Chronic dyspepsia in general practice. Tapering the use of acid suppressant drugs
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Chapter 3

Evaluation of three non-invasive *H. pylori* tests to exclude ulcer disease in a young chronic dyspeptic population of mixed ethnicity: Reduction of endoscopies by a test and endoscope approach in primary care

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Background
Non-invasive tests to detect *H. pylori* infection are often evaluated in selected hospital patient populations, but seldom in a chronic dyspeptic primary care population of mixed ethnicity < 55 years. Our aim was to evaluate the ability of three non-invasive *H. pylori* tests to exclude ulcer disease in chronic dyspeptic patients.

Methods
*H. pylori* infection in 197 chronic dyspeptic primary care patients < 55 years was assessed by histopathology and culture of gastric biopsy specimens (‘gold standard’). The Whole-Blood-QuickVue-One-Step desktop test, HM-Cap ELISA and Laser-Assisted-Ratio-Analyser 13C-urea-breath-test were evaluated.

Results
The prevalence of *H. pylori* infection was 40% (51/127) in natives and 76% (53/70) in patients born outside the Netherlands (immigrants) (P<0.05). The prevalence of ulcer disease was 13% among natives (17/127) and 29% among immigrants (20/70) (P<0.01). Among native patients, a negative test outcome of the desktop test, ELISA and breath test resulted in a probability of 1%, 0% and 3% having ulcer disease. In contrast, among immigrants these values were 15%, 12% and 5%, respectively. Both desktop- and breath test require operator familiarity.

Conclusions
Performance of non invasive tests to exclude ulcer disease in chronic dyspeptic patients depends on patients population ethnicity composition. Therefore, before introduction, these tests require validation in primary care setting.
Introduction

Testing for presence of *H. pylori* infection is a main topic in the management of dyspepsia. In primary care the detection of *H. pylori* related peptic ulcer disease (PUD) is the target since PUD can be cured by successful eradication of *H. pylori*.

Minimizing the risk of missing cancer and PUD and rational use of endoscopies to be performed are central to the role of general practitioners. Usually, in dyspeptic patients ≥ 55 years endoscopy is recommended because of the higher risk of cancer, so an *H. pylori* related PUD can be diagnosed. The prevalence of serious underlying organic disease is low in patients younger than 55 years. Therefore the topic is whether patients without PUD could be identified without performing endoscopy. Nevertheless, solely on the basis of symptoms it is impossible to differentiate for other most common underlying diseases like PUD, reflux disease, functional dyspepsia or for *H. pylori* infection. However, the selection of *H. pylori* positive patients has become feasible by the development of non-invasive tests like serology, urea-breath tests and the recently described *H. pylori* antigen-based stool assay. Factors in choosing a screening test in primary care include ease of accessibility and use, time required to perform the test, acceptability to the patient, availability of test results on short notice, costs and accuracy.

In a ‘test-and-treat’ approach *H. pylori* eradication of all *H. pylori* positive dyspeptic patients might lead to over-treatment, more anti-microbial resistance, high costs of eradication therapies, doubtful or minute symptom improvement. In a ‘test-and-endoscopy’ approach the general practitioners require tests with a high negative predictive value in order to reassure the exclusion of PUD. This predictive value is dependent on the sensitivity and specificity of the test and on the prior probability (prevalence) of *H. pylori* infection and the prior probability (prevalence) of PUD. These prevalences might differ among patients born in the Netherlands and immigrants, who usually originate from countries with endemic *H. pylori* infections.

Our aim was to evaluate the performance of three non-invasive tests and their ability to exclude *H. pylori* related PUD in a young chronic dyspeptic patient population of mixed ethnicity recruited from general practice. The tests were compared with histology and culture of gastric biopsy specimens obtained by endoscopy ("gold standard").
Materials and Methods

Patient population

Between April 1997 and October 1999 54 general practices were participating in a study on strategies to a more efficacious use of acid suppressant drugs in chronic dyspeptic patients in primary care. Of 54 general practices 1083 chronic dyspeptic patients met eligibility criteria; 434 (40%) of these volunteered to participate in the study and underwent endoscopy. Eligible for one of the diagnostic branches of this study were chronic dyspeptic patients aged 18 to 55 years. Of these 434 patients, all patients aged < 55 years (n=246) participated in this diagnostic study. Nine patients with a successful *H. pylori* eradication in the past, which makes serological testing unreliable, and five patients who refused further participation were excluded (fig 1).

Figure 1 Flow of patients

Chronic dyspepsia was defined as chronic upper abdominal pain/discomfort or reflux disease (symptomatic or oesophagitis grade one) requiring long-term acid suppressant drugs for dyspeptic complaints during at least the preceding 8 weeks before entry. Patients were identified from the computerized medication database of all pharmacists co-operating with the participating general practitioners.

Excluded were patients with documented gastroesophageal reflux disease grade II, III, IV (Savary-Miller); patients with documented significant cardiovascular, pulmonary, renal, hepatobiliary or pancreatic disease or malignancy; patients with sinister symptoms; patients with documented abdominal surgery with relevance to the study; pregnant or lactating women; patients requiring an interpreter; patients taking antibiotics or bismuth containing compounds during the previous month, patients taking NSAID; patients with documented successful *H. pylori* eradication therapy, patients with any condition associated with poor compliance (e.g. drug or alcohol abuse, mental illness or dementia). Patients eligible for
inclusion had the desktop test completed in general practice. Subsequently the patient attended the hospital for upper GI-endoscopy, breath-test and ELISA. The patients were asked to stop ingestion of their acid suppressant medication at least one week prior to endoscopy.

Demographic data included the ethnic background. The ethnic background was defined as natives for patients born in the Netherlands and immigrants for patients born outside the Netherlands.

The study was approved by the Institutional Ethics Committee of the Academic Medical Center and a written informed consent was obtained at the time of endoscopy.

**Endoscopy and H. pylori assessment**

Patients with PUD at entry endoscopy or with a documented history of endoscopic/barium meal positive ulcer disease were regarded as patients with PUD.

During each endoscopy procedure, 3 antral and 3 corpus mucosal biopsy specimens were obtained for histological and bacteriological assessment. The biopsy specimens were processed and assessed as described before. Patients were defined as positive for *H. pylori* (the gold standard) if either one site of the specimen in culture or in histopathology was positive. *H. pylori* infection was absent if bacterial culture and histopathology readings were all negative.

**Non invasive tests for detecting H. pylori infection**

*A. Rapid capillary whole blood desktop test.*

The QuickVue (Quidel Corporation, San Diego, U.S.A.) One-Step *H. pylori* desktop test was performed in the primary care unit by the general practitioner or assistant according to the instructions provided by the manufacturer. Patient’s blood was obtained by puncture of the ring finger. Subsequently, the blood was supplied to the desktop test by capillaries.

*B. Serum ELISA test*

Anti *H. pylori* antibodies were assessed in serum samples by the HM-Cap ELISA, (Enteric Products, Westbury, U.S.A) according to the instructions provided by the manufacturer. Patients were considered to be *H. pylori* negative, indeterminate or positive when their serum had a titer < 1.8, between 1.8 and 2.2 and >2.2, respectively. If borderline values were obtained, the sample was reassessed.

*C. Urea breath test*

Laser-Assisted-Ratio-Analyser urea breath test (Alimenterics B.V., Hoofddorp, Netherlands) was performed routinely according the manufacturers instructions. The LARA-UBT procedure starts with a baseline measurement, then, the patient consumes a nutrient dense meal followed by a solution of 100 mg 13C-labeled urea-powder in 50cc sterile purified
water. Post-ingestion samples were taken at 30 and 60 min. Ingestion of food and drink or smoking was prohibited during the procedure. Analysis of the breath samples was performed by the LARA-UBT analyser.10

Analysis and Statistics
Of the 232 patients a conclusive test result was obtained in 232 desktop tests, in 226 ELISA tests (indeterminate result (n=2) and not performed (n=2) ) and in 199 LARA-UBT results (exclusion of 33 patients due to unreliable breath test result due to low CO2 in patient’s breath sample (n=7), or faulty technique with the LARA-UBT analyser (‘unable to process’ n=15), or LARA test-storage problems (n=11)). For analysis and statistics all patients with a conclusive result for all three non-invasive H. pylori tests (197/232) were included.
Analysis was performed using the SPSS for Windows (version 7.5.3). The Chi-square test was used for comparison of proportions between groups. Significance was set at \( \alpha = 0.05 \) (two-sided). Post test probabilities for peptic ulcer disease were calculated.11

Results
In 197/233 patients all three non-invasive test results were complete. General characteristics of the excluded patients, prevalence of H. pylori infection and PUD among these patients were not significantly different from the patients of the study group. Therefore results are presented of 197 patients who had for all three tests a positive or negative test result.

General characteristics
The mean age of all patients (n=197) was 42 years (range 18-54). The mean age of men (43 years) and women (41 years) did not differ significantly. Forty five percentage of patients (88/197) were male and 65% of patients (127/197) were born in the Netherlands.
The immigrants (n=70) were mainly born in countries with a high prevalence of H. pylori infection namely: Surinam or the Caribbean (N=28), other South-America (N=3), Turkey (N=12), Morocco (N=6), Middle East (N=3), Subsaharan Africa (N=4), Asia (N=9), other (N=5).

Prevalence of H. pylori infection and ulcer disease
Of 197 patients, 104 (53%) were H. pylori positive by culture and histopathology. The prevalence of H. pylori infection differed between men (61%, 54/88) and women (54%, 59/109) (p=0.03). The proportion of H. pylori positive patients among native dutch patients and among immigrants was 40% (51/127) and 76% (53/70), respectively (P<0.0001).(table 1)
PUD was diagnosed in 37 of 197 patients (19%). All PUD patients were H. pylori positive. PUD was less often diagnosed in natives (13%; 17/127) than in immigrants (29%; 20/70)(p<0.01). In patients, who were never investigated for PUD prior to study entry, these
evaluation of three non-invasive *H. pylori* tests

figures were 9%(5/58) and 17%(6/36), respectively (ns). Among patients with investigations prior to this study (n=103) 23 had an history of PUD and 3 patients had PUD diagnosed for the first time. After excluding the patients with a history of PUD, 35% (28/80) had *H. pylori* infection. Of these 28 *H. pylori* positive patients 11% (3/28) had 'de novo' PUD.

Table 1. Prevalence of *H. pylori* infection and peptic ulcer disease stratified for ethnicity in prior uninvestigated (n=94) and in prior investigated chronic dyspeptic patients (n=103).

<table>
<thead>
<tr>
<th>patients</th>
<th>all</th>
<th>prior uninvestigated</th>
<th>prior investigated</th>
</tr>
</thead>
<tbody>
<tr>
<td>ethnicity</td>
<td>n</td>
<td><em>H. pylori</em> infection</td>
<td>PUD</td>
</tr>
<tr>
<td>natives</td>
<td>127</td>
<td>40%*</td>
<td>13%**</td>
</tr>
<tr>
<td>immigrants</td>
<td>70</td>
<td>76%*</td>
<td>29%**</td>
</tr>
</tbody>
</table>

*; **; †; ††; †‡ p<0.05

Comparison of the three tests

The performance of the desktop test among natives (sensitivity: 93.3%, 95%CI 68-100%) was significantly better than among immigrants (sensitivity: 67.4%, 95%CI 52-81%). In hospital we were able to retest 6 patients with a false negative desktop test. Of these 6 patients, all appeared to be positive by retesting with the desktop test. The sensitivity and negative predictive value of the desktop test in the whole population and in immigrants were lower than these values of the ELISA and breath test (p<0.05) (table 2).

Table 2. Test Performance (%) of serology and ¹³C Urea Breath tests for *H. pylori* infection

<table>
<thead>
<tr>
<th>patients</th>
<th>whole population</th>
<th>patients born in the Netherlands</th>
<th>first generation immigrants</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><em>Hp prevalence =53%, n=197</em></td>
<td><em>Hp prevalence =40%, n=127</em></td>
<td><em>Hp prevalence =76%, n=70</em></td>
</tr>
<tr>
<td></td>
<td>desktop</td>
<td>ELISA</td>
<td>¹³C UBT</td>
</tr>
<tr>
<td>sensitivity</td>
<td>78*</td>
<td>95*</td>
<td>93†</td>
</tr>
<tr>
<td>95%CI</td>
<td>70-86</td>
<td>89-98</td>
<td>88-98</td>
</tr>
<tr>
<td>specificity</td>
<td>99</td>
<td>89</td>
<td>100</td>
</tr>
<tr>
<td>95%CI</td>
<td>94-100</td>
<td>83-96</td>
<td>94-100</td>
</tr>
<tr>
<td>positive pv H</td>
<td>99</td>
<td>91</td>
<td>99</td>
</tr>
<tr>
<td>95%CI</td>
<td>93-100</td>
<td>84-96</td>
<td>94-100</td>
</tr>
<tr>
<td>negative pv H</td>
<td>80**</td>
<td>94†</td>
<td>93**</td>
</tr>
<tr>
<td>95%CI</td>
<td>73-100</td>
<td>87-98</td>
<td>86-97</td>
</tr>
</tbody>
</table>

*, †, ‡, §, ††, †‡ p<0.05, pv = predictive value
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The desktop test, ELISA and breath test results were negative in 7/37, 2/37 and 2/37 PUD patients, respectively. For patients with a negative test result, post test probabilities for PUD did not differ significantly (table 3).

Table 3. Pre test prevalence for PUD and post test probabilities for PUD in patients given a negative test result (%), stratified for natives and immigrants.

<table>
<thead>
<tr>
<th>test</th>
<th>patients</th>
<th>pre test</th>
<th>post test</th>
<th>pre test</th>
<th>post test</th>
</tr>
</thead>
<tbody>
<tr>
<td>desktop</td>
<td>native</td>
<td>13</td>
<td>3</td>
<td>9</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>immigrants</td>
<td>29</td>
<td>15</td>
<td>17</td>
<td>11</td>
</tr>
<tr>
<td>ELISA</td>
<td>native</td>
<td>13</td>
<td>0</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>immigrants</td>
<td>29</td>
<td>12</td>
<td>17</td>
<td>0</td>
</tr>
<tr>
<td>13C-UBT</td>
<td>native</td>
<td>13</td>
<td>1</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>immigrants</td>
<td>29</td>
<td>5</td>
<td>17</td>
<td>0</td>
</tr>
</tbody>
</table>

PUD peptic ulcer disease

Discussion
In this study three non invasive tests for the assessment of *H. pylori* infection were evaluated. In contrast with many other studies, the tests were evaluated in the primary care population in which these tests will be used. Primary care patients < 55 years with consisting or relapsing dyspeptic symptoms are the target group of patients for *H. pylori* testing in primary care because the prevalence for PUD among these patients may be higher than among dyspeptic patients consulting the GP for the first time.

Performance of non-invasive tests
Comparison of the desktop test with other studies is difficult due to differences in the choice of gold standard test. In addition, these tests are often used for the assessment of anti-*H. pylori* antibodies in patients' serum instead of patients' whole blood in a face to face setting. Sensitivity in our study was lower (78%) than that claimed by van der Ende et al (97%) using serum samples and one performer, however, the specificity (99%) was comparable (97%).
Remarkably the desktop performance was significantly better in patients born in the Netherlands (sensitivity: 88%) compared to immigrants (sensitivity: 68%). We hypothesised that the *H. pylori* antigens used in this test were different from those present on the *H. pylori* isolated from immigrants, as observed in other studies. However, arguments against this hypothesis may be the good re-testing results of the desktop test in hospital, which indicates
that test performance may improve with operator familiarity, as was observed by others.\textsuperscript{15}
Although, the result of the desktop test is immediately available and its cost is the lowest of the three tests, simplicity should be improved in order to make this test feasible for use in primary care.
In this study, LARA-UBT test and the ELISA serology test had sensitivities and specificities in the same range as reported by others.\textsuperscript{6,16-18} The breath test is the most expensive one, needs an overnight fasting period, is more time consuming in performance and had operator and technical problems. Both ELISA and breath test need analysis in a central laboratory, which delays results a few days. Considering the test characteristics and the aforementioned factors, the ELISA test is the most preferable one of the three tests in our area. From our experiences it is clear that tests need to be validated in primary care before they are used in primary care management policies for dyspepsia.

\textit{Consequences for the management of H. pylori infection and ulcer disease}
Until now, there is only evidence to support the use of \textit{H. pylori} eradication therapy in case of \textit{H. pylori} related PUD(1). The role of \textit{H. pylori} in GERD is not clear and in functional dyspeptic patients conclusions on the effect of \textit{H. pylori} eradication are not uniform with regard to relief of dyspepsia.\textsuperscript{19-25}
Although these tests are developed for detection of \textit{H. pylori} infection only, they may have prognostic value in screening for \textit{H. pylori} related PUD. In general practice, patients with a history of non-NSAID related PUD are treated with an \textit{H. pylori} eradication therapy without further testing. Screening policies for \textit{H. pylori} infection should be performed in groups of patients without a history of investigations to gastro-intestinal disorders. In our study, ‘de novo’ PUD would not have been detected in 4% of patients with a history of investigations
The prevalence of PUD in patients without previous investigation is rather low. In addition, the performance of the non-invasive \textit{H. pylori} tests is only moderate in immigrants. Therefore, a test-and-treat approach in a young chronic dyspeptic population in primary care would lead to an unacceptable high percentage of over-treatment with the risk of side effects and increasing resistance to antibiotics.

In the test-and-endoscope strategy, two aspects are important for a general practitioner: all \textit{H. pylori} positive patients should be detected and false positive diagnoses should be limited.
Since in general practice patients with a negative test result need the reassurance that they do not have an underlying \textit{H. pylori} related PUD, the negative test result must be confident. This means that the ability of the test to identify uninfected patients (the negative predictive value) is most important. This predictive value is dependent on the sensitivity and specificity of the test and prior probability (prevalence) of \textit{H. pylori} infection. The prevalence of \textit{H. pylori} infection among natives and among immigrants are in accordance with the reported prevalence of \textit{H. pylori} infection in the Western world and many different developing
countries. The high prevalence of *H. pylori* infection among immigrants results in poor to moderate negative predictive values of the non-invasive tests for *H. pylori* infection, hence in a poor to moderate ability of these tests to exclude PUD. Therefore, endoscopy will still be needed to exclude PUD in immigrant dyspeptic patients. In natives with low prevalence of *H. pylori* infection all three tests performed well. Among natives, a negative test result lowered the probability of having PUD from 13% to less than three percentage in all three tests with a negative result. Among chronic dyspeptic natives without previous investigation, assessment of *H. pylori* infection by ELISA, our test of choice for detection of *H. pylori* infection, would reduce the endoscopic load with 50% by referring only the *H. pylori* test positive patients for endoscopy.

References


