

## DYSPEPSIA MANAGEMENT

# *Helicobacter pylori* test and treat strategy for young dyspeptic patients: new data

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Decision analysis models have given different conclusions on the value of the *Helicobacter pylori* "test and treat" strategy for the management of dyspepsia. This uncertainty relates to the lack of primary data on this strategy. Four randomised controlled trials have compared the *H pylori* "test and treat" strategy with prompt endoscopy and have allowed a more accurate decision analysis model to be constructed. The model indicates that the *H pylori* test and treat strategy is more cost effective than prompt endoscopy, and should be the new "gold standard" against which other strategies are compared.

dyspepsia. This was as ineffective as the medications used to treat upper gastrointestinal symptoms,<sup>1</sup> and patients consequently suffered. The advent of fiberoptic endoscopy revolutionised the investigation of dyspepsia, and this was followed by the development of acid suppressing drugs to treat peptic ulcer disease and gastro-oesophageal reflux disease. This improvement in diagnosis and treatment has been achieved at a price. Proton pump inhibitors are the most expensive item on the UK drug budget, costing £334 million a year.<sup>2</sup> Endoscopies are also expensive, costing £246 in the UK, with over half a million performed each year.<sup>3</sup>

The popularity of endoscopy stems from a clinician's inherent desire to avoid uncertainty. Dyspepsia can be the presenting symptom of upper gastrointestinal neoplasia and it is natural to want to exclude this possibility by performing an endoscopy. Upper gastrointestinal malignancy is very rare in patients under the age of 45 years, and yet a third of all endoscopies are performed in this age group.<sup>4</sup> The main reason for investigating young dyspeptics is to exclude peptic ulcer disease, as doctors and patients have been conditioned to believe that this is a serious condition which must be identified and treated. Most peptic ulcers are associated with *H pylori*, and the disease is cured by treatment of the infection. A policy of screening dyspeptics who are 45 years of age or younger for *H pylori*, and treating those patients found to be positive for the bacterium, has been suggested.<sup>5</sup> This strategy targets a group that has a lower risk of underlying malignancy and would identify and treat nearly all cases of peptic ulcer. Patients with gastro-oesophageal reflux disease would not be identified but serious reflux causing oesophagitis is rare in the young (<5% of dyspeptics).<sup>4</sup> *H pylori* positive ulcer negative cases may receive antibiotic therapy unnecessarily, but given the level of inappropriate antibiotic prescription in primary care (1.43 prescriptions/person/year) this will have little impact on community antimicrobial resistance rates.<sup>6</sup> The main criticism of the *H pylori* "test and treat" strategy is that there have been no primary data on the efficacy of this approach in managing dyspepsia. There are now however four randomised controlled trials comparing the *H pylori* test and treat strategy with prompt endoscopy.<sup>7-10</sup> It is difficult to design the perfect study to compare these strategies, and this article discusses the strengths and weaknesses of each trial and summarises the results.

### SUMMARY

A policy of screening dyspeptics who are 45 years of age or younger for *Helicobacter pylori*, and treating those who are positive for the bacterium, has been suggested. This strategy targets patients with a low risk of underlying malignancy and would identify and treat nearly all cases of peptic ulcer. Four randomised controlled trials have compared the *H pylori* "test and treat" strategy with prompt endoscopy. A formal meta-analysis of the data would not be appropriate given the variation in trial design and outcome measures. A qualitative and semiquantitative review of the data however can provide useful information to guide dyspepsia management. Three trials measured dyspepsia symptom resolution and found the *H pylori* test and treat strategy to be at least as effective as prompt endoscopy; quality of life was also similar in the two groups. Given that the two strategies have similar efficacy, the most appropriate health economic evaluation is cost minimisation. The decision analysis model indicates that the *H pylori* test and treat strategy is the most cost effective method for managing dyspepsia, costing US\$134/patient/year compared with US\$240/patient/year for prompt endoscopy. The model assumes that health service dyspepsia costs not related to endoscopy or *H pylori* screening are the same in both groups. The age group to which this strategy pertains has not been explored, as there are not enough data to reach definite conclusions. The safest approach would be to restrict the *H pylori* test and treat strategy to dyspeptics under 45 years of age.

### INTRODUCTION

At the turn of the century, clinical opinion was the only method of diagnosing the cause of

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### NEW DATA

#### Patient selection

Ideally, patients should be recruited from primary care, as the trial results will be applied to this

**Table 1** Summary of results of four trials comparing a *Helicobacter pylori* test and treat strategy with prompt endoscopy

Reference	Primary care and treatment costs	Improvement in dyspepsia	Improvement in quality of life	Patient satisfaction
Duggan and colleagues <sup>7</sup>	Same	Same	Same	Endoscopy better
Jones and colleagues <sup>8</sup>	Same	N/A	N/A	N/A
Heaney and colleagues <sup>9</sup>	N/A	Test and treat strategy better	Same	N/A
Lassen and colleagues <sup>10</sup>	Same	Same	Same	Endoscopy better*

N/A, not applicable.

\*In a subgroup of *H pylori* negative patients.

population. Three trials recruited dyspeptics presenting to primary care<sup>7, 8, 10</sup> whereas one study recruited *H pylori* positive cases referred for endoscopy.<sup>9</sup> Patients attending secondary care may be different from dyspeptics seen in primary care, and the results of the latter study may not be generalisable to this setting.

There is uncertainty about the age at which endoscopy is advisable to exclude underlying upper gastrointestinal malignancy. Heaney *et al* selected 45 years of age as the cut off point<sup>9</sup> whereas other studies recruited older patients.<sup>7, 10</sup> The variation in age range of individuals recruited makes it difficult to compare trials directly.

### Sample size and randomisation

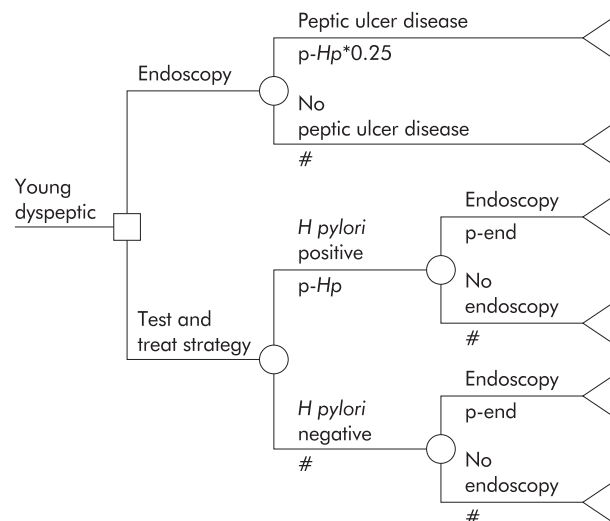
Trials need to recruit sufficient numbers of patients to detect clinically relevant differences in outcome between groups. Heaney *et al* recruited only 52 patients to each arm and could have missed a 30% difference in dyspepsia resolution between the two groups.<sup>9</sup> Duggan *et al* randomised over 100 patients to each strategy and would have missed less than 20% difference in dyspepsia between the two groups.<sup>7</sup> Lassen *et al* recruited 250 patients to each arm and had the power to detect less than 15% difference between the two groups.<sup>10</sup>

Randomisation is the most powerful method of ensuring that known and unknown confounding factors are equally distributed among the study groups. All trials used this method, although Jones *et al* randomised primary care centres rather than patients.<sup>8</sup> Over 200 patients participated in this study but statistical power was limited by the small number of general practices randomised.

The sample size required also depends on the rarity of the outcome being measured. The two studies with power to detect clinically meaningful differences in dyspepsia rates between strategies did not have sufficient sample size to detect differences in the frequency of early cancer rates, as these events are rare.<sup>7, 10</sup> These studies recruited dyspeptics between 45 and 55 years of age, and the *H pylori* test and treat strategy may be inappropriate in this age group. The incidence of gastric and oesophageal cancer increases after 45 years of age and, although these events are still uncommon, early detection by endoscopy may start to become cost effective. Further larger studies are needed to answer this question.

### *H pylori* assessment

Two studies used the <sup>13</sup>C urea breath test to evaluate *H pylori* status.<sup>9, 10</sup> This is the "gold standard" non-invasive test for detection of *H pylori*, with a sensitivity and specificity of more than 95%.<sup>11</sup> The other studies used serology, which is cheaper and more convenient. Local validation is important however as the accuracy of commercial serology kits varies in different populations. Duggan *et al* validated the near patient serology test used in their trial and reported 69% sensitivity and 98% specificity.<sup>7</sup> This low sensitivity may mean that some *H pylori* infected dyspeptic patients would be falsely reassured and some peptic ulcers would be missed. This could lead to a lack of confidence in the *H pylori* test and treat strategy among medical staff and patients due to inaccuracies in the test method.



**Figure 1** Decision analysis model comparing the *Helicobacter pylori* test and treat strategy with early endoscopy. p-Hp, probability of infection with *H pylori*; p-end, proportion of subjects having a test and treat strategy referred for endoscopy; #, 1—probability given in other decision analysis arm.

### Patient assessment

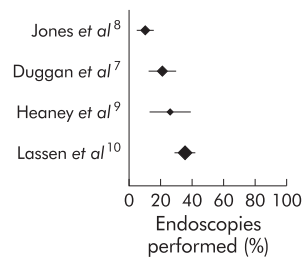
Patients should be assessed in primary care to ensure that their management accurately reflects what happens in general practice. Lassen *et al* recruited patients from primary care but their subsequent investigation and treatment was influenced by the investigators.<sup>10</sup> In particular, patients randomised to the *H pylori* test and treat strategy who did not respond to treatment, or who relapsed during the course of the trial, were required to have an endoscopy. This does not necessarily reflect management in primary care and may overestimate the number of endoscopies performed in the *H pylori* test and treat group.

### Outcome measures

Trials should have an adequate length of follow up and use validated and relevant outcome measures.<sup>12</sup> Three studies followed participants for one year<sup>7, 8, 10</sup> and one for six months.<sup>9</sup> Relevant outcomes include patient satisfaction, health service costs, dyspepsia symptom resolution, and quality of life. Two studies measured all of these outcomes<sup>7, 10</sup> (table 1) and the studies evaluating dyspepsia symptom resolution used validated instruments.<sup>7, 9, 10</sup> Measurement of outcome was a strong aspect of these studies compared with the quality of trials assessing treatments for non-ulcer dyspepsia.<sup>12</sup>

### SUMMARISING THE NEW DATA

The overall quality of the *H pylori* test and treat trials was excellent but a formal meta-analysis of the data would not be appropriate given the variation in trial design and outcome



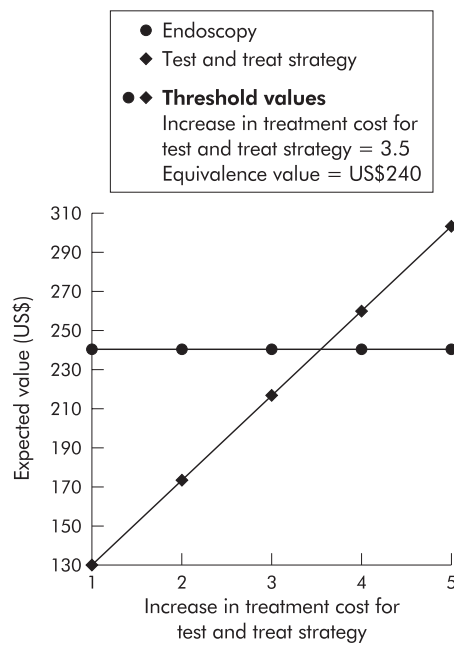
**Figure 2** Summary of the rate of endoscopy referral for patients in the *Helicobacter pylori* test and treat group.

measures. A qualitative and semiquantitative review of the data can however provide useful information to guide dyspepsia management.

The three trials that measured dyspepsia symptom resolution found that a *H pylori* test and treat strategy was at least as effective as prompt endoscopy, and quality of life was also similar between the two groups (table 1).<sup>7-9, 10</sup> Given that the two strategies have similar efficacy, the most appropriate health economic evaluation is cost minimisation analysis (that is, the cheapest policy will be the most cost effective). Data from the four trials can be used to determine the cost of the two strategies. The cost to society is the most relevant information to use but as this is only available from one trial at present, costs from a health service perspective were incorporated into a decision analysis model (fig 1). The most important factor in this model is the proportion of patients in the *H pylori* test and treat group having endoscopy during the follow up period. Results from the four trials indicate that the proportion having endoscopy could be as low as 10% or as high as 40%, with 30% being the best estimate (fig 2). The model also requires other estimates outlined in table 2.

Patient satisfaction has not been incorporated into the analysis as this is a difficult concept to model. Patients having endoscopy were more satisfied with the investigation than patients randomised to the *H pylori* test and treat strategy (table 1). Endoscopy is more technical and expensive, and patients may therefore perceive endoscopy as being “better” even if there is no improvement in quality of life or dyspepsia compared with simpler investigation strategies. This is analogous to consumers preferring an expensively packaged product to an identical but less well marketed item. Health services should acknowledge these desires but, as it is difficult to attach a monetary value to these preferences, they have not been incorporated into this model.

The decision analysis model indicates that the *H pylori* test and treat strategy is the cheapest strategy, costing US\$134/patient/year compared with US\$240/patient/year for the prompt endoscopy strategy, using base case values. The *H pylori* test and treat strategy is therefore the most cost effective method for managing dyspepsia. This conclusion remains robust if one or two variables are altered across the ranges stated in table 2 (that is, one and two way sensitivity analyses). The prompt endoscopy strategy only becomes cost effective in the unlikely scenario of endoscopy costing US\$160, the non-invasive test costing US\$80, and a *H pylori* prevalence of less than 20%. The model assumes that health



**Figure 3** Sensitivity analysis on the increase in primary care costs for a *Helicobacter pylori* test and treat strategy.

service dyspepsia costs not related to endoscopy or *H pylori* screening are the same in both groups. This assumption is supported by the data (table 1) but a small increase in primary care visits and antisecretory drug prescriptions for patients in the *H pylori* test and treat group may not have been detected by the trials. The model indicates that these costs would have to be more than 3.5 times more in the *H pylori* test and treat group for prompt endoscopy to be more cost effective over one year (fig 3). The trials had sufficient power to detect this magnitude of difference, reinforcing the conclusion that the *H pylori* test and treat strategy is the most cost effective strategy.

The age group to which this strategy pertains has not been explored as there are not enough data to reach definite conclusions. The safest approach would be to restrict the *H pylori* test and treat strategy to dyspeptics under 45 years of age. This decision analysis model estimates costs over one year, as this is the only information available from the trials. Evaluating expenditure over a longer time frame may be more relevant, and future studies need to address this issue. Empirical *H pylori* therapy for all dyspeptics or *H pylori* testing and endoscopying those infected may be alternative management strategies that are even more cost effective. Trials in these areas are currently being conducted and the results are awaited with interest.

**CONCLUSION**

Decision analysis models have given different conclusions on the value of the *H pylori* test and treat strategy for the management of dyspepsia.<sup>13-15</sup> This uncertainty relates to the

**Table 2** Probabilities and costs incorporated into the decision analysis model

Variable	Baseline value	Range
Probability of endoscopy after <i>H pylori</i> test and treat	0.3	0.1-0.4
Prevalence of <i>H pylori</i>	0.33	0.05-0.9
Cost of endoscopy	US\$240	US\$160-800
Cost of <i>H pylori</i> screening	US\$40	US\$24-80
Cost of <i>H pylori</i> treatment	US\$34	US\$34-68
Cost of primary care visits and treatment	US\$134	

lack of primary data on this strategy. We now have four trials evaluating the *H pylori* test and treat strategy which allow a more accurate decision analysis model to be constructed. The model indicates that the *H pylori* test and treat strategy is more cost effective than prompt endoscopy, and should be the new “gold standard” against which other strategies are compared.

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