In-practice evaluation of whole-blood *Helicobacter pylori* test: its usefulness in detecting peptic ulcer disease

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SUMMARY

Background. *Approximately 10% of patients presenting with dyspepsia to the general practitioner have peptic ulcers; the large majority of which are related to infection with Helicobactor pylori. Office-based tests for H. pylori detection are generally validated and evaluated in selected patient groups.*

Aim. *To evaluate the clinical effectiveness of a whole-blood serology test for infection with Helicobacter pylori in detecting peptic ulcer disease (PUD) in daily general practice.*

Method. *A descriptive study of 171 primary care dyspepsia patients selected for open-access endoscopy in primary care and aged between 18 and 75 years, in 92 general practices in central, southern, and eastern parts of the Netherlands. H. pylori status was assessed using the BM-test Helicobacter pylori, which is identical to the Helisal test. Dyspepsia severity score was measured using a validated symptom score. Symptom characteristics and probability of relevant disease were assessed by the general practitioner. Endoscopy was carried out in local hospitals. Diagnostic outcome of both endoscopy and H. pylori reference test was supplied by local specialists. The BM-test was evaluated against endoscopic results.*

Results. *A high number (61.8%) of false-negative BM-tests resulted in a low sensitivity (95% confidence interval [CI] = 48–75%) for detection of H. pylori infection. Only 12 out of 32 patients with PUD had a positive BM-test, resulting in a positive likelihood ratio (LR) for PUD of 1.41 and a negative LR of 0.85.*

Conclusions. *This study confirms the relatively poor performance of the BM-test in daily general practice, and shows the limited diagnostic value of H. pylori office-tests for detecting PUD in primary care. The discriminative value of the test result is too small to support either a 'test-and-endoscope' or a 'test-and-treat' strategy in general practice.*

Keywords: *Helicobacter pylori; peptic ulcer disease; dyspepsia; endoscopy.*

Introduction

SINCE the discovery of *Helicobacter pylori* as a causative organism in peptic ulcer disease (PUD) in 1983,[1] the management of ulcer disease has changed dramatically.[2] Because peptic ulcers are present in less than 10% of dyspeptic patients in general practice,[3] discussion has started over the optimal management strategy of *H. pylori* infection in dyspepsia in primary care.[4] The poor overall response of infected subjects with non-ulcer dyspepsia to eradication of *H. pylori*[5] makes a 'test-and-treat' strategy for all dyspeptic patients in general practice unrewarding. Although the relationship has been established between *H. pylori* and gastric cancer,[6,7] there is no substantial evidence that eradication of *H. pylori* will reduce the risk in treated patients.

Testing for *H. pylori* could help the general practitioner (GP) detect or exclude PUD in dyspeptic patients. For example, testing patients just before endoscopy has proved effective in reducing the endoscopic workload in the United Kingdom.[8] This is based on the knowledge that absence of *H. pylori* infection and absence of non-steroidal anti-inflammatory drug use practically nullifies the risk of PUD in a dyspeptic patient.

Infection is usually confirmed through invasive techniques: rapid urease, histology, and culture all require endoscopy and are all commonly used. Non-invasive techniques like polymerase chain reaction, breath test, and serology are available in western Europe, but only serology is used to some extent by GPs.[9] Serology, using enzyme-linked immunosorbent assay (ELISA), has proved reliable in diagnosing *H. pylori* infection, though less so for control of treatment success.[10] Whole-blood serology tests seem fairly reliable compared with other tests, but require local validation in the population 'at risk'; i.e. the general practice population.[11] Local validation is needed because of the geographical variation of *H. pylori* antigens and because diagnostic test characteristics depend on the prevalence of disease in a population.[12]

We used the BM-test *Helicobacter pylori* (Cortecs, UK), which is identical to the Helisal test, in order to detect *H. pylori* infection in a cohort study of unselected dyspepsia patients in general practice. At least five different full-paper validation studies of this test have been published in peer-reviewed journals, and showed a sensitivity of 75% to 96% and a specificity of 67% to 91%.The patients included in these studies generally had a mean age of well over 50 years old, a *Helicobacter* infection prevalence of 45% to 63%, and ulcer prevalence of 11% to 31%.[13-16] This selection bias might impair the generalisability of the results for daily general practice. In fact, a recent study from Australia that evaluated test characteristics of the Helisal test in general practice showed a much poorer sensitivity.[17] No studies have been published that investigate the incorporation of a near-patient test in the diagnostic process of ulcer disease in general practice.

We aimed to establish the effectiveness of the BM-test *Helicobacter pylori* under working conditions in Dutch general practice. First, we related the test characteristics to endoscopic reference tests, then we examined the test's contribution to the clinical process of diagnosing PUD.

Method

Of 836 patients enrolled in a cohort study of patients with dys-

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peptic complaints in general practice, 175 patients who had been selected for open-access endoscopy were included in our study. Patients came from the central, southern, and eastern parts of The Netherlands from 92 practices and all signed Informed Consent. The study was approved by the Medical Ethical Committee of the University Hospital Utrecht. Pregnant patients, patients with severe (cardiac, pulmonary, or malignant) comorbidity or a history of major abdominal surgery, and patients who had previously received eradication therapy, were excluded.

Participating GPs first assessed symptom severity with a previously validated dyspepsia score,[18] and characterised symptoms as ulcer-like, reflux-like, motility-like, or non-specific, according to national guidelines of the Dutch College of General Practitioners.[19] They then indicated the probability of serious disease and registered further management of choice: lifestyle advice, drug therapy, referral, or additional diagnostic procedures. The BM-test *Helicobacter pylori* was carried out in every patient at first consultation by the practice assistant.

Endoscopy was performed in patients with alarming symptoms, elderly patients, patients with poor response to treatment, or in case of a patient's anxiety. GPs requested local hospital staff to perform standard endoscopic assessment, including *H. pylori* status. This was not always granted by the endoscopist because *H. pylori* testing is not always part of routine procedure. Endoscopic assessment was conducted according to the local method of choice; i.e. rapid urease, histology, culture, or a combination. An ELISA serology test was also performed in a few patients. All of these methods show high sensitivity and specificity for the diagnosis of *H. pylori* infection.[12] Patients were considered *H. pylori*-infected if one of the endoscopic tests was positive. When two reference tests were carried out and were discordant, the reference was still considered positive, since a false-negative result is more likely to occur than a false-positive one.

Results of the BM-test *Helicobacter pylori* were validated against results of the endoscopic *H. pylori* status. They were then related to the endoscopic diagnosis of PUD, and positive (LR+) and negative (LR-) likelihood ratios for predicting PUD were calculated. The LR is calculated as the proportion of positive tests in individuals with disease, divided by the proportion of positive tests in individuals without disease. Diagnostic procedures are considered at least moderately helpful in decision-making when LR+ is 3.0 or more or the LR- is 0.3 or less. Decisive tests require a LR+ of 10.0 or LR- of 0.1. Generally, given the prior probability and pre-test odds of a disease, LR+ is used to calculate the post-test odds and, from there, the probability of disease once a test is positive. Vice versa, LR- is used to calculate the probability of absence of a disease given a negative test result. Odds are the chance of disease versus the chance of non-disease. In formula:

pre-test odds = prevalence/(1 - prevalence);
post-test odds = pre-test odds x likelihood ratio;
post-test probability = post-test odds/(post-test odds + 1).[20]

Diagnostic endoscopic categories comprised 'no abnormalities', 'minor abnormalities', including hiatus hernia and non-erosive gastritis/bulbitis, 'oesophagitis', 'PUD', 'malignancy', and 'other disease'. Duodenal scarring, erosive bulbitis, and erosive gastritis were regarded as 'PUD'. Patients with both minor and major abnormalities were registered as major. If both oesophagitis and ulcer disease were present, the patient was booked as PUD. For calculation of confidence intervals (CI) we used the statistical program CIA (confidence interval analysis), approximate procedure.[21]

Results

Four patients were excluded because of previous *H. pylori* therapy. Mean patient age was 46.1 years (SD = 13.6 years) and 48.5% were male. The general *H. pylori* infection rate was 25%.

The diagnostic outcome of the endoscopies is listed in Table 1. Oesophagitis was the commonest finding with major clinical relevance (25.7%); only one (0.6%) patient had gastric cancer. Eighty-six (50.3%) patients had no abnormalities or abnormalities with only minor clinical relevance, such as hiatus hernia or non-erosive mucosal inflammation.

Histopathology was the most frequently used invasive diagnostic test for *H. pylori* infection (Table 2). Surprisingly, culture was performed more often than rapid urease. The 31 patients in whom *H. pylori* reference test was not performed generally had no abnormalities or only oesophagitis; no test was conducted in at least one patient because the presence of a duodenal ulcer was considered sufficient evidence of infection. Multiple reference tests were performed in 28 (16.4%) patients with discordant results in two patients: one patient had a positive histology with negative culture and urease, and the other patient had a positive histology and negative urease.

Of 55 patients with confirmed *H. pylori* infection, only 34 (sensitivity = 61.8%; 95% CI = 47.7–74.6%) had a positive BM-test. Of 39 patients with a positive BM-test, 34 were true positive (positive predictive value [PPV] = 87.2%; 95% CI = 72.6–95.7%). BM-test characteristics remained unchanged when only histopathology results were used as reference (Table 3).

BM-test was negative for 20 out of 32 (62.5%) patients with ulcer disease. Of 139 patients without ulcer disease, 37 (26.6%) had a positive test result. The likelihood ratio of a positive test result for the presence of ulcer disease was 1.41 and that of a negative test was 0.85.

Table 1. Results of endoscopy (n = 171).

Diagnosis	Number (%) of patients	Number (%) of diagnosed patients with positive Hp-BM
No abnormalities	44 (25.7)	14 (31.8)
Minor abnormalities	42 (24.6)	11 (26.2)
Oesophagitis	44 (25.7)	5 (11.9)
Peptic ulcer diseasea	32 (18.7)	12 (38.7)
Duodenal scar	3 (1.8)	2 (66.7)
Erosive gastritis	16 (9.4)	4 (25.0)
Gastric ulcer	4 (2.3)	4 (100)
Erosive bulbitis	7 (4.1)	4 (57.1)
Duodenal ulcer	7 (4.1)	2 (28.6)
Malignancy	1 (0.6)	–
Other disease[b]	8 (4.6)	3 (37.5)
Total	171 (100)	45 (26.3)

[a]Five patients had two diagnoses within 'peptic ulcer disease' category; [b]dysplasia, disturbed emptying, atrophy, mechanical irritation, polyps, and bile reflux were all registered once; one patient had no specification.

Table 2. Reference tests performed (n = 171).

Type of test	Number (%) of patients	Number (%) found positive
Serology (ELISA)	10 (5.8)	6 (60.0)
Rapid urease	33 (19.3)	8 (24.2)
Histopathology	89 (52.7)	33 (37.1)
Culture	44 (25.7)	21 (47.7)
No test carried out	31 (18.1)	–

Table 3. BM-test Helicobacter pylori test characteristics versus reference test.

Characteristic	All reference tests (%) (n = 139)[a]	95% confidence interval	'Histopathology only' reference (%) (n = 88)[b]
Sensitivity	34/55 = 61.8	47.7–74.6	60.6
Specificity	79/84 = 94.0	86.7–98.0	92.7
Positive predictive value	34/39 = 87.2	72.6–95.7	83.3
Negative predictive value	79/100 = 79.0	69.7–86.5	79.7
Reliability	113/139 = 81.3	74.8–87.8	80.7

[a]No reference test was done in 31 patients. The BM-test was found to be uninterpretable in two patients, one with and one without a reference test. Both were excluded from the analysis. [b]BM-test was uninterpretable in one patient. The patient was excluded from the analysis.

Discussion

Our study evaluated the performance of a well-known office-based finger-prick test for diagnosis of *Helicobacter pylori* infection and its contribution to the detection of PUD in day-to-day general practice. Validation studies so far have shown an acceptable performance for this test in (pre-) endoscopy patients, but generally did not consider its use in the detection or exclusion of PUD.

The test shows many false-negative results in our study, and therefore has a lower sensitivity than reported in most studies. The test results contribute very little to the diagnosis of ulcers; a positive result raises the prior probability of 18.7% to a posterior probability of 24.6%, and a negative result reduces the probability to 16.3%. We therefore question the validity and effectiveness of the test for wide-scale use in general practice.

H. pylori infection prevalence in our study population is low, although it is within the range found in other studies from The Netherlands.[22] Endoscopic results are also comparable with those from open-access gastroscopy studies.[23,24] Our test characteristics confirm the results of Talley *et al*, who studied general practice patients in Australia and demonstrated a much poorer sensitivity than previous validation studies.[17] Test characteristics in the general practice population studied by Jones *et al* were in line with other validation studies, but *H. pylori* prevalence was twice as high as in our study, selection was directed towards ulcer-like symptoms, and the use of ELISA as the 'gold standard' increased the likelihood of an above-normal concordance between results.[16]

The observed differences between our study and the validation studies may be explained by three factors. First, mean antibody level in infected subjects may be lower in a population with a relatively low prevalence of *H. pylori*-related disease than in one with a higher prevalence of disease. This could reduce the antibody–antigen reaction of some of the tests so that they do not reach the threshold for positive colouring. There is, however, no strong relation between antibody titre and presence of ulcer disease.[25] Secondly, the performance of a serology test depends, among others, on the local variety of *H. pylori* antigens. It is possible that a whole-blood test produced outside The Netherlands contains antibodies that are less sensitive to local Dutch antigens. Thirdly, there may have been a problem interpreting the test. The test result depends on the appearance of a second purple spot next to the first one, indicating a positive result. Although all practice assistants were trained in reading the results, it is possible that slight colouring of the second spot is sometimes overlooked and misinterpreted as a negative result. Misinterpretation as the most likely cause of lower sensitivity is supported by the Talley *et al* study. Their BM-test was re-read one day later by trained hospital staff and resulted in a lower number of false-negative readings.[17]

Questions may be raised about the 'gold standard' reference tests we used. Since our aim was to avoid selection bias that arises from referral to specific study centres and to evaluate the BM-test under working conditions, we had to rely on numerous endoscopy units, usually with three or four specialists per unit using their own preferred reference tests. Because a false-negative result of invasive assessment is more likely to occur than a false-positive one, the use of two or three reference tests may affect the specificity more than the sensitivity. We did show, however, that selecting only those patients who had histopathology as the reference test did not change the results of the BM-test characteristics.

Two strategies, 'test-and-endoscope' and 'test-and-treat', are advocated to integrate *H. pylori* testing in the management of dyspepsia in primary care. In the 'test-and-endoscope' approach, *H. pylori* testing is used as preselection for endoscopy. This approach requires a high negative predictive value (NPV) of the test used. Although we found an NPV of 79%, 20 out of 32 (63%) peptic ulcers would have been missed if endoscopies had been cancelled because of a negative test result. The limited contribution of the *H. pylori* test to exclude PUD is also expressed by the LR- of 0.85, which hardly lowers the probability of PUD (from 18.7% to 16.3%). Clinical contribution is limited even with a better *H. pylori* test performance: using the reference test instead of the BM-test (LR- = 0.51) did not exclude PUD satisfactorily (post-test probability of peptic ulcer 10.5%).

In the alternative 'test-and-treat' approach, *H. pylori* testing and subsequent treatment is used to treat peptic ulcers without using endoscopy. This approach requires a high PPV of the *H. pylori* test. In our study (PPV = 87%), this approach would have benefitted 12 of out 58 (21%) *H. pylori*-positive patients. Again, LR is a good expression of the contribution to clinical decision-making: with a positive BM-test (LR+ = 1.41), the probability of PUD is raised from 18.7% to 24.6%. This poor discriminative power is only partially dependent on BM-test characteristics: using the reference test raises the probability to 31.7% in the case of a positive result. When we consider erosive gastritis as a non-ulcer condition, the calculated LR+ and LR- become slightly more favourable at 1.85 and 0.68 respectively. Nevertheless, these values are not adequate for diagnosing peptic ulcer disease.

We conclude, therefore, that the added value of testing for *Helicobacter pylori* in general practice in order to diagnose PUD is generally overestimated, and that both 'test-and-treat' and 'test-and-endoscope' strategies do not benefit the majority of patients. The suboptimal performance of the near-patient test also does not influence this conclusion. Our study shows that, next to validation studies, 'real-life performance' evaluation studies are required in order to evaluate the contribution of diagnostic tests to clinical problem-solving.

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