for uninvestigated dyspepsia: (1) initial *H. pylori* treatment for all, (2) initial *H. pylori* test and treat, and (3) initial antisecretory therapy. The authors concluded that invasive strategies are more expensive and less effective than empiric strategies, and that the relative cost-effectiveness of test and treat and antisecretory therapy relies on several factors, including the specific prescribing strategy taken. Although their model addresses similar clinical issues to ours, there are significant differences between the studies. First, the model of Delaney et al. does not incorporate the strategy supported by current AGA guidelines, in which patients failing up-front test and treat progress directly to upper endoscopy. Although these authors consider "test and scope" (i.e., T→EGD) and test and treat followed by PPI therapy, they model neither T&T→EGD nor PPI→T&T→EGD. Second, whereas these authors do not consider severity of dyspepsia, we attempt to model various case mixes of symptom severity and measure QALYs for each strategy. Third, Delaney et al. rely on cost estimates from the United Kingdom, which in several cases are significantly different from the U.S. Medicare reimbursement costs incorporated in our model. For example, the costs of upper endoscopy and *H. pylori* eradication therapy in the United Kingdom are 45% and 80% less expensive, respectively, than the comparable Medicare reimbursement when converted into dollars (US). These estimates tend to favor the test and treat–based strategies in the United Kingdom, which rely more heavily on antibiotic therapy and upper endoscopy than the PPI-based approaches (Table 7). Despite these substantive differences, our study appears to corroborate the findings of Delaney et al. that empiric antisecretory therapy may be an economically feasible approach, and amplifies their data by demonstrating the cost-effectiveness of PPI-based strategies in achieving improved symptom relief and dyspepsia-related quality of life versus current AGA guidelines in a Medicare population in the United States.

This study has limitations. As with any decision analysis, the results depend on the validity of the base-case estimates. Our understanding of the relationship between *H. pylori* and dyspepsia is constantly evolving, and it may be premature to rely on fixed clinical probability estimates. Several of our assumptions, although derived from a systematic review of the literature, may be controversial. However, where data were equivocal or absent, we assigned values that tended to bias the model in favor of the current guidelines. Despite this bias, our model indicates that the current guidelines may not be cost-effective compared with alternative strategies. This finding persists when key clinical assumptions are varied over a range of values exceeding clinical likelihood.

Because dyspepsia is a chronic condition, our 1-year time horizon may be inadequate to realistically portray the natural history of dyspeptic patients. Previous economic models used a similar time horizon, but the discrete event simulation model developed by Delaney et al. followed patients for a 5-year period.[112] Although extending our time horizon beyond 1 year might provide more clinically meaningful results, we are limited by the data derived from the original reports. In particular, most of the existing dyspepsia trials, including the reports we used to derive our base-case estimates, observed patients for 1 year or less. Extrapolating our findings beyond these published data could produce misleading conclusions. Until more trials with extended follow-up periods are published, accurately predicting the relative cost-effectiveness of competing strategies over time horizons exceeding 1 year will remain difficult.

Our model assumes that patients rendered asymptomatic with PPI therapy continue once-daily PPI therapy indefinitely. In reality, however, most patients rendered asymptomatic discontinue maintenance PPI and resume intermittent courses of antisecretory therapy as symptoms dictate. Although data on the effectiveness of repeated PPI courses are limited, it is logical to presume that most patients with underlying esophagitis or NUD rendered asymptomatic once may be cured again by a second course of therapy. Patients with *H. pylori*–positive ulcers healed by PPI therapy are at significant risk for an ulcer relapse following discontinuation of PPI. Whether a subset of these patients with initially symptomatic ulcers cured by PPIs may redevelop their diathesis in the absence of symptoms, and subsequently develop complications that could have been avoided by up-front *H. pylori* eradication, remains unclear. Therefore, it may be argued that the potential for subsequent ulcer complications from noncompliance with PPIs tends to support test and treat–based approaches.

Despite the substantial costs of ulcer complications, however, this clinically feasible concern is not likely to make a substantial impact on overall cost-effectiveness for PPI-based strategies. With even the most liberal base-case assumptions, we estimate that no more than 1% (Value derived from following liberal assumptions: probability of underlying PUD=22%; probability PUD is *H. pylori* positive=90%; probability of noncompliance with maintenance PPIs=90%; probability of ulcer recurrence in *H. pylori*–positive patient after discontinuing PPIs=80%; probability that ulcer recurrence is asymptomatic and therefore not treated=50%; [.22 × .90 × .90 × .80 × .50 × .10 = 0.7%].) of patients with uninvestigated dyspepsia (rather than PUD alone) receiving up-front PPIs are at risk for developing ulcer complications that may have been prevented by initial *H. pylori* eradication. Using these assumptions, we estimate that the additional costs generated by increased ulcer complications in the PPI→EGD and PPI→T&T→EGD strategies are more than offset by the cost savings from reduced PPI use caused by noncompliance (Table 10). In fact, the PPI-based strategies gain cost-effectiveness in our model as the rate of noncompliance increases, as long as patients are prompted to restart therapy in response to recurrent symptoms. Therefore, our requirement that all patients continue PPI therapy tends to bias the model in favor of, rather than against, the test and treat strategies.

Our analysis does not consider all possible clinical outcomes, including personal discomfort as a result of an invasive procedure or a complication of therapy and anxiety over the lack of a confirmed diagnosis. Early endoscopy may improve outcomes because it reduces patient anxiety and provides diagnostic assurance for both patients and physicians.[121–123] The T&T→PPI→EGD strategy postpones endoscopy compared to current guidelines and thus may be less effective than our analysis suggests. However, patients rendered asymptomatic by PPI therapy before endoscopy are presumably less concerned about their underlying diagnosis than those with persistent symptoms. Although the T&T→PPI→EGD strategy postpones endoscopy in favor of empiric PPI therapy, it ensures that all patients with persistent dyspepsia eventually receive this intervention.

Of additional concern, recent case reports indicate that empiric PPI therapy may mask the symptoms of early gastric cancer.[95,96] Our analysis does not consider the impact on cost-effectiveness from delayed or missed diagnoses of gastric cancer. However, most patients with underlying malignancy are not rendered asymptomatic by a 6-week trial of PPI therapy.[96] Therefore, fewer than 1 in 1000 patients younger than age 45 with simple dyspepsia may be at risk for a delayed diagnosis of gastric cancer caused by PPI-based strategies. Moreover, most patients in the United States found to have gastric cancer by early investigation have already developed advanced disease by the time of diagnosis.[124] Although the small risk of delaying gastric cancer may not be acceptable to some clinicians, it should be noted that the strategy supported by current guidelines

Table 10. Results of Cost-Effectiveness Analysis Considering 90% Noncompliance With Maintenance PPI Therapy

Strategy	Cost/ patient treated	Marginal cost[a]	Effectiveness (% symptom-free at 1 year)	Marginal effectiveness[b]	Average cost-effectiveness ($/symptom-free at 1 year)	Marginal cost-effectiveness[c]
T&T→EGD (current guidelines)	$1584	—	75%	—	$2112	—
T&T→PPI→EGD	$1318	−$266	84%	+9%	$1569	Negative value
PPI→EGD	$1279	−$305	78%	+3%	$1640	Negative value
PPI→T&T→EGD	$1389	−$195	84%	+9%	$1654	Negative value

[a]Cost per patient treated versus current guidelines.
[b]Proportion of symptom-free patients at 1 year versus current guidelines.
[c]Cost per additional symptom-free patient at 1 year versus current guidelines.

is subject to similar risks, because it also uses high-dose PPI therapy before endoscopy as part of the standard *H. pylori* eradication regimen.

Our model is purposefully designed to simplify dyspepsia management and thus may not successfully incorporate the intricacies of caring for an individual patient. For example, patients with endoscopic evidence of esophagitis who subsequently do not respond to PPI therapy might be referred for 24-hour ambulatory pH monitoring, whereas we model continuous antisecretory therapy. Similarly, patients with resistant NUD might be referred for motility studies, whereas we model amitriptyline. However, to maintain a balanced model, we specifically avoid several literature-based recommendations that could bias the model against the current guidelines. In particular, a recent guideline suggests that all patients with confirmed *H. pylori*–positive PUD undergo urea breath test confirmation after antibiotic treatment, even if rendered asymptomatic.[7] It has been further suggested that all patients rendered asymptomatic with PPI attempt step-down or on-demand therapy with less-expensive agents, such as histamine$_2$ receptor blockers. If incorporated into the analysis, these clinically feasible recommendations would bias the model against the current guidelines, which use more urea breath tests and less antisecretory therapy than the PPI-based strategies.

However, the cost of PPI therapy is soon expected to decrease because of upcoming patent expirations. Despite incorporating the cost of brand-name PPI, our analysis reveals a cost-effectiveness advantage for the 3 strategies that rely on empiric PPI. We estimate that a 50% reduction in price will make the PPI→EGD strategy the most cost-effective overall. Although the precise cost of generic PPI therapy has not been determined, any reduction from the current cost will tend to favor the PPI-based management strategies over the current guidelines.

To our knowledge, the T&T→PPI→EGD strategy has not been previously described or formally evaluated. Nonetheless, this novel and simple approach is already practiced by many primary care physicians, who intuitively question why an otherwise healthy and functional patient that does not respond to a test and treat approach must undergo immediate endoscopy.[125] Most dyspeptic patients in this setting do not respond to test and treat and, under current guidelines, are committed to an invasive, time-consuming, and expensive intervention that may not alter subsequent management. The T&T→PPI→EGD strategy respects this clinical reality by forgoing invasive procedures in favor of a PPI trial, while reserving endoscopy for patients with persistent symptoms.

In conclusion, our analysis suggests that the current guidelines for the management of uninvestigated dyspepsia are not cost-effective compared with PPI-based approaches. Each of the 3 PPI-based strategies in our analysis appears to reduce unnecessary invasive procedures while achieving improved symptom control and quality of life at a lower overall cost compared with the current AGA guidelines. We estimate that the T&T→PPI→EGD strategy costs $2500 less per additional symptomatic cure than the current guidelines, a finding that could potentially result in extraordinary savings if multiplied by the millions of dyspeptic patients treated annually. Although our data are unlikely to be precisely reproduced in clinical practice, sensitivity analysis suggests that the current guidelines could never gain a cost-effectiveness advantage over PPI-based approaches under even extreme clinical conditions. Selecting among the remaining PPI-based strategies is more difficult, however. Our analysis reveals that the sequential use of *H. pylori* eradication with PPI therapy may be more cost-effective than PPI therapy alone, particularly when accompanied by a high likelihood of underlying PUD or NUD or extreme symptom severity. Conversely, our analysis suggests that PPI therapy alone may be more cost-effective than the sequential use of PPI therapy and *H. pylori* eradication when there is a high likelihood of underlying erosive esophagitis, a low likelihood of *H. pylori* prevalence, or low symptom severity. Therefore, selecting the optimal PPI-based strategy will ultimately depend on several individual factors, including the pretest likelihood of a specific underlying condition, the local prevalence of *H. pylori*, the effectiveness of anti–*H. pylori* therapy, and the severity of dyspepsia symptoms. We therefore suggest that the endorsement of current guidelines be reappraised, and that a prospective trial comparing alternative PPI-based management strategies be conducted.

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