Possible role of *Helicobacter pylori* serology in reducing endoscopy workload

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Summary: We validated a commercial enzyme-linked immunosorbent assay (ELISA), Helico-G, in diagnosing *H. pylori* in 129 patients (mean age 50 years, range 15–86). We analysed the results of endoscopy against serology to see whether there was a possibility of adopting the strategy of not endoscopic dyspeptic subjects under the age of 45. *H. pylori* infection was considered present if either histology and/or culture were positive. The ELISA had a sensitivity of 88%, specificity of 72%, positive predictive value of 85%, negative predictive value of 77% and accuracy of 82% in detecting *H. pylori*. In a subgroup of 52 subjects aged 45 or less (mean age 35 years, range 15–45), 17 out of 25 patients with positive endoscopic findings were *H. pylori* seropositive while 16 out of 27 patients had normal endoscopic findings. Eighteen out of the 52 patients (35%) were *H. pylori* seronegative and normal endoscopically except for five patients (10%) who had mild to moderate oesophagitis and two who had non-erosive gastritis (4%). All patients with duodenal ulcer disease (7) were seropositive giving predictive values of positive and negative serology for a diagnosis of duodenal ulcer disease as 28% and 100%, respectively.

Therefore adopting a strategy of endoscopic subjects under the age of 45 only if they were *H. pylori* seropositive would have saved 35% of endoscopies in this age group but missed oesophagitis in 10%. Negative serology would tend to exclude duodenal ulcer disease while positive serology discriminates poorly for it. Serology may be a useful adjunct in screening to reduce endoscopy workload provided that patients with gastro-oesophageal reflux symptoms are excluded.

Introduction

The serological tests for *Helicobacter pylori* that have been developed recently have many uses in epidemiology and other research,¹ but their role in clinical practice is still under evaluation. Dyspepsia is a very common symptom in the community² and its investigation constitutes a major workload for both radiology and endoscopy services. Most centres have experienced a steady increase in the yearly number of gastrointestinal endoscopies over the past decade.³ Investigating all dyspeptic patients by endoscopy would result in a low diagnostic yield; up to 75% of patient attending gastroenterology clinics with upper abdominal pain are diagnosed as having non-ulcer dyspepsia.⁴ Only about 20% of investigated patients prove to have peptic ulcer disease and 1–2% have gastric cancer.⁵

As *H. pylori* infection of the stomach is strongly associated with peptic ulcers, and duodenal ulcer disease in particular, it has been suggested that

noninvasive tests for the presence of the organism could be used as an adjunct or an alternative to endoscopy in diagnosing dyspepsia. There are two methods by which *H. pylori* can be detected noninvasively: serology and carbon-labelled urea breath tests. Serological tests have the advantage over carbon-labelled urea breath tests as they are cheap and simple to use, requiring just a blood sample. Thus serological screening for *H. pylori* antibodies has been suggested as a method to reduce endoscopy workload by excluding seronegative patients from endoscopy, as they would be less likely to have significant pathology. In order to avoid missing gastric carcinoma, an upper age limit of 45 years is imposed on those to be screened as gastric carcinoma is extremely rare in this age group (at least in the UK) constituting only 1.8% of cases.⁵

Our aims were: (1) to validate a commercial enzyme-linked immunosorbent assay (ELISA), Helico-G (Porton Cambridge, UK), against the currently accepted standards of histology, culture and urease tests for diagnosing the presence of *H. pylori*; and (2) to analyse the results of endoscopy against serology to see whether there was a possibility of adopting the strategy of not endoscopic

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subjects under the age of 45 who were *H. pylori* negative by serology.

Methods

Ethical approval for the study was granted by the Altnagelvin Medical Executive Committee and all patients gave written informed consent. Patients fasted for at least 8 hours prior to an endoscopy, which was performed with the Fujinon Electronic Video Endoscopy system. Before reuse, the endoscope and the biopsy forceps were washed, cleaned and soaked in glutaraldehyde solution for 10 minutes and thoroughly washed again with sterilized water.

A total of 129 consecutive patients (mean age 50 years, range 15–86) undergoing diagnostic endoscopy for dyspepsia, and a few other reasons such as chest pain and anaemia were tested for *H. pylori* antibodies by ELISA using an acid glycine extract of the bacterium (Helico-G, Porton Cambridge) to validate the test. From this group, all 52 subjects with dyspepsia aged 45 or less (mean age 35 years, range 15–45) were analysed for possible utility of *H. pylori* serological screening to reduce endoscopy workload. Two antral biopsy specimens were taken for histology (organism detected using cresyl fast violet stains), two for culture (immediate transfer to laboratory, Columbia blood agar with *H. pylori* selective supplement, micro-aerophilic conditions, 37°C, 5–7 days) and one for urease (CLO, Delta West, Western Australia) tests. The activity of gastritis (normal, mild, severe) and degree of colonization with *H. pylori* (none, few, plenty of bacteria) were assessed semiquantitatively. ELISA analysis, histological examination and culture were performed independently without knowledge of endoscopic diagnosis. *H. pylori* was considered present when either histology or culture, or both were positive. The ELISA was considered seropositive for *H. pylori* infection if the antibody level was greater than 10 units/ml.

The Kruskal–Wallis non-parametric test followed by Mann–Whitney *U*-test was used to compare antibody levels of *H. pylori* with activity of gastritis and degree of *H. pylori* colonization. *P* < 0.05 was considered significant.

Results

A total of 73 out of 83 patients colonized with *H. pylori* were seropositive and 33 out of 46 patients not colonized with *H. pylori* were seronegative (Table I). Thus the ELISA had a sensitivity of 88% (95% confidence limits 76–92%), specificity of 72% (57–84), positive predictive value of 85% (76–92), negative predictive value of 77% (61–88)

and accuracy of 82% (75–88) for *H. pylori* infection. A total of 71 out of 83 patients colonized with *H. pylori* were CLO test positive and 45 out of 46 patients not colonized with *H. pylori* were CLO negative (Table II). Thus in comparison, the CLO test had a sensitivity of 86% (95% confidence limits 76–92), specificity of 98% (88–99.9), positive predictive value of 99% (93–99.9), negative predictive value of 79% (66–88) and accuracy of 91% (83–95).

The median (interquartile range) antibody levels of *H. pylori* from the ELISA increased significantly in relation to the activity of gastritis (*P* < 0.05), with 6 (4–7), 38 (14–70) and 76 (38–93) units/ml for normal, mild and severe gastritis, respectively. The median (interquartile range) antibody levels of *H. pylori* from the ELISA for few and plenty of bacteria were significantly increased when compared to no bacteria (*P* < 0.05), and showed a trend to increase when compared to each other (*P* > 0.05): 7 (5–18), 47 (23–83), 69 (39–93) U/ml for none, few and plenty of bacteria, respectively.

In the 52 patients aged 45 or less, 17 out of 25 patients with positive endoscopic findings were *H.*

Table I Comparison of ELISA for the detection of *H. pylori* (positive indicating presence of *H. pylori*) with histology and culture (*H. pylori* being considered present if histology and/or culture were positive) in 129 patients

	ELISA positive	ELISA negative
<i>H. pylori</i> present	73	10
<i>H. pylori</i> absent	13	33
(95% CI intervals)		
Sensitivity	88% (76–92)	
Specificity	72% (57–84)	
Positive predictive value	85% (76–92)	
Negative predictive value	77% (61–88)	
Accuracy	82% (75–88)	

Table II Comparison of CLO for the detection of *H. pylori* (positive indicating presence of *H. pylori*) with histology and culture (*H. pylori* being considered present if histology and/or culture were positive) in 129 patients

	CLO positive	CLO negative
<i>H. pylori</i> present	71	12
<i>H. pylori</i> absent	1	45
(95% CI intervals)		
Sensitivity	86% (76–92)	
Specificity	98% (88–99.9)	
Positive predictive value	99% (93–99.9)	
Negative predictive value	79% (66–88)	
Accuracy	91% (83–95)	

pylori seropositive while 11 out of 27 patients with normal endoscopic findings were *H. pylori* seronegative. Out of the patients with positive endoscopic findings, 10 had oesophagitis, one had a duodenal ulcer, six had duodenitis (presence of significant erythema, friability, oedema or erosions), five had gastritis, one had Barrett's oesophagus, one had Mallory–Weiss tear and one had oesophageal candidiasis. A total of 18 out of 52 patients (35%) were *H. pylori* seronegative and out of these, five (10%) had mild to moderate oesophagitis and two (4%) had non-erosive gastritis. Duodenal ulcer disease is defined as the presence of a duodenal ulcer or duodenitis. Seven out of 25 seropositive patients had duodenal ulcer disease while all 27 who were seronegative did not have it. The predictive values of positive and negative serology for a diagnosis of duodenal ulcer disease were 28% and 100%, respectively (Table III).

Discussion

Our results suggest that the Helico-G ELISA kit has acceptable sensitivity, specificity, positive and negative predictive values and accuracy for the noninvasive detection of *H. pylori*. These are comparable with findings by other investigators with sensitivities ranging from 79% to 91% and specificities ranging from 47% to 91%,^{6–9} and also to other ELISA kits.^{6,8} Compared to the CLO test, the latter shows higher specificity, positive predictive value and accuracy, but has the disadvantage of being invasive; these figures being consistent with those found by Dill *et al.*¹⁰

We assessed a widely suggested strategy of using *H. pylori* serology as a screening procedure to reduce endoscopy workload. Patients with dyspepsia who were found to be *H. pylori* seropositive would go on to endoscopy to determine whether they had peptic ulcer disease, while negatives would be reassured and treated for non-ulcer dyspepsia. To avoid missing early gastric carcinoma, an upper age limit of 45 years would be used as discussed in the introduction. The assumption is that the chief aim of endoscopy in most patients is to detect ulcer disease rather than minor pathologies.

Table III Serological results and predictive values in all dyspeptic patients with and without duodenal ulcer (DU) disease (duodenal ulcer or duodenitis)

	ELISA positive	ELISA negative
DU disease present	7	0
DU disease absent	18	27

The predictive values of positive and negative serology for a diagnosis of duodenal ulcer disease were 28 and 100%, respectively.

We found that if this strategy had been employed, 35% of endoscopies would have been saved and we did not miss patients with duodenal ulcer disease; duodenitis is considered as part of the spectrum of duodenal ulcer disease consistent with current opinion.¹¹ The strategy detected all the seven (13%) patients with duodenal ulcer disease. The high negative predictive value of the serology for duodenal ulcer disease suggests that negative serology would probably exclude duodenal ulcer disease, while its low positive predictive value for this suggests that it discriminates poorly for it. Our study supports the findings of Collins *et al.*,¹² although they used an in-house non-commercial ELISA.

However, using this strategy, oesophagitis (10%) and gastritis (4%) would have been missed. The clinical relevance of gastritis is uncertain. The presence of oesophagitis is probably clinically significant. To avoid missing this, a patient with a history suggestive of oesophageal reflux may be excluded from this strategy to be endoscoped regardless of serology results as there is good correlation between the symptoms of gastro-oesophageal reflux disease and endoscopic findings.¹³ In addition the value of endoscopy in managing this type of patient is arguable. Endoscopy is not the gold standard for the diagnosis of reflux disease^{14,15} and, if serology can act as a tool in the diagnostic process by excluding concurrent peptic ulcer disease, then the indications for endoscopy are diminished. The reason that *H. pylori* serology is probably of little help in screening for oesophagitis is because the association between the condition and *H. pylori* is at present uncertain.¹⁶

It is presently not known what happens to the patients who are seronegative and hence not endoscoped. The total number of endoscopies being performed may not be saved if these patients end up having an endoscopy anyway perhaps after a brief therapeutic tussle in the outpatient clinic. A prospective study of this group of patients is required if endoscopy saving is to be confirmed. As serological tests have a high sensitivity for *H. pylori*, the peptic ulcers missed will be *H. pylori* negative ulcers. The clinical importance of missing such a diagnosis is uncertain as it is not known whether they follow a different clinical course to *H. pylori*-positive peptic ulcers or not.

In conclusion, the Helico-G ELISA provides a useful noninvasive serodiagnostic test for *H. pylori* comparing favourably with current established standards. It may be useful as part of a screening programme to reduce endoscopy workload provided that patients with symptoms suggestive of gastro-oesophageal reflux are excluded from this. However, further larger prospective studies would be required to confirm this.

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