Chapter III

*Helicobacter pylori* testing in dyspeptic patients suspected of peptic ulcer disease in primary care; development of a simple diagnostic scoring rule

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Abstract

Objectives: To develop an easy applicable diagnostic scoring rule to determine the presence of peptic ulcers in dyspeptic patients in the primary care setting, and to evaluate whether Helicobacter pylori (H pylori) testing has added value to optimal history taking.

Design: Cross-sectional study.

Setting: Patients selected from general practitioner’s offices in the area of Utrecht, the Netherlands.

Participants: 565 primary care patients consulting the general practitioner with dyspeptic complaints lasting at least two weeks.

Main outcome measures: The presence or absence of peptic ulcer. Independent predictors of the presence of peptic ulcer as obtained from history taking and the added value of H pylori testing were quantified using multivariable logistic regression analyses.

Results: A history of peptic ulcer, pain on an empty stomach and smoking were strong and independent diagnostic determinants of peptic ulcer disease with odds ratios of 5.5 (95% CI 2.6-11.8), 2.8 (95% CI 1.0-4.0) and 2.0 (95% CI 1.4-6.0), respectively. The ROC area of these determinants together was 0.71. Adding the H pylori test increased the ROC area to only 0.75. However, in a high-risk patient group, identified by means of a simple scoring rule based on history taking, the predictive value for the presence of peptic ulcer increased from 16% to 26% after a positive H pylori test.

Conclusions: In the total group of dyspeptic patients in primary care H pylori testing has no value in addition to history taking in diagnosing peptic ulcer disease. In a subgroup of patients at high risk for having peptic ulcer disease, however, it might be useful to test-and-treat for H pylori infections.
Introduction

Dyspepsia is a common problem. Although the vast majority of patients presenting with dyspepsia in primary care has no organic disease, a small minority of patients suffers from peptic ulceration and would benefit from specific treatment, notably if the ulcer is related to Helicobacter pylori (H pylori) infection. Although the number of H pylori-negative peptic ulcers is increasing in time, the majority is still related to H pylori infection and accounts for significant morbidity and mortality. In view of this, non-invasive test-and-treat policies for H pylori infections have been promoted in order to improve early ulcer detection and treatment in dyspeptic patients. In a recently published systematic review, Moayeddi et al. stated that H pylori eradication is also of modest benefit in patients with non-ulcer dyspepsia. However, (15 non-ulcer dyspepsia patients should receive H pylori eradication therapy to reduce complaints in only one patient) seems too small to promote H pylori test-and-treat strategies for all dyspeptic patients. Furthermore, although a test-and-treat strategy or the alternative strategy of direct endoscopy in all dyspeptic patients may be cost-effective, this cost-effectiveness would be lower in the primary care setting, with its lower prevalence of peptic ulcers. In addition, the strategy involving routine endoscopy would lead to considerable burden to the patients.

Many dyspepsia guidelines, among which those of the Dutch College of General Practitioners, still recommend to restrict H pylori eradication to patients with a proven peptic ulcer. Thus, preselection by general practitioners of dyspeptic patients at increased risk of having peptic ulcer disease based on symptoms and signs remains crucial. So far the performance of such symptom-based diagnostic algorithms predicting the presence of peptic ulcer is rather poor, although the statistical power of most studies was limited. Furthermore, the value of a diagnostic rule combining optimal history taking with additional H pylori testing has not been explored.

Therefore we carried out a diagnostic study to quantify which parameters from history taking independently contribute to determining the presence of peptic ulcer disease in patients with dyspeptic complaints in general practice, and whether H pylori testing provides any added diagnostic value. In addition, we aimed at developing an easy applicable scoring rule to facilitate the diagnosis of peptic ulcer in primary care.
Methods

Population
Data were obtained from three different studies with similar in- and exclusion criteria, performed at our department, all regarding primary care patients with dyspeptic complaints that were referred to open access endoscopy facilities in the greater Utrecht area, between June 1996 and January 2000. Patients were eligible for the present diagnostic study if they had had dyspeptic complaints for at least two weeks before visiting their general practitioner. Excluded were patients who were pregnant or presented with alarm symptoms (i.e. weight loss, anaemia, dysphagia, gastric bleeding, vomiting and previous gastric surgery).

Diagnostic work-up
Using a standard form, the following potential diagnostic determinants were registered by the general practitioners: age, gender, medical history, smoking behaviour, co-morbidity, medication and current complaints and symptoms. Subsequently, in all patients the \textit{H pylori} status was determined with at least one of the following tests: a whole blood test, \textit{BM-Test$^\text{®}$ Helicobacter pylori} (Roche diagnostics, Rotkreuz, Switzerland), an ELISA test, \textit{Pyloriset$^\text{®}$ EIA-G} (Orion diagnostics, Espoo, Finland), and a carbon 13 urea breath test, \textit{Pylobactell$^\text{TM}$} (BSIA/Torbett laboratories, Chatham, United Kingdom). If one of these tests proved to be positive, an individual was considered \textit{H pylori}-infected. Finally, all patients were referred for endoscopy in one of the participating centres to establish a definite diagnosis (reference standard). The study was approved by the Medical Ethics Committee of the University Medical Center, Utrecht and written informed consent was obtained from all participating patients.

Outcome definition
The outcome of the study was the presence or absence of peptic ulcer disease. A peptic ulcer was considered present in case of an endoscopically demonstrated duodenal or gastric ulcer, an erosive gastritis or a duodenitis.

Data analysis
First, the (univariable) association between each potential diagnostic determinant obtained from history taking, and the presence of peptic ulcer disease was quantified using the odds ratio (OR) and 95% confidence interval (95% CI). All determinants with a p-value < 0.25, were then entered together in
Hp diagnostic scoring rule

A multivariable logistic regression model to evaluate which of these was independently associated with the presence of peptic ulcer disease. From this overall model, model reduction was performed by excluding variables with p-values > 0.05 in order to retain a more reduced and simple diagnostic model containing only the strongest determinants of the presence of peptic ulcer disease. Subsequently, this reduced model was extended with the H pylori test result to quantify its added value in predicting the presence or absence of peptic ulcer disease. Of each of the diagnostic models, the reliability (goodness of fit) was assessed using the Hosmer & Lemeshow test and the ability to discriminate between patients with and without peptic ulcer was quantified using the area under the Receiver Operating Characteristic curve (ROC area).

The ROC area is a suitable parameter to summarise the discriminative power of a diagnostic model and can range from 0.5 (no discrimination, like a coin flip) to 1.0 (perfect discrimination). A value of greater or equal to 0.7 is considered to be reasonable and over 0.8 as good. Differences in diagnostic discriminative value between different (reduced and extended) models were estimated by comparison of ROC areas taking into account the correlation between the models as they were based on the same cases.

Subgroup analyses
We analysed the ability to detect peptic ulcer disease for subsets of relevant diagnostic determinants obtained from history taking. Taking into account the independent diagnostic determinants we identified a high-risk and low-risk patient group using the odds ratios of the history model. The (added) value of a non-invasive H pylori test in detecting peptic ulcer disease in these subgroups was assessed by creating two by two tables and computing the Chi-square statistic and the posterior probability of a positive and negative H pylori test.

Results
A total of 612 patients was enrolled in the study. In 565 of these, complete data on medical history, current complaints, and the diagnosis according to endoscopy were available (table 1 and table 2). Of the 565 patients, 38 (6.7%) had a peptic ulcer detected at endoscopy. Of these 38, 22 (58%) peptic ulcers were H pylori-related according to the non-invasive H pylori test.
Table 1  Characteristics of primary care dyspepsia patients with and without peptic ulcer (n=565)

<table>
<thead>
<tr>
<th>characteristic</th>
<th>peptic ulcer (n=38)</th>
<th>no peptic ulcer (n=527)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>age (years)</td>
<td>46.3</td>
<td>45.3</td>
<td>0.67</td>
</tr>
<tr>
<td>male sex</td>
<td>55.3%</td>
<td>46.3%</td>
<td>0.32</td>
</tr>
<tr>
<td>NSAID use</td>
<td>7.1%</td>
<td>20.1%</td>
<td>0.32</td>
</tr>
<tr>
<td>hiatal hernia</td>
<td>2.7%</td>
<td>9.4%</td>
<td>0.24</td>
</tr>
<tr>
<td>pain after meal</td>
<td>39.5%</td>
<td>49.5%</td>
<td>0.24</td>
</tr>
<tr>
<td>obstruction</td>
<td>23.7%</td>
<td>25.2%</td>
<td>0.84</td>
</tr>
<tr>
<td>history of PUD</td>
<td>36.8%</td>
<td>7.6%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>smoking</td>
<td>52.6%</td>
<td>32.2%</td>
<td>0.013</td>
</tr>
<tr>
<td>pain on empty stomach</td>
<td>71.1%</td>
<td>45.0%</td>
<td>0.002</td>
</tr>
<tr>
<td>use of H₂-antagonists</td>
<td>43.2%</td>
<td>36.4%</td>
<td>0.48</td>
</tr>
</tbody>
</table>

PUD = peptic ulcer disease; NSAID = non-steroidal anti-inflammatory drug

Table 2  Endoscopic diagnosis of the 565 individuals presenting with dyspepsia to their general practitioner included in the decision rule

<table>
<thead>
<tr>
<th>Endoscopic diagnosis</th>
<th>number of individuals</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>malignancy of gastrointestinal tract</td>
<td>4</td>
<td>(0.8%)</td>
</tr>
<tr>
<td>gastric ulcer</td>
<td>5</td>
<td>(0.85%)</td>
</tr>
<tr>
<td>duodenal ulcer</td>
<td>33</td>
<td>(5.8%)</td>
</tr>
<tr>
<td>mucosal damage *</td>
<td>214</td>
<td>(37.9%)</td>
</tr>
<tr>
<td>other relevant disease †</td>
<td>5</td>
<td>(0.85%)</td>
</tr>
<tr>
<td>minor disease ‡</td>
<td>179</td>
<td>(31.7%)</td>
</tr>
<tr>
<td>no abnormalities</td>
<td>125</td>
<td>(22.1%)</td>
</tr>
</tbody>
</table>

* Mucosal damage: oesophagitis, bullitis, severe gastritis
† Other relevant disease: achalasia, polyps, Schatzki’s ring, oesophagus varices
‡ Minor disease: hiatal hernia, gastro-oesophageal prolaps, chronic gastritis
Table 3  Relationship between history variables and the presence of peptic ulcer disease in 565 patients presenting with dyspepsia in primary care. Results of univariable and multivariable analyses.

<table>
<thead>
<tr>
<th></th>
<th>unadjusted odds ratio (95% CI)</th>
<th>adjusted odds ratio (95% CI)</th>
<th>adjusted odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>age per year</td>
<td>1.0 (0.9-1.1)</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>NSAID use</td>
<td>0.3 (0.04-2.3)</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>hiatal hernia</td>
<td>0.3 (0.03-1.9)</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>pain after meal</td>
<td>0.6 (0.3-1.2)</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>obstruction</td>
<td>0.9 (0.4-2.0)</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>history of PUD</td>
<td>6.4 (3.1-13.5)</td>
<td>5.5 (2.6-11.8)</td>
<td>4.6 (2.1-10.1)</td>
</tr>
<tr>
<td>smoking</td>
<td>2.2 (1.2-4.3)</td>
<td>2.0 (1.0-4.0)</td>
<td>1.9 (0.9-3.8)</td>
</tr>
<tr>
<td>pain on empty stomach</td>
<td>3.0 (1.5-6.2)</td>
<td>2.8 (1.4-6.0)</td>
<td>2.8 (1.3-5.9)</td>
</tr>
<tr>
<td>non-invasive Hp test</td>
<td>3.1 (1.6-6.0)</td>
<td>*</td>
<td>2.7 (1.4-5.5)</td>
</tr>
</tbody>
</table>

NSAID: non-steroidal anti-inflammatory drug; PUD: peptic ulcer disease; CI: confidence interval  
* not included in multivariable regression analysis.

History of peptic ulcer disease, smoking, pain on empty stomach and the non-invasive *H pylori* test were associated with the presence or absence peptic ulcer disease (table 3) and selected for multivariable analyses. Of these four history variables, only smoking, pain on an empty stomach and history of peptic ulcer disease were independent predictors of peptic ulcer disease (table 3). The ROC area of this history model based on these three history items was 0.71 (95% CI: 0.62-0.81). Adding the non-invasive *H pylori* test to this model increased the ROC area to 0.75 (95% CI: 0.66-0.83, figure 1). This increase was not statistically significant (p=0.46). The goodness-of-fit of both models proved to be sufficient. Although the *H pylori* test was independently associated with the presence or absence of peptic ulcer disease in the total patient group, as indicated by the odds ratios with 95% confidence interval in table 3, it did not contribute to a better discrimination beyond history taking, as indicated by the small increase in ROC area.

Subsequently, the value of *H pylori* testing in subgroups of patients with high- or low-risk of peptic ulcer disease, based on history taking, was estimated.
Figure 1 ROC curves deduced from multivariable logistic regression analyses including the three diagnostic determinants (history of peptic ulcer, smoking and pain on empty stomach) \textit{without or with} additional non-invasive $H$ \textit{pylori} testing (n=565).

AUC 1: area under the curve of the diagnostic function including the 3 diagnostic determinants from patient history: 0.71 (SE: 0.05)
AUC 2: area under the curve of the diagnostic function including the 3 diagnostic determinants and a non-invasive $H$ \textit{pylori} test: 0.75 (SE: 0.05)

Using the odds ratios in table 3 a scoring rule was developed, including history of PUD (weight=2), smoking and pain on empty stomach (both weight=1). The high-risk group was defined as a score of 2 or higher and the low-risk group as <2. Accordingly, 135 high- and 430 low-risk patients were identified. The a priori probability (prevalence) of peptic ulcer disease in the high-risk group was 16\% (22/135) and only 4\% (16/430) in the low-risk group (table 4). In the
Association between the result of non-invasive \textit{H pylori} testing and the presence of peptic ulcer disease in dyspeptic patients in primary care (n=565). Patients were categorised as being at a high- or low risk of peptic ulcer disease according to a scoring rule, based on history taking.

<table>
<thead>
<tr>
<th></th>
<th>high-risk$^\dagger$</th>
<th>low-risk$^\ddagger$</th>
<th>total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ulcer+</td>
<td>Ulcer-</td>
<td>Ulcer+</td>
</tr>
<tr>
<td>\textit{H pylori}+</td>
<td>14</td>
<td>40</td>
<td>8</td>
</tr>
<tr>
<td>\textit{H pylori}-</td>
<td>8</td>
<td>73</td>
<td>8</td>
</tr>
<tr>
<td>Total</td>
<td>22</td>
<td>113</td>
<td>16</td>
</tr>
</tbody>
</table>

$^\dagger$ High-risk group (2 or more points according to the scoring rule) contains the following individuals:
- history of peptic ulcer or
- smoking and pain before the meal or
- history of peptic ulcer, smoking and pain before the meal

$^\ddagger$ Low-risk group contains all individuals not included in the high-risk group

Ulcer+: peptic ulcer
Ulcer-: no peptic ulcer
\textit{H pylori}+: \textit{H pylori} infection according to non-invasive Hp test
\textit{H pylori}-: no \textit{H pylori} infection according to non-invasive Hp test

High-risk group a positive \textit{H pylori} test result increased the prior probability from 16% to a posterior probability of 26% (14/54), i.e. the positive predictive value. A negative test result decreased the probability to 10% (8/81), i.e. the negative predictive value. In the low-risk group the positive and negative predictive value were 7% and 2.5%, respectively.

Discussion

Our study indicates that \textit{H pylori} testing in all patients with dyspepsia in primary care has no value in addition to history taking in diagnosing peptic ulcer disease. However, in a subgroup of patients at high risk of peptic ulcer disease (based on our scoring rule including the three history variables smoking, pain on empty stomach and history of peptic ulcer) a non-invasive \textit{H}}
 pylori test provides additional diagnostic information as indicated by relevant post-test changes in the probability of the presence or absence of peptic ulcer disease.

Applying a so called test-and-treat strategy (i.e. perform a non-invasive H pylori test and initiate eradication therapy in those with a positive H pylori test and provide acid suppressive therapy to the remaining patients) in all patients presenting with dyspepsia in primary care, would lead to prescription of eradication therapy in as much as 31% of all patients, while in only 12.6% of these a peptic ulcer is present. This would exhibit unnecessary costs and potential side effects, including the development of resistance to antibiotics. Restriction of non-invasive H pylori testing to patients preselected as high-risk patients according to our scoring rule based on history variables, seems a more appropriate recommendation. In these individuals the risk of having a peptic ulcer is considerable (16.3%) and peptic ulcer treatment could be initiated without prior gastroscopy. A H pylori test-and-treat strategy in these patients would result in prescription of eradication therapy in only 9.6% of all dyspeptic patients, while in 26% of these a peptic ulcer is present. In this high-risk group the ratio of patients “correctly” (those with peptic ulcer) or “incorrectly” (those without peptic ulcer) receiving eradication therapy is reasonable (1:3), while the corresponding ratio in the total group of dyspeptic patients presenting in primary care is 1:7.

Recently Moayyedi et al reported in a systematic review that an early H pylori test-and-treat strategy might be cost-effective in non-ulcer dyspepsia and Lassen et al. concluded from their own research that a test-and-treat strategy is as efficient and safe as prompt endoscopy for the management of dyspeptic patients in primary care.\textsuperscript{11-12} We believe that both research groups failed to recognise the benefit of preselection of patients by adequate history taking before H pylori testing is considered and that implementation of their recommendations would provoke many unjustified eradication therapies.

Several limitations of our study need to be addressed. Our analyses were based on data from three previous studies by our group. As a result, different H pylori tests were used with varying test characteristics. This might have accounted for an underestimation of H pylori infected individuals and H pylori-related peptic ulcers.\textsuperscript{28-29} This is confirmed by the fact that the H pylori infection rate found at endoscopy in our patients (using biopsy specimens) was higher (41%) than the infection rate found with non-invasive tests (31%). By using more reliable non-
invasive test methods a higher number of *H pylori*-related peptic ulcers would have been detected, which would have improved the performance of our scoring rule. The scoring rule we developed obviously awaits prospective evaluation in other primary care populations, in particular since the performance of the scoring rule critically depends on the prevalence of *H pylori* infection and peptic ulcer disease. Currently, the rule is being tested in several general practitioner groups in the Netherlands.

We conclude that only for patients at high risk of having peptic ulcer disease, adding *H pylori* infection testing might be useful. It will avoid endoscopies in some, and lead to a more accurate treatment of peptic ulcer disease in most subjects.

**Acknowledgements**

We wish to thank Roche Diagnostics (Almere, the Netherlands) and the Imphos/Zambon group (Amersfoort, the Netherlands) for supplying the whole blood tests and ELISAs and Peter Zuithoff MSc, for statistical advice.
References


