Helicobacter pylori in the critically ill patient
van der Voort, P.H.J.

Citation for published version (APA):
van der Voort, P. H. J. (1999). Helicobacter pylori in the critically ill patient

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: http://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.
DETECTION OF HELICOBACTER PYLORI IN MECHANICALLY VENTILATED PATIENTS: THE LARA-13C-UREA BREATH TEST AND SEROLOGY.

P.H.J. van der Voort1,2, R.W.M. van der Hulst3,4, D.F. Zandstra2, A. van der Ende5, A.A.M. Geraedts6, and G.N.J. Tytgat6

1 Dept. of Intensive Care, Medisch Centrum Leeuwarden, Leeuwarden
2 Dept. of Intensive Care, Onze Lieve Vrouwe Gasthuis, Amsterdam
3 Dept. of Internal Medicine, Kennemer Gasthuis, Haarlem
4 Dept. of Gastroenterology and hepatology, Academic Medical Center, Amsterdam
5 Dept. of Microbiology, Academic Medical Center, Amsterdam
6 Dept. of Gastroenterology and hepatology, Onze Lieve Vrouwe Gasthuis, Amsterdam

Clinical Intensive Care 1999;10:91-95
Abstract

Objective: Of critically ill patients in intensive care 0.6 to 9% will develop ulcerations in the stomach with overt bleeding. Recently the presence of antibodies against *Helicobacter pylori* was found to be associated with an increased rate of upper gastro-intestinal bleeding in critically ill patients. The exact role of *H. pylori* in the pathophysiology of stress ulceration is not known but is currently investigated without prior validation of diagnostic tests in this specific patient population. Therefore we studied the accuracy of the commonly used diagnostic tests for *H. pylori* in mechanically ventilated patients.

Design: Prospective study comparing the ambulant to the mechanically ventilated LARA-¹³C-urea breath test in the same patients. Also antibodies against *H. pylori* are detected in both ambulant and mechanically ventilated state.

Setting: A 20 bed mixed medical, surgical and cardio-surgical ICU in a major teaching hospital in the centre of Amsterdam.

Subjects: One hundred consecutive patients admitted for elective cardiac surgery were included.

Interventions: A pre-operative ambulant Laser Assisted Ratio Analyser ¹³C-urea breath test (LARA-¹³C-UBT) was performed to detect *H. pylori* and was used as the “gold standard”. Post-operatively a second LARA-¹³C-UBT was performed in the same patient at the intensive care unit during mechanical ventilation. Serum antibodies against *H. pylori* were also determined in ambulant and mechanically ventilated state.

Endpoints: The LARA-¹³C-UBT and serology in mechanically ventilated state were compared to the LARA-¹³C-UBT and serology in ambulant state.

Measurements and main results: The LARA-¹³C-urea breath test during mechanical ventilation reached a sensitivity of 94% and a specificity of 92% compared to the ambulant test. Positive predictive value was 88% and negative predictive value was 96%. The mean serum *H. pylori* antibody titre of all patients decreased from 4.09 U/l to 3.34 U/l (16%) postoperatively (p<0.0001) in all probability due to blood loss and haemodilution which resulted in three false negative tests post-operatively. Six false positive pre-operative serological tests could be related to antibiotic use in the previous year. Sensitivity of post-operative serology was 72% and specificity 70%.

Conclusions: The LARA-¹³C-urea breath test is an accurate and non-invasive method to detect *H. pylori* in mechanically ventilated patients and is easy to carry out. Serum antibody testing is less accurate due to blood loss, haemodilution and previous antibiotic use and should therefore be interpreted with caution.
Helicobacter pylori in the critically ill patient

**Introduction**

In the western world 20 to 60% of the population, depending on age and geographical area, are infected with *Helicobacter pylori*. The role of *H. pylori* in duodenal and gastric ulcer disease and their bleeding complication is well-known. Endoscopic studies show that stress ulceration occurs in 20% of patients in intensive care. Bleeding related to stress ulceration occurs in 0.6% to 9% of patients in intensive care though usually not confirmed by endoscopy. Major independent risk factors for these upper gastrointestinal bleeding are mechanical ventilation and clotting disorders. The role of *H. pylori* in the pathophysiology of stress ulceration and related bleeding in intensive care patients is not well known. Antibodies against *H. pylori* are more often found in patients with upper gastro-intestinal tract bleeding stress ulcers, suggesting that *H. pylori* plays a causal role.

Serological assessment is the easiest way to detect *H. pylori* in critically ill patients. But it is known that antibody measurement has a rather low accuracy and elevated titres persist even after successful eradication therefore not always indicating present *H. pylori* infection. In ambulant patients a $^{13}$C-urea breath test is an accurate method to detect current *H. pylori* infection. The Laser Assisted Ratio Analyser (LARA)-$^{13}$C-urea breath test uses small volume breath samples that can be collected at the bedside and can be stored for at least 2-3 months before analysis.

In the present study the accuracy of the LARA-$^{13}$C-urea breath test and serology for the detection of *H. pylori* was evaluated in patients before and after admittance to the intensive care unit for elective cardiac surgery, in order to have a reliable and convenient tool to perform further studies to the relation between stress-ulceration and *H. pylori* infection.

**Methods**

**Patients**

One hundred consecutive patients admitted for elective cardiac surgery were included in the study after written informed consent was obtained. The study was approved by the local ethical and scientific committees. Inclusion criteria were admission to hospital for elective cardiac surgery and mental and physical ability to perform the LARA-$^{13}$C-urea breath test. Exclusion criteria were previous gastrectomy, current use of antibiotics, and pregnancy.

**Study design**

One to three days before cardiac surgery, and after an overnight fast, patients performed the LARA-$^{13}$C-urea breath test. Serology was added as
an additional diagnostic test in the second half of the study. Blood samples were taken for serological detection of antibodies against *H. pylori* on the same day as the LARA-\(^{13}\)C-urea breath test. Patients were intubated shortly before cardiac surgery. Immediately after cardiac surgery patients were admitted to the intensive care unit. Within one hour after admission to the intensive care unit a LARA-\(^{13}\)C-urea breath test was performed during mechanical ventilation. A second blood sample was drawn concurrently for serological assessment of antibodies against *H. pylori*. In each patient the LARA-\(^{13}\)C-urea breath test and serology results in the ambulant condition were compared to the test results in mechanically ventilated condition.

**The Laser Assisted Ratio Analyser-\(^{13}\)C-urea breath test**

The test (Alimenterics, New Jersey, USA) is based on the urease production of *H. pylori*. Non-radioactive \(^{13}\)C labelled urea will be degraded to \(^{13}\)CO\(_2\). The laser assisted ratio analyser determines the ratio of \(^{13}\)CO\(_2\) to \(^{12}\)CO\(_2\) in the exhaled air. A ratio of more than 6.1 delta units is considered as a positive test result. In ambulant patients the LARA-\(^{13}\)C-urea breath test indicates the presence of *H. pylori* with a sensitivity of 93% and a specificity of 93%\(^a\). First a base-line exhaled breath is captured in a breath collector. A test meal (237 ml Ensure) is then ingested, followed immediately by 100 mg of \(^{13}\)C-labelled urea in 50 ml sterile water. Thirty and 60 min after ingestion of the urea a second and third breath sample is collected. When the exhaled air in one of the breath collectors is not collected properly, a “low CO\(_2\)” error results. During mechanical ventilation the breath collector was placed between the endotracheal tube and a self-inflating ventilation bag using a swivel and a connecting piece (figure 1). After inflating the lungs with the ventilation bag a passive exhalation takes place. At the end of this exhalation the breath collector is closed and alveolar air is captured in the collector. The urea breath test was performed without test meal during mechanical ventilation assuming reduced gastric emptying in critically ill patients\(^b\) and the water containing urea was given through a naso-gastric tube. Storage of the breath collectors is possible for at least two months and can be mailed to the analysing laboratory.

**Serology**

Serum IgG antibodies against *H. pylori* were quantitative detected in blood samples before and after cardiac surgery by enzyme linked immunosorbent assay (HM-CAP™ ELISA Enteric Products, Inc. Stony Brook, NY). A cut off level of 1.8 U/l was used. Sensitivity of this test compared to urea breath test was 98.7%, specificity and positive predicting value were both 100% and negative predicting value was 98.6%\(^10\).
**Helicobacter pylori** in the critically ill patient

**Statistical analysis**

Sensitivity, specificity, negative and positive predicting values and likelihood ratio of the mechanically ventilated LARA-\(^{13}\)C-urea breath test to detect *H. pylori* were calculated with *H. pylori* status determined by the LARA-\(^{13}\)C-urea breath test in the ambulant state. T-test was used to compare means of antibody titre for paired serological samples. A two tailed p value <0.05 was considered to be statistically significant.

**Results**

**LARA-\(^{13}\)C-urea breath test**

In two of the 100 patients the breath samples could not be evaluated because of technical failure of the breath sample analyser. One patient was excluded because of low CO\(_2\) in the ambulant breath test, 14 were excluded because of low CO\(_2\) in the mechanical ventilated urea breath test and one because of low CO\(_2\) in both urea breath tests. *H. pylori* was detected in 36 of 96 patients with adequately performed ambulant breath tests (38%) and in 35 of 83 patients with well performed breath test during mechanical ventilation (42%). In 82 patients both tests were evaluated (table 1). Thirty of these 82 patients had a *H. pylori* positive LARA-\(^{13}\)C-urea breath test result in both tests and in 46 patients a negative test result in both tests was found. The mechanically ventilated test revealed a false positive test in 4 and a false negative test in 2 patients. Therefore the sensitivity of the mechanically ventilated test is 94% and the specificity 92% (table 2).

<table>
<thead>
<tr>
<th>N=82</th>
<th>Amb-UBT positive</th>
<th>Amb-UBT negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>MV-UBT positive</td>
<td>30</td>
<td>2</td>
</tr>
<tr>
<td>MV-UBT negative</td>
<td>4</td>
<td>46</td>
</tr>
</tbody>
</table>

Amb-UBT, ambulant urea breath test; MV-UBT, mechanically ventilated urea breath test
Serology

In 49 patients blood samples were drawn both pre- and post-operatively. Serology was positive in 32/49 (65%) patients before cardiac surgery and in 29/49 (59%) patients afterwards (p=0.11). The mean titres of antibodies were 4.09 U/l (range 0.17 - 8.16 U/l, SD 2.65) pre-operative and 3.34 U/l (range 0.13 - 7.85 U/l, SD 2.43) post-operative. This decline of 0.94 U/l (16%) was significant (p < 0.0001) and resulted in conversion from a positive test result into a false negative test result in 3 patients. These 3 patients had a pre-operative test result with a mean titre of 2.56 U/l and a post-operative test result with a mean titre of 1.39 U/l.

LARA-13C-urea breath test and serology

In 41 patients both breath samples as well as both blood samples were evaluable. In 16 patients pre-operative serology and breath sample both detected H. pylori. In 15 patients both tests were negative for the detection of H. pylori. Sensitivity and specificity rates are shown in table 2 using the ambulant urea breath test as the "gold standard". A positive pre-operative serological test with negative breath test was found in 10 patients. Six of these 10 patients were treated with antibiotics for various infections in the previous year. One patient ingested omeprazol. Excluding these 7 patients the pre-operative serologic specificity improved from 60 to 83% and the post-operative serologic specificity improved from 72 to 85%.

Discussion

Stress ulceration in critically ill patients is thought to occur due to mucosal ischaemia and gastric mucosal breakdown. It is hypothesised that chronic gastritis with H. pylori can pre-dispose for this mucosal damage. A potential role for H. pylori in the pathophysiology of stress ulceration in mechanically ventilated critically ill patients has been suggested in preliminary reports but needs to be determined in clinical studies. Therefore detection of H. pylori in these patients needs to be validated. In ambulant patients biopsy based detection by culture and histopathology is thought to be the most appropriate way to detect H. pylori and is usually considered the gold standard. However, upper gastro-intestinal endoscopy is an invasive technique that is expensive and unsuitable for screening. Moreover, even with this detection technique sampling error may occur especially in case of atrophy and proton pomp inhibitor use, owing to the patchy distribution of the micro-organism. Serological detection is more easy to perform but accuracy is still insufficient and false positive tests easily occur especially after previous antibiotic treatment. In contrast, the LARA-13C-urea breath test is easy to use in
Table 2
Helicobacter pylori detection rates of MV-UBT and pre- and postoperative serology compared to the ambulant LARA-¹³C-urea breath test.

<table>
<thead>
<tr>
<th>method of detection</th>
<th>No.</th>
<th>No.</th>
<th>Sens.</th>
<th>Spec.</th>
<th>PPV</th>
<th>NPV</th>
<th>LR(+)</th>
<th>LR(-)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MV-UBT (N=82)</td>
<td>32</td>
<td>50</td>
<td>94</td>
<td>92</td>
<td>88</td>
<td>96</td>
<td>11.7</td>
<td>0.068</td>
</tr>
<tr>
<td>pre-op ELISA (N=41)</td>
<td>26</td>
<td>15</td>
<td>100</td>
<td>60</td>
<td>62</td>
<td>100</td>
<td>2.5</td>
<td>0</td>
</tr>
<tr>
<td>post-op ELISA (N=41)</td>
<td>23</td>
<td>18</td>
<td>100</td>
<td>72</td>
<td>70</td>
<td>100</td>
<td>3.57</td>
<td>0</td>
</tr>
</tbody>
</table>

Hp, Helicobacter pylori; UBT, urea breath test; MV, mechanically ventilated; LARA, Laser Assisted Ratio Analyser; pre-op, pre-operative; post-op, post-operative; PPV, positive predicting value; NPV, negative predicting value; LR, likelihood ratio; ELISA, Enzyme linked immunosorbent assay.

Figure 1
Position of the LARA breath sample collector. From left to right: tube, connecting piece, breath sample collector, connecting piece, self-inflating ventilation bag.
ambulant patients and reveals high sensitivity and specificity. In the present study it is proven for the first time that even in the mechanically ventilated state the LARA-\(^{13}\)C urea breath test is highly accurate. The advantage of the LARA-\(^{13}\)C urea breath test is that breath collection occurs during one single exhalation in a breath collector that is easily placed in between a self-inflating ventilation bag and the endotracheal tube through which mechanical ventilation takes place. In ambulant patients breath is collected during active exhalation. Sedated and mechanically ventilated patients exhale passively and may therefore produce more often breath samples containing low CO\(_2\). Therefore we were not able to evaluate 15/98 tests in mechanically ventilated patients after cardiac surgery (15%) while only 2/98 of the tests in ambulant patients could not be evaluated (2%). An other study including unselected patients with prolonged mechanical ventilation showed roughly the same amount of breath tests that were unable to evaluate. An additional reason may be the inexperience of the intensive care nurses with this new technique as later in the study, due to a learning curve, the breath collectors low CO\(_2\) less often. Breath tests are compared within each patient and therefore the non-eligible tests are not encountered in the analysis. We used a self-inflating ventilation bag without additional oxygen because a high oxygen content of the inhaled air appeared to disturb the LARA analyser. The sensitivity and specificity of the LARA-\(^{13}\)C-urea breath test in ambulant patients were 93% and 93% respectively using culture or histology as the "gold standard". In the present study similar sensitivity and specificity of 94% and 92% respectively, were obtained in mechanically ventilated patients using the ambulant LARA-\(^{13}\)C-urea breath test as the "gold standard". We could use the ambulant LARA-\(^{13}\)C-urea breath test as the "gold standard" because the test result is independent of the mechanically ventilated LARA-\(^{13}\)C-urea breath test and each mechanically ventilated LARA-\(^{13}\)C-urea breath test was compared to the ambulant test in the same patient. Serology was assessed before and after cardiac surgery in the last 49 included patients. The 16% reduction in antibody titre occurred probably because of blood loss and infusion of crystalloid and albumin during surgery. The exact amount of haemodilution in these patients could not be assessed accurately by the volume of the infusion fluid because fluid shifts to and from the interstitial space result in unpredictable changes in intravascular volume. Detection of \textit{H. pylori} antibodies in serum after blood loss or haemodilution led to 7% (3/41) false negative results and therefore underestimation of \textit{H. pylori} prevalence. Many intensive care patients have an extensive medical history with antibiotic use. This previous use of antibiotics led to 15% (6/41) false positive serological test results in this study. Peterson et al. also found that antibiotic monotherapy can lead to eradication of \textit{H. pylori} and therefo-
The prevalence of stress ulceration in critically ill patients detected by upper gastrointestinal endoscopy is 20%\textsuperscript{14}. The prevalence of stress ulcer related bleeding differs from 0.6% to 9%.\textsuperscript{5,7} The aetiology of stress ulceration and related bleeding is complex. It is generally accepted that mucosal ischaemia is the most important factor that leads to stress ulceration\textsuperscript{15}. Clotting disorders and mechanical ventilation are known to be independent risk factors\textsuperscript{6}. Recently a higher titre of IgA antibodies against \textit{H. pylori} was detected in critically ill patients with upper gastro-intestinal bleeding compared to patients without bleeding (odds ratio 1.76, 95% CI 1.08 - 2.87)\textsuperscript{7}. The validity of these results can be questioned as the present study shows that previous antibiotic use led to 15% false positive serologic test results and haemodilution, which often happens due to infusion of resuscitation fluids, led to 7% false negative serologic test results. In contrast, the LARA-\textsuperscript{13}C-urea breath test is not influenced by these possible flaws and is proven to be an accurate test, which is suitable for examining the role of \textit{H. pylori} in stress ulcer formation in mechanically ventilated patients.
References


12. Halm U., Fathollahi F., Thein D., Mohr F.W., Mössner J. *Helicobacter*
Helicobacter pylori in the critically ill patient

