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Serology for *Helicobacter pylori* compared with symptom questionnaires in screening before direct access endoscopy

M A Mendall, R P Jazrawi, J M Marrero, N Molineaux, J Levi, J D Maxwell, T C Northfield

Abstract

This prospective study aimed to compare serology for *Helicobacter pylori* with two, symptom questionnaires in screening patients before direct access endoscopy. Methods were compared in terms of the number of endoscopies saved and pathology missed in 315 patients referred to a gastroenterology unit by 65 local GPs. The serology used was based on an acid glycine extract of *H pylori*. One in-house questionnaire was based on the Glasgow dyspepsia (GLADYS) system and the other questionnaire was that reported by Holdstock *et al*. A cut off point of 6·3 U/ml for *H pylori* serology was selected for screening patients (97% sensitive and 75% specific). Serology was combined with a history of NSAID usage in determining who should have endoscopy. For the in-house questionnaire, a cut off score of more than 8 out of a possible maximum of 18 was chosen, after prior evaluation in 118 patients referred for direct access endoscopy (the sensitivity for detection of peptic ulcer was 88%, specificity 61%). A cut off score of more than 412 was used for the Holdstock questionnaire. In patients under 45 years, serology detected more peptic ulcers than the in-house questionnaire and the Holdstock questionnaire (27/28 *v* 24/28, NS and *v* 20/28, $p<0·05$ respectively). The Holdstock questionnaire saved significantly more endoscopies than the other two methods (76/149 *v* 57/149 for the in-house questionnaire, $p= 0·05$ and 59/149 for serology, $p=0·05$). In all age groups combined, serology was significantly better than the in-house and Holdstock questionnaires at detecting peptic ulcers and gastric cancer (61/63, 52/63, $p<0·02$, and 50/63, $p<0·01$ respectively). But serology saved significantly fewer endoscopies (89/315, 135/315, $p<0·005$, and 119/315, $p<0·05$ respectively). Serology was inferior to the Holdstock questionnaire at detecting severe oesophagitis. It is concluded that serology is the method of choice in screening before direct access upper gastrointestinal endoscopy in those under 45 years. It best combines a high sensitivity for peptic ulcer disease with a large reduction in unnecessary negative endoscopies.

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Keywords: *Helicobacter pylori*, serology, symptom questionnaire, direct access endoscopy.

Department of Medicine, St Georges Hospital Medical School, London
M A Mendall
R P Jazrawi
J M Marrero
N Molineaux
J Levi
J D Maxwell
T C Northfield

Correspondence to:
Professor T C Northfield, Division of Biochemical Medicine, St Georges Hospital Medical School, Cranmer Terrace, London SW17 0RE.

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Endoscopy is the investigation of choice in dyspepsia. Direct access endoscopy can reduce the time between presentation and diagnosis. It saves on unnecessary outpatient consultations, and can reduce inappropriate prescribing,[1] but results in an increased workload.[2] Thus, some method of screening out subjects who are at low risk of clinically important pathology is desirable.

Helicobacter pylori is an important factor in the pathogenesis of peptic ulcer. Ninety five per cent of duodenal ulcers and 67–87% of gastric ulcers are associated with this infection,[3] while many of the *H pylori* negative ulcers are associated with the use of non-steroidal anti-inflammatory drugs (NSAIDs).[4] We and others have assessed a strategy of not endoscoping those *H pylori* seronegative subjects aged less than 45 who are not taking NSAIDs and have shown it to have a sensitivity of 96–97% for detecting pathology while enabling the avoidance of 23–30% of endoscopies when performed in all age groups.[5 6]

Attempts have been made to derive scoring systems, based on symptoms, which predict the presence or absence of pathology on endoscopy, the advantage of this approach being cost. Varying results have been reported, with sensitivities for the detection of major pathology from 86–96% and savings in endoscopic workload varying from 23–33%.[7 8]

We compared prospectively a screening strategy of not endoscoping *H pylori* seronegative subjects who were not taking NSAIDs with two symptom questionnaires in a direct access endoscopy clinic population. One of the symptom questionnaires was that of Holdstock which gives the best results of any so far reported, and the other was one developed in-house from the Glasgow computerised dyspepsia questionnaire by Crean.[9]

Methods

PRIOR VALIDATION OF SEROLOGY

The serology was validated on 295 consecutive subjects (mean age 51, range 15–93) referred from a gastrointerology clinic for endoscopy. Upper gastrointestinal endoscopy was performed after an overnight fast. Three biopsy specimens were taken from the antrum within 3 cm of the pylorus. Two biopsy specimens were submitted for histology for the identification of *H pylori* after staining with haematoxylin and eosin and one was used to perform a biopsy urease test (CLO test), positive in 24

hours. Patients were considered infected if either of the tests was positive.

PRIOR VALIDATION OF SYMPTOM QUESTIONNAIRES

The in-house questionnaire consisted of 14 questions which covered the following: epigastric pain, its relief by food, its duration, vomiting, smoking, alcohol intake, previous ulcer, history of ulcer treatment and family history. The answers were given weights of 0, 1, or 2. The questions and score were based on criteria developed in Glasgow as part of the development of the GLADYS diagnostic computer system.[9] It was validated on 118 patients (mean age 36, range 22–75) referred for direct access endoscopy.

The Holdstock questionnaire[7] comprised 6 questions with different weights. These questions concerned age, sex, smoking, history of peptic ulcer, family history of peptic ulcer, and hiatus hernia. A cut off score of more than 412 gave a sensitivity for the detection of serious pathology of 97% with potential savings of 26% of all endoscopies in the assessment previously reported.[7]

STUDY DESIGN

The GPs who referred patients for direct access endoscopies were given guidelines for referral according to the British Society of Gastroenterology's recommendations. GPs were advised that subjects with sinister symptoms (that is, anaemia, weight loss, dysphagia) were not suitable for direct access endoscopy. They were asked to stop their patients taking H_2 antagonists two weeks before endoscopy and appointments were booked for two weeks later if at the time of the request the subject was taking these drugs.

Information on NSAID use was collected from the direct access patients and from 205 of the clinic patients. A history of regular NSAID use was deemed to be present when the use of NSAIDs in anything other than low dosage preceded the onset of symptoms.

Approval was obtained from the local hospital ethical committee.

The two questionnaires and the serology were tested prospectively on 315 consecutive subjects (median age 48, range 15–86, 54% male) directly referred by their GP for investigation of dyspepsia. Questionnaires were administered by a research nurse before the endoscopy, and the endoscopist was unaware of the results. All subjects were endoscoped irrespective of their serological or questionnaire findings in order to assess the pathology that would have been missed in those screened out of endoscopy by the different procedures.

Serological testing for *H pylori* infection was performed using an ELISA based on an acid glycine extract (Helico-G, Porton, Cambridge). The test was performed in duplicate according to the manufacturer's instructions.

Statistical analysis of savings in endoscopies and pathology detected was by the χ^2 test, using continuity corrections where appropriate.

TABLE I *Prospective comparison of serology and questionnaire screening for dyspepsia in the under 45 year olds with respect to findings on esophagoduodenogastroscopy*

Test	*Normal, n=120 (% in whom endoscopy not required)*	*Duodenal ulcer, n=26 (% detected)*	*Gastric ulcer, n=2 (% detected)*	*Moderate/severe oesophagitis n=1 (% detected)*
Serology+NSAID use	48	96	100	100
In-house questionnaire (score 8+)	44	88	50	100
Holdstock questionnaire (score 412+)	57	73	50	100
Holdstock questionnaire (score 368+)	45	73	100	100

Results

VALIDATION OF THE SEROLOGY AND THE QUESTIONNAIRES

For serology, intra-assay variation was 6% and interassay variation 10%, as previously reported. Of 295 subjects referred from the clinic for upper gastrointestinal endoscopy, 62% were positive for *H pylori* on biopsy based tests. A cut off point of 6·3 U/ml was selected for the purpose of screening the direct access patients. This optimised sensitivity at 98% and specificity at 75%, as previously reported. The strategy tested prospectively was to endoscope only seropositive subjects using this cut off point, as long as they were not taking regular NSAIDs. This was defined as subjects taking NSAIDs most days for a period of at least one week, or subjects whose recent symptoms postdated the ingestion of these drugs, except cardioprotective doses of aspirin. If subjects did not fulfil these criteria, their endoscopies were said to be 'saved'.

For the in-house questionnaire, a cut off score of more than 8 out of a possible maximum of 18 was chosen (sensitivity for detection of peptic ulcer 88%, specificity 61%). Subjects with scores of less than this were considered to have had their endoscopies 'saved'.

Only 12 subjects had a positive history of NSAID use. Three of these were under the age of 45; one was seropositive and had a gastric ulcer, one was seropositive and had a normal endoscopy, and the third was seronegative. In the over 45 years age group, there was one seronegative, but NSAID positive ulcer; six NSAID positive, *H pylori* positive subjects with a normal endoscopy; and two NSAID positive subjects who were seronegative.

PROSPECTIVE COMPARISON OF SEROLOGY AND QUESTIONNAIRE SCREENING IN THE UNDER 45 YEAR OLDS

The pathology detected in the under 45s and all age groups combined is shown in Tables I and II. Serology detected all pathology except one duodenal ulcer. The in-house questionnaire missed four duodenal ulcers and one gastric ulcer, whereas the Holdstock questionnaire missed six duodenal ulcers and one gastric ulcer. Proportions of normal endoscopies which would have been saved were similar. In all age groups combined, serology and the Holdstock questionnaire detected both gastric cancers, unlike the in-house questionnaire.

TABLE II *Prospective comparison of serology and questionnaire screening for dyspepsia in all age groups with respect to findings on oesophagoduodenoscopy*

Test	*Normal, n=236 (% in whom endoscopy not required*	*Duodenal ulcer, n=52 (% detected)*	*Gastric ulcer n=9 (% detected)*	*Gastric Ca, n=2 (% detected)*	*Moderate/severe oesophagitis, n=16 (% detected)*
Serology+NSAID use	35	98	89	100	69
In-house questionnaire (score 8+)	51	88	67	0	75
Holdstock questionnaire (score 412+)	45	79	78	100	100
Holdstock questionnaire (score 368+)	31	85	89	100	100

Table III shows the number and the proportion of endoscopies saved in the under 45s and all age groups combined. It excludes moderate to severe oesophagitis (there was only one case in the under 45s). In the under 45s, serology detected more pathology than both questionnaires, but this difference was significant only when compared with the Holdstock questionnaire.

Because the Holdstock questionnaire performed less well than reported, the optimal cut off point of a score of 368 was selected because it maximised sensitivity and specificity for pathology. It also gave a similar specificity to that in the initial report. Using the revised cut off for the Holdstock questionnaire the difference from serology in detecting peptic ulcer disease became of borderline significance in the under 45s while remaining significant in all age groups. The number of endoscopies saved became similar to serology in both the under 45s and all ages combined.

If only two peptic ulcers were to be missed by the Holdstock questionnaire in the under 45s (that is the same as with serology) the cut off point would have to be lowered to 350 and then only 16 endoscopies would have been saved, significantly fewer than serology. The effect of lowering the cut off of the in-house questionnaire in the under 45s was also examined. Lowering the cut off to 6 would have missed three peptic ulcers, but would have saved only 31 endoscopies, significantly fewer than serology, while lowering the cut off point to 5 would have missed one gastric ulcer and saved just 30 endoscopies.

If the in-house questionnaire were performed first, and only those subjects with a score of more than 5 had serology performed, then 75/149 (50%) of endoscopies would have been saved and only one gastric ulcer missed. Thirty fewer serological tests would have been performed.

Discussion

In all age groups taken together, serology for *H pylori* was better than the two questionnaires in detecting peptic ulcer disease and gastric cancer in an unselected direct access endoscopy population. This was at the cost of saving fewer endoscopies. Worryingly, the in-house questionnaire would have missed both gastric cancers in the older age group.

In the under 45 age group, where the risk of gastric cancer is low, serology again detected a higher proportion of peptic ulcers, although this difference failed to reach significance. The differences in the number of endoscopies saves were less and non-significant, except for the Holdstock questionnaire which used the higher cut off point. The effect of lowering the cut off points of the two questionnaires was also examined, and it was found that to detect the same proportion of pathology as serology, significantly fewer endoscopies would have been saved than with serology.

Any investigation should only be used if it is going to alter management. In this respect serology for *H pylori* is a more rational investigation than a questionnaire. Apart from detecting peptic ulcer disease, which can be treated effectively by either *H pylori* eradication therapy or by stopping NSAIDs, the management of other conditions is not altered by endoscopic diagnosis. The management of oesophagitis is symptomatic except when the disorder is complicated by stricture formation, at which time the warning symptoms of subjects not suitable for screening will be present. Furthermore, moderate to severe oesophagitis is rare in the under 45s. Both gastric cancers were detected by serology as were all the gastric cancers in two previous studies which have employed the same test, raising the possibility that it could be applied in older age groups as well. However, the smaller proportion of endoscopies which could be saved in these subjects makes screening less attractive.

In our hands, the Holdstock questionnaire did not perform as well for screening as indicated by the author's report. The reason for this is unclear. It could be due to differences in referral patterns or in the populations being screened. The Holdstock questionnaire is heavily weighted towards endoscoping older subjects, unlike the serology test and the in-house questionnaire. Our population, which comes from an inner city area of high deprivation with a large number of ethnic minorities and a high prevalence of *H pylori*, had considerable peptic ulcer disease at a young age, whereas the Holdstock questionnaire was originally validated in an area of higher social class. It may be argued that serology and the in-house questionnaire yield different results when applied to different populations. However, one can extrapolate from the results

TABLE III *Comparison of the different screening methods with regard to the proportion of endoscopies saved and pathology detected*

Test	*Endoscopies saved <45s (%)*	*Pathology detected <45s (%)*	*Endoscopies saved all ages (%)*	*Pathology detected all ages (%)*
Serology	59/149 (40)	27/28 (96)	89/315 (28)	61/63 (97)
In-house questionnaire	57/149 (38)	24/28 (86)	135/315 (43)*	52/63 (83)†
Holdstock questionnaire	76.149 (51)*	20/28 (71)†	119/315 (38)*	50/63 (79)†
Holdstock questionnaire (cop 368)	61/149 (41)	21/28 (75)‡	81/315 (26)	55/79 (87)†

*Saved significantly more endoscopies than serology, $p<0.05$; †detected significantly less pathology than serology $p<0.05$; ‡detected less pathology than serology $p=0.06$.

of the present study, that if serology were to be applied as a screening procedure in a low *H pylori* prevalence population, a larger proportion of endoscopies would be saved.

Serology is more expensive than a questionnaire, but the reduced chance of missing peptic ulcer disease is adequate compensation. Furthermore, serology is considerably less expensive than endoscopy. The serology test described here costs approximately £10 per patient tested including technician time, which compares favourably with the cost of an endoscopy (about £150). If screening were targeted at the under 45s only, the cost would be about £20 per endoscopy saved.

In conclusion, questionnaires 'save' more negative endoscopies, but at the expense of missing pathology. If greater importance is given to not missing pathology, serology for *H pylori* infection is the screening method of choice before endoscopy, particularly in the under 45s. Whether it can be usefully combined with a simple questionnaire needs prospective evaluation.

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