

Randomised trial of endoscopy with testing for *Helicobacter pylori* compared with non-invasive *H pylori* testing alone in the management of dyspepsia

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Abstract

Objective To compare the efficacy of non-invasive testing for *Helicobacter pylori* with that of endoscopy (plus *H pylori* testing) in the management of patients referred for endoscopic investigation of upper gastrointestinal symptoms.

Design Randomised controlled trial with follow up at 12 months.

Setting Hospital gastroenterology unit.

Participants 708 patients aged under 55 referred for endoscopic investigation of dyspepsia, randomised to non-invasive breath test for *H pylori* or endoscopy plus *H pylori* testing.

Main outcome measure Glasgow dyspepsia severity score at one year. Use of medical resources, patient oriented outcomes, and safety were also assessed.

Results In 586 patients followed up at 12 months the mean change in dyspepsia score was 4.8 in the non-invasive *H pylori* test group and 4.6 in the endoscopy group (95% confidence interval for difference -0.7 to 0.5, $P=0.69$). Only 8.2% of patients followed up who were randomised to breath test alone were referred for subsequent endoscopy. The use of non-endoscopic resources was similar in the two groups. Reassurance value, concern about missed pathology, overall patient satisfaction, and quality of life were similar in the two groups. The patients found the non-invasive breath test procedure less uncomfortable and distressing than endoscopy with or without sedation. No potentially serious pathology requiring treatment other than eradication of *H pylori* was missed.

Conclusion In this patient group, non-invasive testing for *H pylori* is as effective and safe as endoscopy and less uncomfortable and distressing for the patient. Non-invasive *H pylori* testing should be the preferred mode of investigation.

Introduction

More than 1% of the population of the United Kingdom undergo gastroscopy each year.¹ Despite this widespread use of the procedure, a recent qualitative systematic review concluded that "the preponderance of available data does not support the effectiveness of

endoscopy in the management of dyspepsia."² One of the main reasons for performing endoscopy in patients with dyspepsia is to detect underlying ulcer disease. However, non-invasive testing for *Helicobacter pylori* has been shown to be a useful predictor of endoscopic diagnosis in patients with dyspepsia.³⁻⁶

Considerable interest exists in using non-invasive *H pylori* testing in place of endoscopy to determine the management of patients presenting with upper gastrointestinal symptoms. Patients with a negative *H pylori* test could be reassured that they do not have underlying ulcer disease and could be treated symptomatically, as would occur after an endoscopic examination showing no abnormality or evidence of oesophagitis. Patients with a positive *H pylori* test could all be given treatment to eradicate *H pylori*, which would cure the subgroup with underlying ulcer disease.

We present the results of a randomised trial comparing non-invasive testing for *H pylori* with endoscopy in the management of patients referred for endoscopic investigation of upper gastrointestinal symptoms.

Methods

We recruited participants from patients referred by their general practitioners to the hospital for endoscopic investigation of upper gastrointestinal symptoms. Exclusion criteria were age 55 or over, use of non-steroidal anti-inflammatory drugs (excluding low dose aspirin), presence of sinister symptoms (dysphagia, recent weight loss of more than 3 kg, persistent vomiting, recent evidence of upper gastrointestinal bleeding), first degree relative with upper gastrointestinal malignancy, or history of gastric surgery.

Baseline assessment

At their single visit to the clinic, the patients had a structured interview by either a consultant gastroenterologist or a specialist registrar in gastroenterology. Details recorded included the character of the patient's predominant symptom and any history of use of non-steroidal anti-inflammatory drugs or other drugs. We assessed the severity of symptoms over the six months



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Table 1 Characteristics of the two groups at randomisation. Values are numbers (percentages) unless stated otherwise

	Endoscopy plus breath test (n=352)	Breath test alone (n=356)
Mean (SD; range) age in years	35.5 (9.4; 17-54)	36.6 (8.9; 18-57)
Male	190/352 (54)	187/356 (53)
Smokers	133/349 (38)	161/353 (46)
<i>Helicobacter pylori</i> positive	181/352 (51)	171/356 (48)
Mean (SD; range) Glasgow dyspepsia severity score	10.2 (2.1; 4-16)	10.3 (2.3; 4-16)
Median duration of dyspepsia (scored <0.5, 0.5-2, 2-5, 5-10, >10 years)	2-5 years	2-5 years
Proportion taking prescribed antisecretory drugs most days in previous six months	116/352 (33)	132/355 (37)
Heartburn or acid reflux as predominant symptom	87/352 (25)	120/353 (34)
Epigastric pain or discomfort as predominant symptom	199/352 (57)	181/353 (51)
Mean (SD; range) concern about condition (0-10 scale)	5.0 (2.2; 0-10)	5.2 (2.4; 0-10)
Mean (SD; range) concern about underlying serious disease (0-10 scale)	4.1 (2.4; 0-10)	4.4 (2.4; 0-10)

preceding the visit with the Glasgow dyspepsia severity score.⁷

We assessed quality of life with the short form health survey (SF-36).⁸ We asked patients about their degree of worry about their condition and about their degree of concern that they might have a sinister underlying disease. These were recorded on a 0-10 Likert-type scale.

Intervention

We then invited all eligible patients to participate in the study by being randomised to endoscopy plus breath test for *H pylori* or breath test alone. Immediately after allocation, patients underwent either endoscopy plus the breath test or the breath test alone. During the endoscopy, we took biopsies from both the antrum and body region for histology and urease slide test. We performed the ¹⁴C-urea breath test as previously described,⁹ except that we used a citric acid drink in place of a fatty drink in order not to obscure the endoscopic view. The patients randomised to endoscopy also underwent the breath test. The breath test was analysed on site, and the result was available within 30 minutes.

Patients who had undergone endoscopy were informed of the findings and of their *H pylori* status. Patients who had only the breath test were also informed of the result. If it was positive, we told them that they might have an underlying ulcer that would benefit from treatment of the infection and that studies in our population also indicated symptomatic benefit from treating the infection even in the absence of an ulcer.¹⁰ We reassured patients with a negative breath

test result that they were very unlikely to have an ulcer and that their symptoms were likely to be due to gastro-oesophageal reflux disease or non-ulcer dyspepsia. All patients testing positive for *H pylori* were given a seven day course of *H pylori* eradication treatment consisting of omeprazole 20 mg twice daily, clarithromycin 250 mg three times daily, and amoxicillin 500 mg three times daily. All patients were told to see their general practitioner for further treatment if their symptoms persisted.

Before they left the clinic, we asked patients to score the degree of discomfort or distress caused by their diagnostic test on an 0-6 integer scale. In addition, we asked them if they would have the same test again happily, reluctantly, or never. We asked patients who had had an endoscopy whether they would have it again with or without sedation.

Follow up

One year after randomisation, the Glasgow dyspepsia severity score and the SF-36 quality of life assessment were repeated. Details were also obtained from the patient about visits to the general practitioner or hospital for dyspepsia or other conditions, further investigations, and use of prescribed and over the counter drugs for dyspepsia or other conditions since randomisation. In addition, patients were asked about their concern regarding their condition, their concern about possible missed underlying disease, and their overall satisfaction with their initial investigation and management. The patients also had a ¹⁴C-urea breath test to re-check their *H pylori* status.

Results

From October 1997 to October 1999, we saw 967 patients aged under 55 at the one stop dyspepsia clinic, which represented 81% of those who had been sent appointments. Of these 967 patients, 248 were not eligible for randomisation and 11 refused. In total, 352 patients were randomised to endoscopy with *H pylori* testing and 356 patients to non-invasive *H pylori* testing alone. The two groups were similar at baseline (table 1). Table 2 shows the endoscopic findings in the patients randomised to that investigation, subclassified according to predominant symptom and *H pylori* status.

One year after randomisation 292 (83%) of the 352 patients randomised to endoscopy and 294 (83%) of the 356 patients randomised to non-invasive *H pylori* testing could be reassessed. The *H pylori* eradication rates at one year in the two groups were 79% (119/150) and 84% (118/141).

Primary outcome

One year after randomisation, the mean change in the Glasgow dyspepsia severity score was similar in the endoscopy and non-invasive *H pylori* testing groups at 4.8 and 4.6 (95% confidence interval for difference -0.7 to 0.5, P=0.69). The mean scores at one year were similar at 5.4 and 5.6 in the two groups. The proportion of patients with complete resolution of dyspepsia (score <2) was similar in the two groups at 42/291 (14%) and 33/293 (11%) (-2% to 9% for difference, P=0.25).

Subsequent use of medical resources

The two groups were similar at one year with respect to proportions attending their general practitioner and

Table 2 Endoscopic diagnosis and relation to *Helicobacter pylori* status and predominant symptom in patients randomised to endoscopy plus *H pylori* testing. Values are numbers of patients

	<i>H pylori</i> positive (n=172)		<i>H pylori</i> negative (n=165)	
	Heartburn or acid reflux (n=37)	Other symptom (n=135)	Heartburn or acid reflux (n=49)	Other symptom (n=116)
Normal	24	94	38	95
Oesophagitis grade I	9	9	8	15
Oesophagitis grade II	1	2	2	1
Gastric ulcer (including prepyloric ulcer)	—	9	—	2
Duodenal ulcer	3	19	1	3
Gastric ulcer plus duodenal ulcer	—	1	—	—
Low grade MALToma	—	1	—	—

hospital and use of prescribed and over the counter drugs over the 12 month period since randomisation. They were also similar with respect to repeat referral for further non-endoscopic investigations (table 3).

Of the 292 patients randomised to initial endoscopy and followed up, five (1.7%) were referred for a further endoscopy, compared with 24 (8.2%) of the 294 patients randomised to initial non-invasive *H pylori* testing (95% confidence interval for difference 3% to 10%, $P < 0.001$).

Patient oriented outcome

One year after randomisation, mean overall concern of patients about their disease and concern about missed pathology were similar in the two groups (table 3). The relative reassurance after non-invasive *H pylori* testing compared with endoscopy was unaffected by the magnitude of concern about serious disease at the time of randomisation (see [bmj.com](#)). Overall satisfaction with initial investigation and management and SF-36 quality of life scores at one year after randomisation were similar in the two groups (see [bmj.com](#)).

We also assessed the patients' experience of the two investigational procedures on an integer scale of 0 to 6, with 0 indicating no recollection, 1 no discomfort, and 6 severe distress. After the breath test, 96% of patients gave the test a score of 1, whereas only 13% of patients randomised to endoscopy had a score of 0 or 1 (95% confidence interval for difference 78% to 87%, $P=0.000$) (see [bmj.com](#)). Of the patients randomised to endoscopy, 20% elected to have intravenous sedation with midazolam. Of those sedated, 32% could not remember the procedure, and the median score in the remainder was 2. The median score after the endoscopy without sedation was 4. After non-invasive *H pylori* testing, 341/342 (99.7%) said they would happily have it again compared with 38/66 (58%) after endoscopy with sedation and 79/256 (31%) after endoscopy without sedation. After endoscopy without sedation, 66/253 (26%) said they would take sedation if they had to have the procedure again (see [bmj.com](#)).

Safety

The only potentially serious abnormality detected was a low grade gastric mucosal associated lymphoid tumour (MALT) identified in a routine biopsy from one of the *H pylori* positive patients (table 2). Further investigation indicated that this was confined to the gastric mucosa and needed no treatment other than the *H pylori* eradication treatment that had been given under the routine study protocol. The endoscopic diagnosis in the 24 patients randomised to non-invasive *H pylori* testing and then referred later for endoscopy showed no abnormality in 17 patients, oesophagitis grade I in three, oesophagitis grade II in two, and duodenal ulcer in one; the remaining patient could not tolerate the examination.

Discussion

Safety

A concern about widespread implementation of non-invasive *H pylori* testing in place of endoscopy is that upper gastrointestinal malignancy may be missed in some patients. For that reason, we excluded patients with sinister symptoms and those aged 55 or over. A previous retrospective study in our catchment area¹¹

Table 3 Comparison of the two randomised groups over the subsequent year. Values are numbers (percentages) unless stated otherwise

	Endoscopy plus breath test (n=292)	Breath test alone (n=294)
Mean (SD; range) Glasgow dyspepsia severity score	5.4 (3.4; 0-15)	5.6 (3.4; 0-15)
Frequency of:		
Visit to general practitioner for dyspepsia	98/292 (34)	108/293 (37)
Attendance at hospital outpatient clinic for dyspepsia	19/292 (7)	18/293 (6)
Endoscopy	4/292 (1)	24/294 (8)
Repeat breath test (in patients testing positive on entry)	27/292 (9) (26/156 (17))	19/294 (6) (18/142 (13))
Barium meal	5/292 (2)	1/294 (0.3)
Ultrasonography	3/292 (1)	10/294 (3)
Other gastrointestinal investigations	11/292 (4)	7/294 (2)
Drug usage (% treated) (median length of treatment):		
Proton pump inhibitor	69/291 (24) (24 weeks)	77/292 (26) (20 weeks)
H ₂ receptor antagonist	56/291 (19) (10 weeks)	68/293 (23) (20 weeks)
Antacids	82/291 (28) (18 weeks)	90/293 (31) (10 weeks)
Alginates	73/290 (25) (12 weeks)	82/291 (28) (6 weeks)
Patient oriented outcomes (0-10: 0=no concern, 10=extreme concern)		
Mean (SD; range) overall concern about symptoms	2.4 (2.6; 0-10)	2.4 (2.4; 0-10)
Mean (SD; range) concern about missed disease	1.7 (2.3; 0-10)	1.9 (2.5; 0-10)
Mean (SD; range) overall satisfaction with management	8.9 (1.6; 0.8-10)	8.9 (1.7; 0-10)

and one from another region in the United Kingdom¹² indicated that underlying malignancy in such patients presenting for endoscopy was extremely rare and when present was rarely curable. In this study, of the 352 patients who were randomised to initial endoscopy only one had a potentially serious condition.

It is often assumed that non-endoscopic investigation strategies will be inappropriate for patients who are particularly worried about an underlying serious disease at initial presentation. However, our study indicated that the most worried patients had equivalent reassurance from endoscopy and non-invasive breath test.

Generalisability

Are the results of our study generalisable to other regions and populations? The prevalence of infection with *H pylori* in our patients with dyspepsia was approximately 50%, which is similar to the mean value of 55% reported in a large meta-analysis of the prevalence of *H pylori* in patients with non-ulcer dyspepsia.¹³ However, the prevalence of the infection varies considerably, depending largely on the socioeconomic status and age of the group being studied.¹⁴ In populations with a very low prevalence of the infection and of *H pylori* related ulcer disease, both investigation strategies may be superfluous.

There is only one previous study randomising patients with upper gastrointestinal symptoms to non-invasive *H pylori* testing or endoscopy.¹⁵ That study concluded that the test and eradicate *H pylori* strategy was as efficient and safe as prompt endoscopy. However, slightly fewer patients were very satisfied one year after non-invasive *H pylori* testing (56%) than after endoscopy (62%). In contrast, we found that satisfaction was similar after the two strategies, and this may be related to our specialist team providing the patients with a fuller description of the relative merits of the two modes of investigation.

One previous study compared the cost of management by non-invasive *H pylori* testing or by endoscopy by randomising general practices to the two investiga-

What is already known on this topic

Endoscopy is a commonly used investigation for upper gastrointestinal symptoms, but its effectiveness has been questioned

Non-invasive testing for *Helicobacter pylori* has been shown to predict endoscopic diagnosis in patients with dyspepsia

What this study adds

In patients less than 55 years of age with uncomplicated dyspepsia, non-invasive testing for *H pylori* is as effective and as safe as endoscopy

Non-invasive *H pylori* testing is as reassuring to the patient as endoscopy and is less uncomfortable and distressing

tion strategies.¹⁶ Over the 12 months after randomisation, the total cost of consultations, referrals, investigations, and treatment was on average £404.31 in the endoscopy group compared with only £205.67 in the non-invasive *H pylori* testing group.

Two smaller studies have compared *H pylori* testing with endoscopy in subgroups of patients with dyspepsia referred for endoscopy.^{4,6} No differences were found between the two investigation strategies with respect to resolution of dyspepsia, use of drugs, or visits to the general practitioner. Use of endoscopy was reduced by 83% over the two year follow up.

Conclusion

Our current study and the previous studies, therefore, all indicate that non-invasive testing for *H pylori* is as effective as endoscopy in managing patients with uncomplicated upper gastrointestinal symptoms. The non-endoscopic strategy has two potential benefits. The first is that patients find the procedure of non-invasive *H pylori* testing less uncomfortable and distressing than endoscopic examination. The second is that non-invasive *H pylori* testing is substantially cheaper than endoscopy. For these reasons, non-invasive *H pylori* testing seems to be the preferred investigation for patients with uncomplicated dyspepsia.

Finally, it should be emphasised that our study provides information on the relative merits of only two investigational strategies. It is likely that other approaches, such as empirical treatment without investigation or the use of other investigations, will be more appropriate for certain patients.

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Corrections and clarifications

ABC of clinical electrocardiography: Atrial arrhythmias
At least one reader noticed that in this article by Steve Goodacre and Richard Irons (9 March, pp 594-7), the electrocardiogram at the top of p 597 should have been captioned "Multifocal atrial tachycardia" [not fibrillation].

Protein conjugate pneumococcal vaccines
In this editorial by Vana Spoulou and colleagues (30 March, pp 750-1), our zeal to avoid too much repetition of "protein conjugate pneumococcal vaccine" unfortunately may have led to some confusion. The first sentence of the second paragraph should have read: "The need for a strict, objective assessment of the vaccine is further enhanced by serious concerns raised recently when pneumococcal polysaccharide vaccine [not "this vaccine"] was unexpectedly found to increase the rates of pneumonia in HIV infected individuals."

Minerva

Amar Alwitary and Roger Holden, the authors of the picture story about a patient with a visual field defect that was thought to be caused by excessive upper eyelid skin but was in fact secondary to an intraocular tumour (23 February, p 494), were unhappy with the tone of the text that accompanied their picture. The problem arose because the *BMJ* did not receive the correct wording. The authors apologise for any offence caused and have since supplied us with the version they intended us to use; this can be read at www.bmj.com/cgi/eletters/324/7335/494#203951