SUPPRESSION OF *Helicobacter pylori* INFECTION IN THE CRITICALLY ILL PATIENT: A CONTRIBUTION TO STRESS ULCER PREVENTION?

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Abstract

Introduction: Helicobacter pylori is known for its causative role in duodenal and gastric ulcer disease. The importance of H. pylori in the formation of stress ulceration in critically ill patients is unknown. We hypothesise that the presence of viable H. pylori may be obligatory for the development of stress ulceration. The aim of the study is to determine prospectively in a cohort of consecutive critically ill patients whether H. pylori infection is suppressed by antibiotic use during intensive care stay and whether this may be advantageous in critically ill patients in preventing stress ulcer related bleeding.

Study design: Prospective observational patient cohort study

Methods: Three-hundred consecutive mechanically ventilated patients are included. H. pylori infection is detected by Laser Assisted Ratio Analyser (LARA)-\(^{13}\)C-urea breath test (UBT) and serology. All patients are treated with selective decontamination of the digestive tract containing cefotaxime 1 g iv. four times daily for 4 days and a mixture of Polymyxin 100 mg, Tobramycin 80 mg and Amphotericin B 500 mg (PTA) four times daily by naso-gastric tube during the complete intensive care stay. A paste containing 2% of the PTA regimen is applied in the mouth four times daily. Other antibiotics are prescribed as needed. Stress ulcer prophylaxis is not prescribed. Endoscopy is performed in case of upper gastro-intestinal bleeding with persisting need of transfusion or with persistent bloody gastric aspirates after correction of coagulation disorders. The predicted mortality is determined by APACHE II, SAPS II, MPM 0 and MPM 24. In addition, the observed mortality is determined.

Results: The prevalence of H. pylori infection on admission is 37.6% as detected by LARA-\(^{13}\)C-urea breath test. This prevalence declines to 7.7% on the third day after admission. All patients with a positive UBT on admission converted to a negative UBT on the 7th day, as a result of the antibiotic treatment. In contrast, conversion from a negative test into a positive test is observed only once. H. pylori prevalence is not related to observed or predicted mortality. However, in patients without detectable antibodies against H. pylori mortality is significantly higher as a result of more severe disease on admission to the intensive care. Stress ulcer related bleeding occurs in 1.0% (3/300) of the patients. These three patients with stress ulcer related bleeding were not infected with H. pylori on admission or at the time of bleeding.

Conclusions: Short term systemic antibiotic treatment with prolonged topical antibiotic treatment for gut decontamination results in rapid suppression of H. pylori infection monitored by LARA-\(^{13}\)C-urea breath test. The virtual absence of stress ulcer related bleeding may be related to the prevention of...
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H. pylori associated stress lesions by effective suppression of this microorganism but further studies are warranted to test this hypothesis.

Introduction

Stress ulcer related bleeding in critically ill patients shows a decreasing incidence but still occurs in 1 - 9% of patients in the intensive care unit [1-3]. Mucosal ischaemia and endotoxaemia predispose to mucosal damage with subsequent erosions and ulcer formation. Ulceration of the upper gastro-intestinal tract that is not stress related is strongly associated with the presence of Helicobacter pylori once NSAID's and aspirin use are excluded [4]. It has previously been hypothesised that H. pylori plays also a role in the pathogenesis of stress ulcerations in the critically ill patient [5,6] but so far this has not been supported by conclusive studies. In a recent study [3] higher IgA antibody levels against H. pylori were found in critically ill patients with upper gastrointestinal bleeding as compared to patients without gastrointestinal bleeding. Serological detection of H. pylori however, does not necessarily indicate the presence of actual H. pylori infection. In contrast, the Laser Assisted Ratio Analyser (LARA)-13C-urea breath test is an easy and reliable method to detect ongoing H. pylori infection [7]. This test was recently validated to detect active H. pylori infection in mechanically ventilated patients during their treatment on the intensive care unit [8]. If H. pylori plays a pathogenetic role in the formation of stress ulceration, viable H. pylori should be present in the stomach of affected patients when stress ulceration develops. Previously we found a low incidence of stress ulcer related bleeding in a cohort of critically ill patients who were treated with selective gut decontamination [9]. Antibiotics used for gut decontamination may affect H. pylori infection. If H. pylori plays a role in the formation of stress ulceration, the low incidence of stress ulcers and related bleeding found in our previous study [9], may to some extend be related to the suppression of H. pylori by gut decontamination. Therefore this prospective observational patient cohort study determines both the presence of active H. pylori infection and the incidence of stress ulcer related bleeding during intensive care stay whilst being treated with gut decontamination.

Methods

Patients

Consecutive patients were included from December 1997 until September 1998. Patients admitted to the intensive care unit for emergency reasons with an expected stay of at least 24 hours and requiring mechanical ventila-
tion were included in the study. Informed consent was obtained from the nearest relatives. Exclusion criteria were admission after uncomplicated elective surgery, gastric perforation and gastric surgery within 24 hours before admission. Patients with pulmonary oedema requiring positive end expiratory pressure (PEEP) ventilation with pressures of 15 cm H$_2$O or more were excluded because of inability to perform an urea breath test in this situation. The local ethical and scientific committees approved the study. Scoring systems for determination of severity of disease (APACHE II, SAPS, MPM 0 and MPM 24) were calculated in the first 24 hours after admission. A patient was categorised as a surgical patient when an operation was performed within 7 days prior to admission to the intensive care. A patient was categorised as ‘cardiac surgery’ when the cardiac surgery was performed within 7 days prior to admission. All other patients were categorised as medical patients.

**Standard treatment**

All patients were mechanically ventilated and received a nasogastric tube. After testing for *H. pylori*, antibiotic prophylaxis for selective decontamination of the digestive tract was administered to all patients using cefotaxime 1000 mg qid intravenously for four days and a mixture of Polymyxin 100 mg, Tobramycin 80 mg and Amphotericin B 500 mg qid (PTA) instilled by nasogastric tube during intensive care stay. In addition a 2% PTA containing solution in orabase paste was administered to the oropharynx qid during intensive care stay. In case of a bacterial infection unsusceptible these antibiotics, other antibiotics were given as indicated. Stress ulcer prophylaxis was not routinely prescribed but histamine$_2$-receptor antagonists or proton pump inhibitors were continued only in patients who used this medication for previously proven ulcer disease or gastro-oesophageal reflux disease (GERD). All patients were treated with dopamine at least 2 mg/kg/min and with at least one of the vasodilators ketanserin, nitro-glycerine or enoximone. On admission to the intensive care unit all patients received a single dose of 100 mg dexamethason intravenously. In case of pneumonia or persistent inflammatory response prednisolon therapy was maintained for 7 days with tapering of the dosage.

**Detection of *H. pylori***

The Laser Assisted Ratio Analyser (LARA)-$^{13}$C-urea breath test (Alimenterics Inc., New Jersey, USA) was used to detect current *H. pylori* infection as previously described [8]. The test is performed by collecting exhaled air at base line, 30 and 60 minutes after administering 100 mg of $^{13}$C-urea through the nasogastric tube. The LARA determines the ratio of
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$^{13}\text{C}_2$ to $^{12}\text{C}_2$ in the exhaled air. A ratio of more than 6.1 delta units in either the 30 minutes or the 60 minutes breath sample was considered a positive test result indicating the presence of \textit{H. pylori}. We validated this test previously in mechanically ventilated patients [8].

Serum IgG antibodies against \textit{H. pylori} were quantitatively determined 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 [10].

\textbf{Follow up}

Both LARA-$^{13}$C-urea breath test and serology were performed within one hour after the institution of mechanical ventilation and were repeated after 3 days and every 7th day after admission until discharge from the intensive care unit.

\textbf{Upper gastrointestinal endoscopy}

Gastric aspirates were inspected at least four times daily for the presence of blood but more frequently in case of hypotension or drop in haemoglobin level. Upper gastrointestinal bleeding was diagnosed when bloody material was aspirated from the stomach. Coagulopathy was immediately corrected after the detection of upper gastrointestinal bleeding by infusion of protamine, fresh frozen plasma or thrombocytes according to protocol and to the decision of the attending physician. The patients were endoscoped when a persisting need of blood transfusion occurred or when bloody gastric aspirates persisted after correction of coagulopathy.

\textbf{Statistical analysis}

A comparison of means was performed using the T-test in case of normal distribution. In case of skewed distribution a log transformation was performed to reach a normal distribution. A comparison of categorical data between groups was performed by the Chi Square test. The statistical analysis was made with the SPSS statistical analyser release 8.0.0 (SPSS inc., USA, 1997). A p value < 0.05 was considered to be statistically significant.

\textbf{Results}

Three hundred consecutive patients were included in the study. Of the included patients 60% were male, 40% were female. The mean age was 65.3 years (range 16-92, SD 15.3). 64% were medical patients, 20% were admitted after cardiac surgery because of complications necessitating prolonged intensive care treatment and 16% were surgical patients. Table 1 summarises the APACHE II, SAPS II, MPM 0 and MPM 24 scores and associated
mortality prediction. Patients with positive *H. pylori* serology on admission had a lower predicted mortality in all scoring systems compared to patients with negative serology. These differences were significant for APACHE II score and APACHE II predicted mortality and for SAPS II.

The LARA-\(^{13}\)C-urea breath test was performed in all patients. Fifty-eight of the included patients were not eligible because the LARA-\(^{13}\)C-urea breath test was unable to be processed: in 39 patients the LARA-\(^{13}\)C-urea breath test produced a low CO\(_2\) result because of incorrect breath sample collection and in 19 patients the breath sample could not be analysed by the LARA machine because of interference with a high fraction of oxygen used for mechanical ventilation which was necessary because of severe respiratory failure. In the remaining 242 patients the prevalence of active *H. pylori* infection determined by a positive UBT result was 37.6%. Repeated tests were performed on the 3\(^{rd}\) and every 7\(^{th}\) day after admission when patients were still being treated in the intensive care unit. Results are shown in table 2. One hundred and four out of 242 patients were discharged from the intensive care within 3 days. For the other 138 patients a repeated breath test was done. Thirty-four of these repeated tests could not be processed. Of the remaining 104, 8 were positive for the presence of *H. pylori* after 3 days (7.7%). Thus *H. pylori* infection rate fell from 37.6% to 7.7% in 3 days. Of the 104 patients with a repeated test on the third day, 39 had a positive UBT on admission. Thirty-two (82%) of them converted into a negative test due to 3 days of intensive care treatment, indicating suppression of *H. pylori* infection. *H. pylori* infection could not be detected in any patient after 7 days of intensive care treatment. One patient with a negative UBT on admission converted to a positive test result after 3 days. After the third day this patient was discharged to another hospital. Otherwise all other negative tests remained negative when assessed during intensive care treatment.

The presence of anti-*Helicobacter* antibodies was assessed in the sera from 290 out of the 300 included patients. From the other 10 patients blood samples for serology were not drawn because of various reasons. *H. pylori* serology was positive in 57.7% of the 290 patients. The higher initial sero-prevalence of *H. pylori* compared to LARA-\(^{13}\)C-urea breath test was thought to be due to antibiotic use prior to intensive care admission as fifty percent of all patients appeared to have used antibiotics within one week prior to intensive care admission. In those patients with prior anti-microbial therapy, urea breath test was positive in only 19.4% of patients. In patients not treated with antibiotics the LARA-\(^{13}\)C-urea breath test was positive in 47% of patients. Repeated serological tests were drawn on the 3\(^{rd}\) and every 7\(^{th}\) day. The mean *H. pylori* antibody titre declined from 3.19 to 1.84 U/l during intensive
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care treatment (table 3), indicating H. pylori suppression during intensive
care treatment.
Upper gastrointestinal endoscopy was performed in 4 out of 300 patients
(1.3%) because of the presence of bloody gastric aspirates at day 3, 9, 14
and 18 respectively. In these 4 patients endoscopy revealed duodenal ulcer
in one, multiple superficial ulcers in stomach and duodenum in two, and
esophageal varices in one patient. Therefore in 3 out of 300 patients (1.0%)
overt gastro-intestinal bleeding occurred due to (stress)ulceration. These 3
patients all had a negative H. pylori LARA-13C-urea breath test on admission,
one patient had a positive serological test on admission. At the time of blee­
ding all patients had a negative urea breath test.

Table 1

Scoring systems for severity of disease with predicted and observed morta­
ity rates. SD; standard deviation. APACHE; Acute Physiology And Chronic
Health Evaluation. SAPS II; Simplified Acute Physiology Score. MPM;
Mortality Probability Model. UBT; urea breath test, Hp; Helicobacter pylori.

<table>
<thead>
<tr>
<th></th>
<th>all patients</th>
<th>Hp UBT positive (SD)</th>
<th>Hp UBT negative (SD)</th>
<th>Hp Serology positive (SD)</th>
<th>Hp Serology negative (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (yrs)</td>
<td>65</td>
<td>70</td>
<td>65</td>
<td>67</td>
<td>63</td>
</tr>
<tr>
<td>M/F (%)</td>
<td>58/42</td>
<td>60/40</td>
<td>60/40</td>
<td>62/38</td>
<td>55.5/44.5</td>
</tr>
<tr>
<td>APACHE II</td>
<td>24.1 (8.2)</td>
<td>23.6 (6.2)</td>
<td>23.9 (8.8)</td>
<td>23.1 (7.3)</td>
<td>25.6 (9.1)</td>
</tr>
<tr>
<td>APACHE II predicted mortality</td>
<td>0.45 (0.28)</td>
<td>0.44 (0.25)</td>
<td>0.45 (0.28)</td>
<td>0.41 (0.27)</td>
<td>0.50 (0.29)</td>
</tr>
<tr>
<td>SAPS II</td>
<td>52.2 (18.1)</td>
<td>52.5 (18.0)</td>
<td>51.6 (17.5)</td>
<td>50.0 (18.0)</td>
<td>55.1 (20.3)</td>
</tr>
<tr>
<td>SAPS II predicted mortality</td>
<td>0.49 (0.29)</td>
<td>0.50 (0.26)</td>
<td>0.48 (0.28)</td>
<td>0.47 (0.28)</td>
<td>0.52 (0.30)</td>
</tr>
<tr>
<td>MPM</td>
<td>0.43 (0.28)</td>
<td>0.47 (0.26)</td>
<td>0.42 (0.28)</td>
<td>0.42 (0.27)</td>
<td>0.46 (0.29)</td>
</tr>
<tr>
<td>MPM 24</td>
<td>0.48 (0.24)</td>
<td>0.50 (0.23)</td>
<td>0.47 (0.23)</td>
<td>0.47 (0.23)</td>
<td>0.51 (0.24)</td>
</tr>
<tr>
<td>Observed mortality</td>
<td>0.33</td>
<td>0.320</td>
<td>0.326</td>
<td>0.420</td>
<td>0.276</td>
</tr>
</tbody>
</table>
Table 2

LARA-\textsubscript{13}C-urea breath test results on admission and during follow up from 300 included patients. UAP; unable to process. Pos: \textit{H. pylori} infection present. Neg: \textit{H. pylori} infection not present.

<table>
<thead>
<tr>
<th>Duration</th>
<th>Pos</th>
<th>UAP</th>
<th>Neg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Admission (N=300)</td>
<td>91</td>
<td>58</td>
<td>151</td>
</tr>
<tr>
<td>3 days (N=138)</td>
<td>8</td>
<td>34</td>
<td>96</td>
</tr>
<tr>
<td>7 days (N=57)</td>
<td>0</td>
<td>17</td>
<td>40</td>
</tr>
<tr>
<td>14 days (N=23)</td>
<td>0</td>
<td>3</td>
<td>20</td>
</tr>
<tr>
<td>21 days (N=8)</td>
<td>4</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>28 days (N=2)</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>
Helicobacter pylori in the critically ill patient

Table 3

Immunoglobulin G antibody titres during intensive care treatment (U/l). SD; standard deviation

<table>
<thead>
<tr>
<th>Titre</th>
<th>N</th>
<th>Minimum</th>
<th>Maximum</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Admission</td>
<td>290</td>
<td>0.05</td>
<td>11.8</td>
<td>3.19</td>
<td>2.49</td>
</tr>
<tr>
<td>Day 3</td>
<td>137</td>
<td>0.04</td>
<td>12.4</td>
<td>3.05</td>
<td>2.49</td>
</tr>
<tr>
<td>Day 7</td>
<td>52</td>
<td>0.41</td>
<td>10.8</td>
<td>2.54</td>
<td>2.09</td>
</tr>
<tr>
<td>Day 14</td>
<td>21</td>
<td>0.37</td>
<td>8.10</td>
<td>2.42</td>
<td>2.02</td>
</tr>
<tr>
<td>Day 21</td>
<td>9</td>
<td>0.63</td>
<td>3.96</td>
<td>1.84</td>
<td>1.04</td>
</tr>
</tbody>
</table>

Discussion

In this study the LARA-\(^{13}\)C-urea breath test on admission to the intensive care unit detected active \textit{H. pylori} infection in 37.6\% of patients. After 3 days \textit{H. pylori} infection was suppressed in the majority of patients and within 7 days active \textit{H. pylori} infection could no longer be detected in any of the patients. Furthermore, once \textit{H. pylori} infection was suppressed, indicated by a negative LARA-\(^{13}\)C-urea breath test, reactivation was prevented as long as topical antibiotics were continued. Therefore, selective decontamination of the digestive tract (SDD) appears to be highly effective in suppressing \textit{H. pylori} infection. SDD effectively decontaminates critically ill patients from potentially pathogenic micro-organisms [11]. A recent meta-analysis showed that ventilator associated pneumonia and urinary tract infections were prevented and that mortality was reduced [12]. The antibiotics used for gut decontamination in this study are a mixture of polymyxin, tobramycin and amphotericin B topically applied in the oropharynx and by nasogastric tube and cefotaxime intravenously for four days to prevent primary endogenous infection [11]. The anti- \textit{H. pylori} properties of these antibiotics have not been extensively studied. \textit{H. pylori} appears to be susceptible to tobramycin and cefotaxime (unpublished data). On the other hand \textit{H. pylori} is resistant to polymyxin and amphotericin B in vitro. As cefotaxime was given for 4 days intravenously and topically applied tobramycin was continued during the entire intensive care stay, patients received a form of dual therapy during 4 days and thereafter a monotherapy. All patients that converted from a positive into a negative LARA-\(^{13}\)C-urea breath test continued to have negative tests at repeated measurements, indicating effective suppression by tobramycin during a prolonged oral administration. Whether true eradication occurred was not subject of this study.
In stress ulcer formation ischaemia is considered to be an important factor [5]. Mechanical ventilation and coagulation disorders have been identified as risk factors for upper gastro-intestinal bleeding [1,13]. However, bleeding may also be induced from pre-existing ulcers. Eddleston showed that on admission 20% of intensive care patients have stress ulcerations which will not be recognised unless they bleed [14]. Brown found that 90% of the patients with severe head injury which necessitates mechanical ventilation suffer from gastritis within 24 hours [15]. Sixty-seven percent of surgical intensive care patients had stress ulcerations in the study of Bank and co-workers [16]. \textit{H. pylori} infection was not determined in these studies. It is unknown whether \textit{H. pylori} plays a role in the formation of stress ulceration. \textit{H. pylori} is known to be the most important pathogenic factor for gastric and duodenal ulcer disease. Colonisation with these bacteria results in inflammatory responses, which will finally lead to ulcer formation [4]. In addition, \textit{H. pylori} infection causes increased gastrin secretion and acid production contributing to ulcer formation. In the present study we have shown that SDD suppresses \textit{H. pylori} infection. If we hypothesise that \textit{H. pylori} plays a role in stress ulcer formation than the subsequent elimination of \textit{H. pylori} may explain that in the bleeding patients \textit{H. pylori} could not be detected at the time of bleeding nor on admission. According to that hypothesis the remaining stress ulcers and related bleedings are not \textit{H. pylori} dependant. We identified only 3 out of 300 patients (1.0%) with an upper gastro-intestinal bleeding caused by (stress)ulceration although stress ulcer prophylaxis with histamine receptor antagonists or sucralfate was not used. This 1.0% incidence is very low as compared to the 1.5 to 9% incidence among general intensive care patients, usually under stress ulcer prophylaxis in other studies [1-3]. However, the definition of upper gastrointestinal bleeding in the present study does not fully agree with the definition in other studies. Nevertheless, gut decontamination and suppression of \textit{H. pylori} may have contributed in part to the low incidence of stress ulcer related bleeding in the present study by prevention of \textit{H. pylori} associated stress ulceration. The remaining stress lesions and associated bleeding must be independent of \textit{H. pylori} infection and might be related to other risk factors. A similar low incidence of 0.6% in a previous study is consistent with the present study [9]. However, other components of the treatment than SDD may also have contributed to the low incidence of stress ulceration and related bleeding. The routine use of vasodilators and fluid therapy may have prevented intestinal ischaemia by improving micro-circulation. Corticosteroids diminishes an inflammatory response with associated cytokine release and related mucosal damage. Also iNOS production which leads to mucosal damage is effectively reduced by dexamethason [17].
Helicobacter pylori in the critically ill patient

In the present study antibodies against *H. pylori* were detected in 57.7% of patients on admission to the intensive care. Previous serological studies in critically ill patients found a prevalence of *H. pylori* infection of 57% to 67% [3,18,19]. The lower *H. pylori* prevalence with the LARA-\(^{13}\)C-urea breath test in our study (37.6%) may well be due to previous antibiotic treatment. Antibodies remain detectable for months to years after *H. pylori* eradication and therefore do not allow detection of actual *H. pylori* carrier state [20].

Monotherapy with clarithromycin, which is often used for upper respiratory infections, has been shown to eradicate *H. pylori* in 15 to 54% [21]. Critically ill patients usually have an extensive medical history including previous antibiotic treatment that might have eradicated *H. pylori* and this may explain the difference in prevalence between urea breath test and serology. In our study 50% of admitted patients were treated with systemic antibiotics prior to admission to the intensive care unit. The LARA-\(^{13}\)C-urea breath test was positive in 19% of these patients whereas 47% of the patients not pre-treated with antibiotics had a positive LARA-\(^{13}\)C-urea breath test, indicating a suppressive effect of antibiotic use on *H. pylori* infection.

APACHE II predicted mortality for all patients was 45% and the observed hospital mortality was 33% (table 1). The standardised mortality rate was therefore 0.73 (33/45). Observed mortality in the patients with a positive LARA-\(^{13}\)C-urea breath test on admission was 32.0% compared to 32.6% in patients with a negative urea breath test (p=NS). In patients with negative *H. pylori* serology on admission observed mortality was 42.0% compared to 27.6% of patients with positive *H. pylori* serology (p=0.06). In a previous study we showed that haemodilution and blood loss may reveal false negative serological test results for *H. pylori* antibodies [8]. We wonder whether severely ill patients who need aggressive fluid resuscitation therapy and therefore experience more haemodilution may lead to falsely negative *H. pylori* serological tests. Therefore, the higher mortality in patients with a negative serology may be linked to more severe illness and not directly to the negative *H. pylori* serology. This is confirmed by the higher APACHE II and predicted mortality in the patients with negative serology on admission (table 1). The urea breath test is independent of haemodilution and blood loss. Therefore no differences in mortality and mortality prediction are seen in patients with a positive urea breath test compared to patients with a negative urea breath test.

In conclusion it has been shown that gut decontamination by prolonged topical antibiotics in addition to four days systemic antibiotic treatment results in rapid and effective suppression of *H. pylori* infection monitored by LARA-\(^{13}\)C-urea breath test. Serology is a less appropriate monitoring tool to indicate the actual *H. pylori* infection compared to the LARA-\(^{13}\)C-urea breath test and
therefore may be related to erroneous interpreted associated disease phenomena. The observed low incidence of stress ulcer related bleeding may be related to prevention of *H. pylori* associated stress lesions by effective suppression of this micro-organism but further studies are necessary to proof that hypothesis.
References


