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Reappraisal of non-invasive management strategies for uninvestigated dyspepsia: a cost-minimization analysis

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SUMMARY

Background: The benefits of the *Helicobacter pylori* test-and-treat strategy are attributable largely to the cure of peptic ulcer disease while limiting the use of endoscopy.
Aim: To reappraise the test-and-treat strategy and empirical proton pump inhibitor therapy for the management of uninvestigated dyspepsia in the light of the decreasing prevalence of *H. pylori* infection, peptic ulcer disease and peptic ulcer disease attributable to *H. pylori*.
Methods: Using a decision analytical model, we estimated the cost per patient with uninvestigated dyspepsia managed with the test-and-treat strategy ($25/test; *H. pylori* treatment, $200) or proton pump inhibitor ($90/month). Endoscopy ($550) guided therapy for persistent or recurrent symptoms.
Results: In the base case (25% *H. pylori* prevalence, 20% likelihood of peptic ulcer disease, 75% of ulcers due to *H. pylori*), the cost per patient is $545 with the test-and-treat strategy and $529 with proton pump inhibitor, and both strategies yield similar clinical outcomes at 1 year. *H. pylori* prevalence, the likelihood of peptic ulcer disease and the proportion of ulcers due to *H. pylori* are important determinants of the least costly strategy. At an *H. pylori* prevalence below 20%, proton pump inhibitor is consistently less costly than the test-and-treat strategy.
Conclusions: As the *H. pylori* prevalence, the likelihood of peptic ulcer disease and the proportion of ulcers due to *H. pylori* decrease, empirical proton pump inhibitor becomes less costly than the test-and-treat strategy for the management of uninvestigated dyspepsia. Given the modest cost differential between the strategies, the test-and-treat strategy may be favoured if patients without peptic ulcer disease derive long-term benefit from *H. pylori* eradication.

INTRODUCTION

'Dyspepsia' describes a commonly encountered set of symptoms (upper abdominal pain or discomfort with or without fullness, bloating, nausea or early satiety) caused by a heterogeneous group of disorders. The available initial management strategies for individuals who present with dyspeptic symptoms include prompt visualization of the upper gastrointestinal tract, empirical therapy, such as antisecretory medication, and non-invasive testing for *Helicobacter pylori* infection to direct eradication therapy including antibiotics ('test-and-treat' strategy).

Prompt imaging of the gastrointestinal tract provides the greatest degree of diagnostic certainty, may reduce unnecessary antibiotic use and may provide the greatest degree of patient satisfaction.[1, 2] However, the cost of endoscopy[3] and the suboptimal accuracy of upper gastrointestinal series[4] make immediate gastrointestinal

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imaging impractical for all patients with uncomplicated dyspepsia in the primary care setting. Before the association between *H. pylori* and peptic ulcer disease was elucidated, empirical antisecretory therapy was recommended by professional organizations as first-line therapy for dyspepsia.[5] In the *H. pylori* era, however, empirical antisecretory therapy has been criticized because patients with *H. pylori*-associated peptic ulcer disease are denied the benefits of a reduced recurrence risk of peptic ulcer after successful eradication of the organism.

Numerous practice guidelines have endorsed the test-and-treat strategy for patients with uncomplicated dyspepsia.[6–10] This approach is based on the premise that *H. pylori* eradication therapy yields long-term benefit for patients with *H. pylori*-associated peptic ulcer disease. In addition, when this strategy was initially proposed, it was believed that *H. pylori* eradication might also benefit patients with functional dyspepsia. Cost-effectiveness analyses identified the test-and-treat strategy as a reasonable alternative to prompt endoscopy,[3, 11] and recent data suggest that it can decrease endoscopy utilization and reduce health care expenditures for patients with dyspepsia without compromising clinical outcomes.[2, 12, 13] These benefits are realized even though the benefit of eradicating *H. pylori* in patients with functional dyspepsia is modest at best.[14, 15]

The cost-effectiveness of the test-and-treat strategy is likely to depend on a number of factors, including the epidemiology of *H. pylori* infection and peptic ulcer disease, the response rates to *H. pylori* therapy and the cost of diagnostic testing and therapy. The challenge to clinicians and policy makers is that many of these variables are in a state of flux. Epidemiological data suggest that the prevalence of both *H. pylori* infection and peptic ulcer disease in the USA is falling,[16–21] and it is becoming increasingly clear that the proportion of patients with *H. pylori*-positive peptic ulcer disease is lower than the approximately 90% originally reported.[22–24]

Our aim was to reappraise the non-invasive alternatives for the management of uninvestigated dyspepsia in the primary care setting. We used a symptom-driven decision analytical model to estimate the cost per patient treated with the *H. pylori* test-and-treat strategy compared to empirical antisecretory therapy in the context of the changing epidemiology of *H. pylori* infection and peptic ulcer disease.

MATERIALS AND METHODS

Decision analytical model and study population

A symptom-driven computer simulation was constructed to predict the natural history of peptic ulcer disease, its interaction with *H. pylori* infection and the effects of various diagnostic and therapeutic interventions. The model has been described in detail elsewhere.[3] The analysis started with a cohort of 1000 hypothetical patients with uncomplicated dyspepsia on initial presentation. On entry into the simulation, all patients had dyspeptic symptoms of sufficient severity to justify an empirical course of antisecretory therapy. In addition, it was assumed that patients had no prior evaluation for *H. pylori* or previous documentation of peptic ulcer disease.

After the initial encounter, patients moved among different states of health conditional on the likelihood of symptoms, *H. pylori* infection and peptic ulcer disease, and the impact of the prescribed interventions. Every 6 weeks for 1 year, patients were distributed among different health states. The model captured resource use, such as physician visits, pharmaceutical use, procedures and hospitalizations. The principal outcome measured was health care utilization (cost per patient treated) over the 1-year time course. This time frame obviated the requirement for discounting of clinical benefits and costs.

Diagnostic and therapeutic interventions

Test-and-treat strategy. All patients in this strategy underwent enzyme-linked immunoabsorbent assay serological testing for *H. pylori* (85% sensitivity and 79% specificity; $25) to identify past or present *H. pylori* infection.[25–27] All patients who tested positive were treated with a 14-day course of proton pump inhibitor-based triple therapy ($200), as generally recommended in the USA.[10] Patients who had negative serology were prescribed standard dose proton pump inhibitor therapy for 4 weeks ($90). In the sensitivity analysis, we examined a 7-day course of eradication therapy, as is common in Europe.[10]

Empirical antisecretory therapy. All patients in this strategy were prescribed a 4-week course of standard dose proton pump inhibitor therapy. No diagnostic testing was undertaken on the initial visit.

Subsequent intervention. After the initial intervention, every patient with persistent or recurrent symptoms at the completion of therapy was assumed to return for medical evaluation. As recommended in current guidelines, endoscopy ($550) was performed in these patients and a rapid urease test for *H. pylori* ($25) was performed in those with peptic ulcer disease. If the initial intervention failed to produce symptomatic relief for the 1-year period, endoscopic findings directed all subsequent interventions in both strategies evaluated. Thus, the two strategies differed only in the initial testing for *H. pylori* and the therapy prescribed initially.

Patients who had an ulcer diagnosed by endoscopy at any time were treated with proton pump inhibitor. Eradication therapy was prescribed when there was also objective evidence of *H. pylori* infection. Ulcer patients who remained symptomatic after three complete courses of antisecretory therapy underwent a second endoscopic evaluation to assess ulcer healing and *H. pylori* status. Individuals who became asymptomatic at any time after the initial encounter were assumed not to visit a physician regardless of their underlying diagnosis unless symptoms recurred.

In the sensitivity analysis, we considered a management algorithm incorporating urea breath testing in the test-and-treat strategy for patients with positive *H. pylori* serology who did not achieve symptom resolution after eradication therapy.[10] A second, different course of eradication therapy was prescribed for those with evidence of persistent *H. pylori* infection.

Clinical probabilities

A MEDLINE search was conducted for English language articles to provide pertinent clinical data for the simulation. Bibliographies of accepted articles were reviewed and a search of current issues of the peer-reviewed general medicine, infectious disease and gastroenterology literature was also undertaken to identify additional reports not included in the computerized database. Clinical input probabilities and cost estimates used in the simulation are shown in Table 1.

H. pylori *infection.* The overall prevalence of *H. pylori* infection is falling in most westernized nations.[16] In these nations, advancing age has been associated with a higher prevalence of *H. pylori* infection, but this appears to be primarily the consequence of a birth cohort effect, with improvements in sanitation and widespread use of antibiotics leading to lower rates of *H. pylori* acquisition at present compared to decades ago. The birth cohort hypothesis is supported by the relatively low incidence of new *H. pylori* infection in adults of 0.1–1.1% per year, with the majority of studies reporting an incidence of 0.3–0.5% per year.[16]

There are limited *H. pylori* prevalence data from the USA. In 1991, Graham *et al.* evaluated 490 asymptomatic volunteers and reported an *H. pylori* prevalence of 34% in Caucasians and 70% in African Americans.[17] More recently, a population-based study in over 7000 children and adolescents reported *H. pylori* prevalences of 17% in non-Hispanic whites, 40% in non-Hispanic blacks and 42% in Mexican Americans.[18] The apparent racial differences in *H. pylori* prevalence seem to relate to socio-economic factors.

In our study of US primary care patients tested for *H. pylori*, 21% were seropositive.[13] In European randomized trials of the test-and-treat strategy, *H. pylori* prevalence has ranged from 28% to 41%.[2, 12] In the base case, we chose 25% *H. pylori* prevalence as the input. Given that the overall *H. pylori* prevalence in westernized nations is falling, but that important regional differences exist depending on the characteristics of the local populations, we examined a wide range of *H. pylori* prevalence in our sensitivity analysis (5–95%). In the base case, *H. pylori* status affects the likelihood of ulcer recurrence, but has no independent effect on the development or resolution of symptoms. After successful eradication therapy, *H. pylori* infection was assumed not to recur.

Peptic ulcer disease. The hypothetical cohort was presumed to have a mix of clinical conditions as drawn from the published literature.[7] The overall prevalence of peptic ulcer disease in the USA has decreased in recent decades.[19–21] This trend is probably related to the decrease in *H. pylori* prevalence. It is not clear whether the prevalence of peptic ulcer disease in patients presenting with uncomplicated dyspepsia to clinicians is also decreasing, however. Studies of open access endoscopy units reveal that peptic ulcers not associated with non-steroidal anti-inflammatory drugs (NSAIDs) are found in approximately 20% of

Table 1. Inputs in cost-effectiveness model

Variable	Base case value (range)	Reference
Clinical probabilities		
H. pylori prevalence (%)	25 (10–60)	2, 12, 13, 17, 18, 28, 29
Likelihood of active ulcer disease (%)	20 (10–30)	2, 7, 30
Fraction of ulcers due to *H. pylori* (%)	75 (60–90)	22–24, 31–33
Ulcer healing rate after antisecretory therapy (%)	75 (60–90)	34–36
H. pylori eradication success rate (includes compliance) (%)	80 (70–90)	37–40
Recurrent symptom rate with active ulcer (%)	90 (50–90)	41, 42
Recurrent symptom rate with healed ulcer (%)	10 (0–30)	43
Recurrent symptom rate with no ulcer (%/year)	30 (10–50)	1, 44
Ulcer recurrence with *H. pylori* infection (%/year)	72 (60–90)	31, 45–48
Ulcer recurrence with no infection (%/year)	20 (10–30)	49–53
Sensitivity of *H. pylori* serological test (%)	85 (75–90)	25–27
Specificity of *H. pylori* serological test (%)	79 (70–85)	25–27
Cost estimates ($)		
H. pylori serological test	25	
Endoscopy	550	
Rapid urease test	25	
Proton pump inhibitor therapy (per month)	90	
H. pylori eradication therapy (proton pump inhibitor-based triple therapy for 2 weeks)	200	
Primary care physician office visit	39	
Gastroenterologist office visit	80	
Hospitalization for ulcer complication with no surgery	7095	
Hospitalization for ulcer complication with surgery	24081	

symptomatic patients presenting for medical attention.[7] In the trial by Lassen *et al.* comparing test-and-treat vs. endoscopy, 19% of patients in the endoscopy arm were diagnosed with an ulcer.[2] In a recent study of dyspeptic primary care patients referred to open access endoscopy in The Netherlands, only 6.7% had peptic ulcer disease.[30] In the base case, we used 20% peptic ulcer disease likelihood as the input. In sensitivity analysis, we varied over a wide range the likelihood that a patient with uncomplicated dyspepsia had peptic ulcer disease (0–80%).

In the base case, ulcer status determined the likelihood of symptomatic relief from therapy, and thus determined the need for future physician visits and related medical interventions. Endoscopy was assumed to be a perfect test for the diagnosis of ulcer disease and was presumed to have no associated adverse events. Ulcer recurrence — not associated with NSAID use — was related to *H. pylori* status and concurrent use of antisecretory therapy.[31, 45–53]

Recent studies suggest that the benefit of the eradication of *H. pylori* in patients with functional dyspepsia is modest at best.[14, 15] To explicitly model the potential benefit of *H. pylori* eradication for patients without peptic ulcer disease, we varied the rate of symptomatic relapse for these patients in the sensitivity analysis.

Association between peptic ulcer disease and H. pylori. Initial studies found that 90% of patients with duodenal ulcer and 70% or more of patients with gastric ulcer were infected with *H. pylori*.[31–33, 54] More recent reports have identified an increasing prevalence of *H. pylori*-negative ulcers even when NSAID use is excluded.[22–24] In one report, 48% of ulcer patients were not infected with *H. pylori*.[24]

The proportion of ulcers attributable to *H. pylori* depends in large part on the prevalence of *H. pylori* infection and peptic ulcer disease in the population. For example, it has been estimated that, given a 40% decline in *H. pylori* prevalence, a proportional increase in *H. pylori*-negative ulcers from 24% to 38% of all duodenal ulcers would be observed, provided that the total number of ulcers from other causes remained stable.[55] We chose 75% as our base case input for the proportion of ulcers attributable to *H. pylori*. In the

sensitivity analysis, we varied this proportion from 60% to 90%.

Cost inputs

Cost calculations of medical resource use were based upon third party expenditures. Payments, not charges, were used to determine cost estimates. The national average of charges allowed by the Health Care Financing Administration for Medicare reimbursement was used to determine the lower bound of cost estimates, as the payment for similar services varies between geographical regions and delivery systems. The costs of proton pump inhibitor therapy and *H. pylori* eradication therapy were obtained from the University of Michigan Hospital pharmacy. Indirect costs to the patient (lost productivity, etc.) were not included in the analysis.

For patients whose symptoms were caused by reasons other than peptic ulcer disease, physician visits, diagnostic tests (including endoscopy) and pharmaceuticals were captured in the simulation up to the point at which patients were identified as not having an ulcer on endoscopic evaluation. Recall that, after endoscopy had been performed, endoscopy-directed patient management was identical for both strategies. The exclusion of treatment costs after the demonstration of a non-ulcer cause was consistent with our base case assumption that no immediate clinical benefit resulted from the eradication of *H. pylori* for patients without peptic ulcer disease.

Model validation

As a model validation exercise, we compared the model's results with those of the test-and-treat arm of our randomized trial comparing a test-and-treat intervention to 'usual care' in the primary care setting.[56, 57] In the validation exercise, we used the model inputs in Table 1 and assumed that 75% of ulcers were attributable to *H. pylori*. We used the *H. pylori* prevalence found in the clinical study (43%) and the rate of peptic ulcer disease found in those who underwent endoscopy or gastrointestinal radiography in the study (10%).

Cost-minimization analysis

We performed a cost-minimization analysis comparing the test-and-treat strategy with empirical proton pump inhibitor. Randomized studies have reported comparable clinical outcomes regardless of the initial strategy used in uncomplicated dyspepsia.[1, 2, 12, 58, 59] A cost-minimization analysis is justifiable in our simulation because both strategies in our model direct patients with persistent or recurrent symptoms to endoscopy, patients receive all subsequent therapy based on the endoscopy results and similar clinical outcomes are expected at the year end. To test the appropriateness of a cost-minimization approach, clinical outcomes at the end of the simulation were compared between the two strategies.

Sensitivity analysis

Sensitivity analyses were used to assess the impact of varying the model inputs over the ranges reported in the literature. The key variables in our analysis were the prevalence of *H. pylori*, the likelihood of peptic ulcer disease in patients presenting with uncomplicated dyspepsia and the fraction of ulcers attributable to *H. pylori*.

RESULTS

Model validation

Using the epidemiological parameters from our clinical study,[56, 57] the cost per patient treated with the test-and-treat strategy in our model is $473, compared to an annual median disease-related expenditure of $454 (interquartile range, $162–$932) in the clinical study. In the simulation, 35% of patients undergo endoscopy, 23% ultimately receive maintenance antisecretory therapy and the median expenditure per patient for pharmaceuticals is $164 — compared to results in our clinical study of endoscopy in 30%, maintenance therapy in 31% and median pharmaceutical expenditure of $171 (interquartile range, $83–$369). These results suggest that the simulation's estimates are reasonable reflections of clinical experience.

The clinical outcomes at the end of the simulation are similar under the test-and-treat strategy and empirical proton pump inhibitor, justifying a cost-minimization analysis. In both strategies, using base case inputs, less than 1% of patients have active peptic ulcer disease at 1 year, and approximately 25% of patients receive maintenance antisecretory medication.

Simulation: test-and-treat vs. empirical antisecretory therapy

Base case. The cost per patient treated in the base case is $545 with the test-and-treat strategy compared to $529 with empirical proton pump inhibitor (Table 2).

Sensitivity analysis: H. pylori *and peptic ulcer disease epidemiology.* The cost per patient treated with each strategy is highly dependent on the epidemiology of *H. pylori* infection and peptic ulcer disease in the population with uninvestigated dyspepsia. Table 2 shows the cost per patient treated with the two non-invasive strategies at various levels of *H. pylori* prevalence and peptic ulcer disease likelihood, assuming that 75% of all ulcers can be attributed to *H. pylori*. In each scenario illustrated, the cost difference between the strategies is modest, although the cost is generally lower for empirical proton pump inhibitor.

Figure 1 shows cost-equivalence lines representing conditions under which the costs per patient treated are identical for the test-and-treat strategy and empirical proton pump inhibitor. The figure illustrates the impact of varying the prevalence of *H. pylori* infection (*x* axis; 5–95%), the likelihood that a patient with uninvestigated dyspepsia has peptic ulcer disease (*y* axis; 0–80%) and the fraction of ulcers that can be attributed to *H. pylori* infection (lines representing 60%, 75% and 90%). The area above a given cost-equivalence line represents the combinations of *H. pylori* prevalence and likelihood of having peptic ulcer disease for which the test-and-treat strategy is less costly than the empirical proton pump inhibitor strategy. The area below a given cost-equivalence line represents those circumstances under which the empirical proton pump inhibitor strategy is less costly.

Table 2. Cost per patient treated at various levels of *Helicobacter pylori* prevalence and peptic ulcer disease likelihood, assuming that 75% of all ulcers can be attributed to *H. pylori*

H. pylori prevalence (%)	Likelihood of PUD (%)	Cost per patient treated ($)	
		Test-and-treat strategy	Empirical PPI
Base case			
25	20	545	529
Sensitivity analysis			
20	10	455	420
20	20	541	529
20	25	584	583
30	10	463	420
30	20	549	529
30	30	635	637
40	10	470	420
40	20	557	529
40	30	643	637
40	40	729	746

PPI, proton pump inhibitor; PUD, peptic ulcer disease.

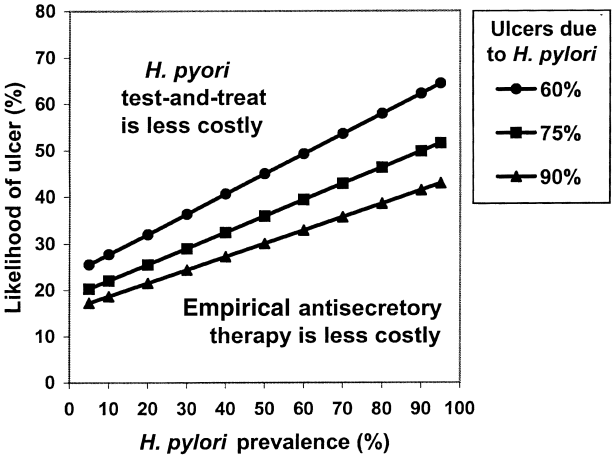

Figure 1. Cost minimization in uninvestigated dyspepsia as a function of the epidemiology of *Helicobacter pylori* infection and peptic ulcer disease. Cost-equivalence lines are shown for varying levels of the association between peptic ulcer disease and *H. pylori.* Along these lines, the test-and-treat strategy and empirical proton pump inhibitor incur identical costs per patient treated. In the area above a given cost-equivalence line, the test-and-treat strategy is less costly than empirical proton pump inhibitor. In the area below a given cost-equivalence line, empirical proton pump inhibitor is less costly.

Figure 1 illustrates several trends. First, given a certain likelihood of having peptic ulcer disease (when the *y* axis value is constant), the test-and-treat strategy is less costly than empirical proton pump inhibitor only below a critical value for the prevalence of *H. pylori*. For instance, if 75% of ulcers can be attributed to *H. pylori*, and the likelihood that a patient with uninvestigated dyspepsia has peptic ulcer disease is judged to be 30%, the test-and-treat strategy is less costly than empirical proton pump inhibitor if the *H. pylori* prevalence is below 35%.

Second, given a certain prevalence of *H. pylori* infection (when the *x* axis value is constant), the test-and-treat strategy is preferred as the likelihood of peptic ulcer disease increases. For example, if 75% of ulcers can be attributed to *H. pylori* and the prevalence of

H. pylori infection is 30%, the test-and-treat strategy is favoured if the likelihood of ulcer is 30% or greater.

Third, as the fraction of ulcers attributable to *H. pylori* decreases, the set of circumstances under which the test-and-treat strategy is less costly than empirical proton pump inhibitor becomes smaller. For instance, if the prevalence of *H. pylori* infection is 40% and the likelihood of ulcer is 30%, the test-and-treat strategy is less costly if 90% of ulcers are caused by *H. pylori*, but empirical proton pump inhibitor is less costly if only 60% of ulcers are caused by *H. pylori*.

We must point out that, at a population level, the possible combinations of *H. pylori* prevalence (x axis in Figure 1) and likelihood of having peptic ulcer disease (y axis in Figure 1) are constrained by the specific fraction of ulcers attributable to *H. pylori*. For example, if the likelihood of having peptic ulcer disease is 20%, and it is assumed that 75% of ulcers can be attributed to *H. pylori* infection, *H. pylori* prevalence must be at least 15% ($0.75 \times 0.20 = 0.15$).

Below an *H. pylori* prevalence of approximately 20%, those combinations of *H. pylori* prevalence and likelihood of peptic ulcer disease that are possible at a population level all represent circumstances under which empirical proton pump inhibitor is less costly than the test-and-treat strategy (Figure 1). This result holds whether the fraction of ulcers attributable to *H. pylori* is 60%, 75% or 90%.

Sensitivity analysis: additional variables. Improving the sensitivity and specificity of the test for *H. pylori* does not make the test-and-treat strategy less costly than empirical proton pump inhibitor. If improved test performance is achieved at the expense of a higher testing cost compared to the base case (for instance, with 'active' urea breath testing with 95% sensitivity and 98% specificity at a cost of $100), test-and-treat ($604 per patient) becomes even more costly than empirical proton pump inhibitor ($529 per patient). Similarly, improving the success rate of *H. pylori* eradication therapy does not make the test-and-treat strategy ($536 per patient with 95% eradication rate in the base case) less costly than empirical proton pump inhibitor ($523 per patient).

Changes in the costs of therapy affect the results minimally. A decrease in the cost of proton pump inhibitor (with the introduction of generic proton pump inhibitor, for instance) increases the cost difference between the strategies only slightly ($469 per patient with test-and-treat compared to $442 per patient with empirical proton pump inhibitor, with the cost of proton pump inhibitor reduced by two-thirds in the base case). Alternatively, a substantially reduced cost for *H. pylori* eradication therapy may provide the test-and-treat strategy with a small cost advantage at moderate levels of *H. pylori* prevalence and likelihood of peptic ulcer disease ($506 per patient compared to $513 per patient with empirical proton pump inhibitor when the cost of eradication therapy is reduced by one-half to $100, illustrating a 7-day instead of a 14-day treatment course). Even if the eradication rate achieved with the 7-day course were somewhat lower than with the 14-day course, the test-and-treat strategy retains this small cost advantage ($512 per patient compared to $516 per patient with empirical proton pump inhibitor, with a 70% eradication rate).

Changing the test-and-treat strategy to incorporate urea breath testing for *H. pylori*-positive patients who did not achieve symptom resolution after eradication therapy substantially decreases the costs of the test-and-treat strategy ($425 per patient with test-and-treat compared to $529 per patient with empirical proton pump inhibitor).

Finally, if the symptom recurrence rate for *H. pylori*-positive patients without peptic ulcer disease were to decrease by 80% in the test-and-treat strategy due to eradication of *H. pylori*, the two strategies would incur comparable costs ($530 per patient with test-and-treat compared to $529 per patient with empirical proton pump inhibitor).

DISCUSSION

Our cost-minimization analysis using a symptom-driven decision analytical model of non-invasive management strategies for uninvestigated dyspepsia suggests that, under most epidemiological conditions, the costs per patient treated differ little between the test-and-treat strategy and empirical proton pump inhibitor therapy, while the two strategies achieve similar clinical outcomes. At the level of individual patients with uninvestigated dyspepsia, the prevalence of *H. pylori* infection, the likelihood that a patient has peptic ulcer disease and the fraction of ulcers attributable to *H. pylori* strongly influence which initial non-invasive management strategy incurs the lowest cost per patient treated. At the level of large patient populations, empirical proton pump inhibitor is consistently less costly than the test-and-treat strategy if the *H. pylori* prevalence is below 20%.

Our simulation clarifies the impact of the changing epidemiology of *H. pylori* and peptic ulcer disease on the management options for uninvestigated dyspepsia. It may seem counterintuitive that, given a certain likelihood of peptic ulcer disease in a patient with uninvestigated dyspepsia, the test-and-treat strategy is less costly than empirical proton pump inhibitor only below a critical value for the prevalence of *H. pylori* in our model. This finding can be understood by imagining a theoretical situation in which the prevalence of *H. pylori* is very high (60%, for instance). Even if the likelihood of peptic ulcer disease is at the high end of the published range (25%), a considerable fraction of patients infected with *H. pylori* will not have peptic ulcer disease. These patients will undergo *H. pylori* testing and will receive eradication therapy without deriving any immediate benefit. (Potential long-term benefits are discussed below.)

The influences of the other two epidemiological variables examined are more intuitive. The *H. pylori* test-and-treat strategy tends to incur lower costs per patient treated when compared to empirical proton pump inhibitor as the likelihood of peptic ulcer disease increases at any given prevalence of *H. pylori* infection, and as the fraction of ulcers that can be attributed to *H. pylori* increases. These conclusions are not surprising, because the importance of a positive *H. pylori* test is greater as the likelihood of peptic ulcer disease or the fraction of ulcers attributable to *H. pylori* rises. Under these circumstances, a larger fraction of those patients who test positive for *H. pylori* actually have peptic ulcer disease and thus derive benefit from *H. pylori* eradication. Conversely, as the likelihood of peptic ulcer disease or the fraction of ulcers that can be attributed to *H. pylori* decreases (reflective of current epidemiological trends), empirical proton pump inhibitor becomes less costly than the test-and-treat strategy.

At an *H. pylori* prevalence below approximately 20%, we found in our model that empirical proton pump inhibitor is consistently less costly than the test-and-treat strategy at those combinations of *H. pylori* prevalence and likelihood of peptic ulcer disease that are possible at a population level. At the level of an individual patient, however, it is conceivable that clinicians practising in communities with low *H. pylori* prevalence could encounter patients whom they consider to have a high likelihood of peptic ulcer disease. Our model suggests that the test-and-treat strategy would be less costly than empirical proton pump inhibitor in such patients. A recent study of dyspeptic patients in primary care found *H. pylori* testing to be of little incremental value beyond the clinical history for predicting the presence of peptic ulcer disease, except in the subgroup of patients at high risk for peptic ulcer disease.[30] These findings are consistent with our model's results that the test-and-treat strategy becomes more attractive as the risk of peptic ulcer disease increases in patients with uninvestigated dyspepsia.

Functional dyspepsia is much more prevalent than peptic ulcer disease,[7] and so the outcomes of patients with functional dyspepsia are relevant to the choice of strategy for the management of uninvestigated dyspepsia. In the base case, we assumed that the symptom recurrence rate for patients without peptic ulcer disease was not affected by the eradication of *H. pylori*.[15] If the annual symptom recurrence rate for such patients were to decrease by 80% in the test-and-treat strategy, test-and treat and empirical proton pump inhibitor would yield comparable costs. However, a benefit of this magnitude is unrealistic given the results of clinical studies.[14, 15]

It is important to note that the cost differences between strategies in our simulation are generally modest. These cost differences are not significantly affected by improving the sensitivity and specificity of testing for *H. pylori* or by improving the success rate of eradication therapy. If improvements in *H. pylori* testing accuracy are achieved at the expense of higher test costs, the test-and-treat strategy emerges as more costly by almost exactly the increased cost of testing. This is due to the fact that every patient incurs the additional testing cost under this strategy, whilst the impact on subsequent interventions and clinical outcomes is minimal. If the cost of proton pump inhibitor falls, the cost differential between strategies is amplified only slightly. This may seem surprising, but can be understood by recognizing that lower proton pump inhibitor costs provide a slight cost advantage for the empirical proton pump inhibitor strategy only during the initial patient contact. The lower proton pump inhibitor cost applies equally to all other proton pump inhibitor use in either strategy (as part of *H. pylori* eradication therapy, ulcer therapy or maintenance therapy). Finally, if the cost of eradication therapy falls, as with 7-day instead of 14-day courses of therapy, the test-and-treat strategy gains a slight cost advantage.

We must emphasize that, in our model, all patients who have persistent or recurrent symptoms undergo

endoscopy under both strategies, with rapid urease test in those with peptic ulcer disease. Thus, the 'non-invasive' strategies evaluated do not preclude endoscopy; they simply reserve its use for individuals who do not achieve complete symptom resolution after the initial intervention, as recommended by multiple guidelines.[6–10] Notably, both non-invasive strategies are significantly less costly than immediate endoscopy in the current simulation (data not shown). The fact that costs are decreased when the test-and-treat strategy is modified to include urea breath testing for patients who remain symptomatic after eradication therapy highlights the importance of the cost of endoscopy, because the overall cost decrease can be attributed in large part to the fact that endoscopy is deferred until a third symptomatic presentation in certain patients. Our simulation is not intended to represent those patients who should undergo immediate endoscopy (such as older patients with new onset symptoms and patients with alarm symptoms such as bleeding, dysphagia or weight loss).

Notes of caution regarding both the test-and-treat strategy and empirical antisecretory therapy are appropriate. First, clinical studies suggest that patient satisfaction may be greatest with prompt endoscopy.[2, 58] Second, an important study of empirical treatment with a histamine-2 receptor antagonist for dyspepsia reported an eventual endoscopy rate of 66% at 1 year with similar clinical outcomes but at higher costs than prompt endoscopy.[1] A more recent study found that empirical proton pump inhibitor followed by test-and-treat for *H. pylori* in the case of symptom relapse resulted in 69% fewer endoscopies, lower costs and equivalent clinical outcomes compared to prompt endoscopy.[59] It remains to be determined whether proton pump inhibitor therapy followed by endoscopy in the case of symptom relapse (as in our simulation) achieves similar outcomes.

Third, as might be expected, the prevalence of asymptomatic *H. pylori* infection at the year end differs between the strategies in our model (4% with test-and-treat and 14% with empirical proton pump inhibitor in the base case). *H. pylori* eradication in patients without peptic ulcer disease may have longer term benefits that are not accounted for in the current simulation. These include the potential to prevent future peptic ulcer disease,[60–63] to reduce the incidence of gastric malignancy,[64–66] to treat symptoms in one of 15 patients with functional dyspepsia[14] and to provide reassurance from a negative *H. pylori* test or from the knowledge that therapy has been provided to eradicate a potential pathogen and carcinogen.[67] On the other hand, these potential benefits could be mitigated if *H. pylori* eradication therapy increases the burden of gastro-oesophageal reflux disease and its complications,[68] or contributes to the problem of antibiotic resistance in *H. pylori* and other bacteria.

In conclusion, our simulation of management strategies for uninvestigated dyspepsia suggests that empirical proton pump inhibitor may hold a modest cost advantage over the test-and-treat strategy as the prevalence of *H. pylori* infection declines, as the risk of peptic ulcer disease falls and as the proportion of patients with *H. pylori*-negative peptic ulcer disease increases in the population. Given that the cost differential between the strategies tends to be modest, however, the test-and-treat strategy may be favoured if any long-term benefit of *H. pylori* testing and treatment extends to patients without existing peptic ulcer disease. If these additional benefits are negligible and long-term outcomes are essentially identical with the two strategies, empirical proton pump inhibitor may be preferred over the test-and-treat strategy on the basis of a small cost advantage.

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