Diagnostic work-up and management of young patients with ulcer-like dyspepsia

A cost-minimisation study

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Objective: We initiated a cost-minimisation modelling study to compare the costs of strategies based on initial endoscopy or initial non-invasive tests for the detection of *Helicobacter* (C13 UBT or serology) from the perspective of the Italian National Health Service. The secondary outcomes were the number of patients undergoing unnecessary *Helicobacter pylori* (HP) eradication treatment and the number of endoscopic examinations spared.
Methods: The study was based on a decision analysis model referring to patients aged less than 45 years with ulcer-like dyspepsia and no alarming symptoms. The probabilities entered in the model were weighted means from published studies, and the costs were derived from the Italian NHS reimbursement schedule. Sensitivity analyses were conducted over a wide range of probability and cost estimates in order to test the robustness of the model.
Results: Non-invasive tests (such as the preliminary work-up of patients with ulcer-like dyspepsia aged less than 45 years) were cheaper than the use of prompt endoscopy. Among the non-invasive strategies, initial serology led to a small cost saving in comparison with initial C13, but this was offset by an increase in the number of endoscopies and the number of patients unnecessarily undergoing eradication treatment. Finally, the use of C13 UBT was cheaper than endoscopy in verifying the effect of eradication in HP-positive patients.
Conclusion: The results of this study show that, from the perspective of the Italian NHS, non-invasive testing would lead to cost savings in the work-up of young dyspeptic patients with ulcer-like symptoms.
Eur J Gen Pract 2001;7:148-53.

Keywords: endoscopy, gastroscopy, costs, HP, dyspepsia, non-ulcer, breath test

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Submitted: 19 March 2001. Accepted: 5 November 2001.

Introduction

'In a health economics perspective, no other decision area in gastroenterology has been more debated than the role of gastroscopy in dyspepsia'.[1] The reasons for this are that dyspepsia is a highly prevalent syndrome (32% of the population),[2] dyspeptic symptoms account for 3-5% of primary care consultations,[3] and their investigation is accompanied by a considerable use of resources. The main question has been whether endoscopy, the gold standard for investigation of dyspepsia, is always necessary in young patients without alarming symptoms. Although endoscopy has the advantage that it detects organic causes as well as the presence of *Helicobacter pylori* (HP), most patients, particularly those aged less than 45 years, will have no organic abnormality.[2-8] The alternative management strategies that have been evaluated so far can be divided into empirical treatment, test-and-scope and test-and-eradicate strategies.

The *empirical treatment strategy* initially consisted of a short course of antisecretory therapy, and the patients were referred for endoscopy only if their symptoms persisted. Although their results are not unequivocal, most studies have shown that the empirical treatment strategy offers no benefit since there is a high rate of recurrent symptoms and endoscopy is postponed rather than avoided.[1]

The *test-and-scope strategy* was developed as a result of the discovery of the role of *Helicobacter pylori* in the pathogenesis of peptic ulcer, which directed the clinical approach towards HP eradication. Test-and-scope therapy is based on non-invasive HP testing followed by the endoscopic examination of seropositive patients. However, a recent study points out that the test-and-scope strategy increases endoscopy rates in comparison with the usual practice in primary care, and the additional cost is not offset by benefits in symptom relief or quality of life.[30]

In 1997, the Maastricht Consensus Group formulated an algorithm for the use of the *test-and-eradicate strategy* in young dyspeptic patients seen in primary care, which was subsequently approved by AGA Medical Position Statement.[6,20] Modelling studies[5,7-10,17-19] and the preliminary reports of randomised trials,[12-16] comparing prompt endoscopy to the test-and-eradicate strategy consistently showed that the latter was safe, led to virtually the same clinical outcomes, and was more cost-effective because of the large number of avoided endoscopies.

We performed this decision analysis modelling study with the aim of comparing the costs to the Italian National Health Service of the test-and-eradicate strategy versus prompt endoscopy in patients aged less than 45 years with uncomplicated dyspepsia.

Methods

The cost-minimisation study presented in this paper was based on a decision analysis model applying the perspective of the Italian National Health Service. The model was developed using DATA decision analysis software (Treeage Software Inc. Boston, Massachusetts, US).

The target population was assumed to consist of patients aged less than 45 years consulting a general practitioner because of pain or discomfort in the upper abdomen lasting at least one month. This theoretical population does not include patients with alarm symptoms, a previous history of peptic ulcer, previous anti-HP therapy, the use of NSAIDs or antibiotics during the previous month, symptoms of gastro-oesophageal reflux disease, nausea, bloating, or irritable bowel syndrome. The model considered a follow-up period of one year.

Data collection

The probabilities entered in the model were derived from a systematic review of the literature. We selected all of the relevant English or Italian articles in the MEDLINE database published between 1 January 1985 and 30 June 1998 using the key words: *Helicobacter* + dyspepsia + diagnosis; *Helicobacter* + dyspepsia + test; *Helicobacter* + therapy. We also reviewed all of the relevant references cited in the selected articles. The probability estimates (prevalence of disease, effectiveness of therapy, sensitivity and specificity of diagnostic tests) were abstracted and weighed on the basis of the size of the underlying population for the primary (base-case) analysis (table 1).

Decision model

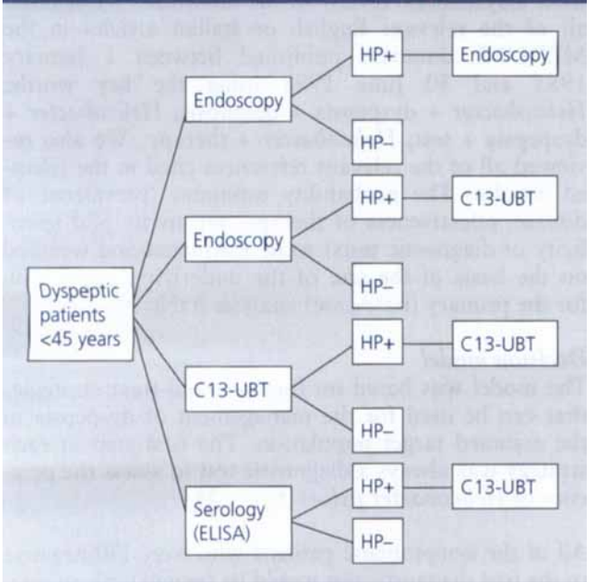
The model was based on four test-and-treat strategies that can be used for the management of dyspepsia in the assumed target population. The first step in each strategy was always a diagnostic test to assess the presence of *Helicobacter pylori* (figure 1).

All of the symptomatic patients who were HP negative to the first diagnostic test would be treated with an antisecretory drug (ranitidine) for a period of eight weeks. All of the HP-positive patients would undergo eradication treatment (omeprazole 20mg bid, claritromycine 250 mg bid, and metronidazole 500 mg bid for one week) regardless of the strategy and three months after the initial visit, they would undergo a

Table 1. Probability estimates in the decision model.

Variable	Base-case value	Range tested *in the* sensitivity analysis
Prevalence of HP+ in patients <45 years with dyspepsia	0.58	0.1-0.99
Probability of effective eradication after first eradication therapy	0.90	0.1-0.99
C13 UBT 75 mg (20 minutes) before treatment		
• Sensitivity	95.9%	0.1-0.99
• Specificity	97.8%	0.1-0.99
C13 UBT 75 mg (20 minutes) after eradication		
• Sensitivity	95.0%	0.1-0.99
• Specificity	95.5%	0.1-0.99
Endoscopy before eradication therapy		
• Sensitivity	100%	
• Specificity	100%	
Endoscopy after eradication therapy		
• Sensitivity	91.7%	0.1-0.99
• Specificity	93.7%	0.1-0.99
Serological investigation		
• Sensitivity	85.0%	0.1-0.99
• Specificity	79.0%	0.1-0.99

Figure 1. Basic decision model.



second diagnostic test in order to evaluate the success of HP eradication. In the case of treatment failure (patients still HP positive), a second course of eradication therapy would be administered (omeprazole 20 mg bid, amoxicillin 1000 mg bid, metronidazole 500 mg bid for a period of two weeks). The patients who remained symptomatic after two courses of eradication therapy would be temporarily treated with antisecretory drugs (ranitidine) and referred for endoscopy in order to ensure that any underlying pathology would be diagnosed.

The decision model compared the costs of four different test-and-treat strategies (pathways). The difference between the pathways hinged on the type of diagnostic tests used in the initial and control HP diagnoses, and on their sequence. The considered diagnostic tests were: a) endoscopy (with biopsy and histological HP testing); b) the C13 Urea HP breath test (UBT), with 75 mg of C13 Urea and 30 minutes latency between the two expirated samples;[4] and c) a qualitative serological commercial enzyme-linked immunosorbent assay (ELISA) test.
Pathway 1 consisted of an initial and control endoscopy; pathway 2 of initial endoscopy and control UBT; pathway 3 of initial UBT and control UBT; and pathway 4 consisted of initial ELISA and control UBT.

Cost estimates

The cost analysis was made from the perspective of a public insurer and was therefore restricted to directly reimbursed medical costs. The costs of the drugs, procedures, and examination were obtained from the 1996 Diagnostic Related Group hospital payment schedules, and the Italian National Health Service drug charges were referred to the year 1999 (table 2). The cost estimate used for UBT was the 1999 official reimbursement rate in the Lombardy region, which, at the time the study was carried out, was the highest in Italy.

Table 2. Cost estimates included in the model.

Variable	Base-case value	Range tested in the sensitivity analysis
First eradication treatment	€ 55.10	0-155
Second eradication treatment	€ 83.65	0-155
Symptomatic treatment	€ 50.69	0-103
Serological test	€ 8.16	0-103
C13 UBT	€ 41.52	0-103
Endoscopy	€ 84.96	0-155

Endpoints

The primary endpoint of interest was the total expected cost of each of the considered pathways. The secondary outcomes were the number of patients (per 1000) undergoing unnecessary HP eradication treatment (false-positive HP patients), and the number (per 1000) of endoscopic examinations

Data analysis

Base-case analysis

Our primary (base-case) deterministic analysis calculated the total expected cost per patient for each pathway by folding back the basic decision tree model. We also calculated the number of patients unnecessarily treated with HP eradication therapy (false positives) and the number of endoscopic examinations per 1000 persons.

Sensitivity analyses

Deterministic analyses yield a point estimate of the total cost that is not accompanied by an estimate of uncertainty. We therefore used one-way sensitivity analyses to evaluate the effects of altering our estimates of probabilities and costs of examinations over a larger range than that which may be expected from the uncertainty of published reports (table 1). We subsequently made two-way sensitivity analyses (varying two variables at the same time) and threshold analyses (finding the value of a variable after which another pathway would be more favourable) of the most clinically significant and potentially influential variables. In addition, we modelled the possibilities that between 0 and 50% of the patients would remain symptomatic even after successful HP eradication therapy and would then be treated with symptomatic therapy.

Table 3. Results of the base-case analyses.

Strategy	Cost/patient	Marginal value*	No. of endoscopies/1000	Patients with unnecessary HP eradication/1000
Serology, control C13 UBT	€ 109.67		140	111
C13 UBT, control C13 UBT	€ 129.21	€ 19.54	79	32
Prompt endoscopy, control C13 UBT	€ 169.49	€ 40.28	1003	24
Prompt endoscopy, control endoscopy	€ 195.35	€ 25.83	1580	33

* Cost difference of strategy in comparison with the previously ranked strategy.

Table 4. Threshold analyses.

Variable	Base case	Threshold*	Required change from base case to reach threshold
Costs of first eradication therapy	€ 55.10	None	Infinite
Costs of second eradication therapy	€ 83,65	None	Infinite
Costs of symptomatic treatment	€ 50,69	None	Infinite
Costs of endoscopy	€ 84.96	€ 25.52[a]	-69.9%
Costs of C13UBT	€ 41.52	€ 19.76[b]	-52.4%
Costs of serological examination	€ 8.16	€ 29.54[c]	+248%
Prevalence of HP	0.58	None	Infinite
Probability of first eradication treatment response	0.90	None	Infinite
Probability of second eradication treatment response	0.87	None	Infinite
Sensitivity of pre-eradication C13 UBT	0.959	None	Infinite
Specificity of pre-eradication C13 UBT	0.978	None	Infinite
Sensitivity of pre-eradication serological examination	0.85	0.559[d]	-34.2%
Specificity of pre-eradication serological examination	0.790	0.205[d]	-88.0%
Sensitivity of post-eradication endoscopic examination	0.917	None	Infinite
Specificity of post-eradication endoscopic examination	0.937	None	Infinite
Sensitivity of post-eradication C13-UBT examination	0.950	None	Infinite
Specificity of post-eradication C13-UBT examination	0.955	None	Infinite

* Threshold is defined as the value of the variable at which the strategy of serology is no longer favourable.
a Below threshold: endoscopy, C13 more favourable than serology strategy.
b Below threshold: C13 UBT strategy more favourable than serology strategy.
c Above threshold: C13 UBT strategy more favourable than serology strategy.
d Below threshold: C13 UBT more favourable than serology strategy.

Results

A literature review regarding the prevalence of *Helicobacter pylori* treatment effects and the diagnostic characteristics of endoscopic examinations revealed that the weighted prevalence of HP infection is 58% among patients aged less than 45 years and suffering from ulcer-like disease (table 1). The probability of effective HP eradication after a first triple therapy with omeprazole, clarithromycine and metronidazole was estimated at 90%. The sensitivity and specificity of detecting *Helicobacter pylori* at a first endoscopic examination (without prior HP eradication treatment) were both estimated at 100% because endoscopy is generally regarded as the gold standard for comparing the sensitivity and specificity assessments of other HP detection tests. After a first eradication treatment, the sensitivity and specificity of the endoscopic detection of *Helicobacter pylori* decrease to 91.7% and 93.7% respectively because of the reduced bacterial load. The sensitivity of UBT (95.9%) is higher than that of serological investigation (85.0%), thus indicating that the number of HP false-negative patients (with consequently delayed HP eradication therapy) would always be lower after UBT. Furthermore, the specificity of UBT (97.8%) is also considerably higher than that of serological examination (79.0%), which means that the percentage of patients with a falsely positive HP test who would therefore receive unnecessary HP eradication therapy would be much higher after serological examination. Table 2 shows the costs of the various tests and treatments used for the primary analysis. The acquisition costs are lowest for the serological examination.

Table 3 shows the expected per patient cost for the different pathways. The cheapest pathway would be a serological examination followed by a UBT as a con-

trol test, which yielded an average cost saving of € 19.5 for the NHS in comparison with the initial UBT pathway. However, this small financial gain was accompanied by a 1.8-fold increase in the number of endoscopies and a 3.5-fold increase in the number of patients undergoing unnecessary HP eradication treatment. The rankings and marginal values (the difference in expected costs from the previously ranked strategy) listed in table 3 show that prompt endoscopy with a control C13 UB test costs € 40.3 more than an initial C13 UB test and led to a slightly smaller number of patients undergoing unnecessary HP eradication treatment, but a more than tenfold increase in the number of endoscopies. Prompt endoscopy followed by a control endoscopy is the most expensive pathway, and leads to an average of 1.58 endoscopies per patient.

Table 4 shows that our base-case analysis was not sensitive (i.e. we did not find any threshold value) to changes in the cost of treatment, prevalence of *Helicobacter pylori* or the probability of response to treatment. The only threshold value we found was related to the cost of endoscopy, the cost of UBT, the cost of serological examinations, and the sensitivity or specificity of the serological examinations themselves. However, only a 70% decrease in the price of endoscopy (to less than € 25.52) would make the endoscopy plus control endoscopy pathway less expensive than initial serology. The UBT plus UBT pathway would become cheaper than serology in the case of a 52% reduction in the costs of UBT or a 248% increase in the costs of the serological examination (see threshold values in table 4). Our primary analysis was not sensitive to the test characteristics of either the pre- or post-eradication UBT examination, nor in relation to the test performance of the post-eradication endoscopic examination. The analysis was not sensitive to the costs of antisecretory therapy, cost of the first or second eradication therapy, or failure rate of the eradication therapy itself. The only test characteristics that could change the conclusions of our primary analysis were the sensitivity and specificity of the serological test. If the sensitivity of the serological examination were less than 56% or its specificity less than 21%, the UBT plus UBT pathway would be less expensive (table 4). A two-way sensitivity analysis of the sensitivity and specificity of a serological test showed that the serology plus UBT pathway would always be economically favourable if its sensitivity increased to 91%. In the current situation, in which its sensitivity is 85%, its specificity should be more than 21%.

Discussion

This study shows that prompt endoscopy leads to higher screening costs than non-invasive tests for *Helicobacter pylori* in patients aged less than 45 years with ulcer-like dyspepsia but without alarming symptoms. Of the non-invasive methods, initial serological examination with a control UBT leads to a cost saving of € 19.3 in comparison with a strategy based on an initial UBT and control C13 UBT.

This economic saving needs to be evaluated in the light of the excess number of endoscopies (61/1000 patients) and the excess number of patients undergoing unnecessary HP eradication treatment (79/1000) but the cost advantage persists even when key clinical assumptions, treatment and test costs, and prevalence of HP infection are changed over a wide range of values. This evidence that the results do not depend on the prevalence of *Helicobacter pylori* is important in view of the large variation in the prevalence of HP in Europe.

Among the patients undergoing prompt endoscopy (conservative method), the UBT is the most cost-effective means of checking the success of eradication therapy. As might be expected in this young population, prompt endoscopy and follow-up endoscopy is the least cost-effective strategy. The marginal difference between double endoscopy and prompt endoscopy/control UBT strategy is € 25.5.

In order to provide conservative estimates, all of our strategies included the verification of *Helicobacter pylori* status after HP eradication therapy. However, although it was recommended in the second Maastricht guidelines (2000), the evaluation of successful eradication is not a widespread practice. The resolution of epigastric pain after eradication is considered a sensitive and reliable sign of success[25,26] even if UBT re-testing can provide reassurance and reduce physician consultations.[27] The omission of a control test would not change the conclusion of our base-case analysis and in any case, re-testing is unavoidable if symptoms persist and should preferably be conducted with C13 UBT (after one month and before three months from the first eradication therapy).

Our analysis does not consider all possible clinical outcomes, such as the underlying pathology (which would be the same for each strategy) or potential changes in the use of symptomatic therapy, changes in eradication strategies, personal discomfort as a result of invasive procedures, the complications of therapy, or anxiety over the lack of a confirmed diagnosis. Although pharmacological treatments may change over time, this is not likely to affect our results since our conclusion was not sensitive to changes in the eradication rate, or to the cost of eradication or antisecretory therapy. Therapeutic complications are rare, and would therefore not change our conclusions; however, from an ethical point of view, their greatest impact would be on initial serology therapy since this has the highest number of patients undergoing unnecessary HP eradication treatment.

Additional studies would be required to include patients' preferences and quality of life into the cost analysis,[29] but a recent study has shown that non-invasive testing offers them sufficient reassurance. Reassurance is slightly higher after endoscopy, but this has only a short half-life[21] and it is questionable whether this justifies the extra costs. One of the most debated objections against non-invasive testing is the fact that it may postpone the diagnosis of the underlying pathology which, in the worst case, may be gastric cancer. However gastric cancer is extremely rare in young patients without any alarm symptoms (0.04-0.1%), and usually only needs to be considered if the symptoms persist.[22-24] There may be a small delay in detection, but this will not change the prognosis.[24] In order to decrease the chance of missing gastric cancer, the primary care physician should always consider endoscopy in patients with persisting, recurrent, or sinister symptoms (as included in our model).

In conclusion, this modelling study shows that non-invasive testing in the diagnostic work-up of young dyspeptic patients presenting to a general practitioner with ulcer-like symptoms is cheaper for the Italian National Health Service. Avoiding endoscopies in these patients would shorten the waiting list for endoscopies that may be better used for more serious patients. ■

Funding
This study was partially supported by Cortex Italia SpA, Milan, Italy.

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