Helicobacter pylori in the critically ill patient
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Chapter 9

INCREASED PREVALENCE OF *Helicobacter pylori* INFECTION IN STRESS INDUCED GASTRIC MUCOSAL INJURY

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Abstract

Introduction: Helicobacter pylori is known for its causative role in gastric and duodenal ulcer disease. However, it is unknown whether H. pylori plays a role in the formation of stress ulceration in critically ill patients. Therefore we studied the presence of H. pylori infection in critically ill patients admitted to the intensive care unit and determined gastric and duodenal mucosal injury in these patients.

Methods: Patients admitted to the intensive care unit for emergency reasons and requiring mechanical ventilation were included. H. pylori was detected by the Laser Assisted Ratio Analyser-13C-urea breath test (UBT). Upper gastrointestinal endoscopy was performed in all patients by the same endoscopist who was blinded for the results of the UBT. Breath test and endoscopy were performed within 6 hours after admission. Gastric and duodenal mucosal injury were assessed according to the so called Brown endoscopic mucosal injury score (EMIS): grade 0: normal mucosa; grade 1: 1 to 5 erosions or submucosal haemorrhages; grade 2: 6 to 20 erosions or haemorrhages; grade 3: more than 20 erosions or haemorrhages. Minor mucosal injury was defined as EMIS 0 or 1 and major mucosal injury as EMIS 2 or 3.

Results: Fifty consecutive patients were included. Six patients were not eligible because the UBT could not be processed. Of the 44 eligible patients 22 were H. pylori positive by UBT and 22 were H. pylori negative. Twenty-nine of the 44 eligible patients showed gastric mucosal injury by endoscopy (EMIS 1 to 3). Ten out of the 29 patients (34.5%) with minor mucosal injury (EMIS 0 or 1) were infected with H. pylori indicated by a positive LARA-13C-UBT. A significantly higher prevalence of H. pylori infection was found in patients with major mucosal injury (EMIS 2 or 3) compared to patients with minor mucosal injury (12/15 or 80%; p=0.004). Two risk factors for the presence of major mucosal injury were identified; the presence of H. pylori infection (RR 4.0, 95% CI 1.3 – 12.2) and NSAID use prior to ICU admission (RR 2.07, 95% CI 0.98 – 4.4). However, after multiple regression analysis H. pylori appeared to be the only significant factor associated with major mucosal injury (p=0.019).

Conclusion: The severity of gastric and duodenal mucosal injury in critically ill patients during mechanical ventilation is highly dependant to the presence of H. pylori infection.
Helicobacter pylori in the critically ill patient

Introduction

Stress ulceration has initially been recognised in burn patients in 1842 [1] and septicaemia in 1867 [2]. Endoscopic studies have shown that the majority of critically ill patients develop stress ulcerations. After head trauma, gastric mucosal lesions are present in 91% of the patients [3]. The incidence of stress ulceration approximates 82% in general surgical patients admitted to the intensive care [4]. However, clinically relevant stress ulcer bleeding occurs much less frequently. Most studies address the incidence of upper gastrointestinal bleeding (UGIB) without performing endoscopy to identify the source of bleeding [5-8]. The reported incidence of UGIB is 0.6 to 9%. The two independent risk factors for UGIB in critically ill patients are coagulopathy and mechanical ventilation [5]. Although the number of intensive care patients with severe disease and associated coagulopathy or mechanical ventilation is increasing over the years, the incidence of UGIB decreases due to improved treatment and care of critically ill patients [9]. Ischaemia, which is thought to be an important determinant for the occurrence of stress ulceration, is prevented by adequate fluid administration and inotropic support. However, other possible reasons should be taken into account as well. Helicobacter pylori is the single most important factor in the pathogenesis of gastric and duodenal ulcer disease when NSAID use is excluded [10]. Whether H. pylori plays a role in the formation of stress ulceration and whether the decreasing incidence of H. pylori may also contribute to the decreasing incidence of stress ulceration is not known. Only one study has identified the presence of H. pylori antibodies as a risk factor for UGIB [7]. In a previous study we have shown that the use of selective decontamination of the digestive tract (SDD) was associated with suppression of H. pylori [11]. The suppression of H. pylori is associated with a low incidence of UGIB [11]. However, endoscopy is not routinely performed in most studies concerning stress ulceration in critically ill patients. Therefore it is not known to what extend stress ulceration contribute to these bleedings compared to other causes like esophagitis and variceal bleeding. Endoscopy is the ideal means of identification of gastro-duodenal mucosal injury and facilitates exclusion of other possible causes of UGIB. We conducted the present study in critically ill patients admitted to the intensive care to determine whether there is any relation between the prevalence of gastric mucosal injury as determined by endoscopy and the presence of H. pylori infection.
Methods

Patients
Consecutive patients admitted to a general intensive care unit and requiring mechanical ventilation within 6 hours were included after given informed consent from the nearest relatives. Patients were excluded when admitted after elective surgery or when informed consent could not be obtained. *H. pylori* infection was detected by Laser Assisted Ratio Analyser (LARA)-¹³C-urea breath test and serology. Endoscopy was performed to detect gastric and duodenal mucosal injury. When coagulopathy was not present biopsies were taken for histopathology. Local ethical and scientific committees approved the study protocol.

Endoscopical mucosal injury score (EMIS)
In all patients an upper gastrointestinal endoscopy was performed within 6 hours after admission to the intensive care. All endoscopies were performed by the same endoscopist. The endoscopist was blinded for the results of the *H. pylori* tests at the time of the endoscopy. Gastric and duodenal mucosal injuries were scored according to Browns criteria [3]. Minor gastric mucosal injury was defined as EMIS 0 or 1 and major gastric mucosal injury was defined as EMIS 2 or 3 (table 1).

LARA-¹³C-Urea breath test (UBT)
The Laser Assisted Ratio Analyser (LARA)-¹³C-urea breath test (Alimenterics Inc., New Jersey, USA) is an easy and reliable method to detect current *H. pylori* infection [12]. The LARA-¹³C-UBT has been validated for mechanically ventilated patients [13]. The test is performed by collecting exhaled air in a 10 ml. breath collector which is connected to the translaryngeal tube, before and after the ingestion of ¹³C-labelled urea. ¹³C-labelled urea will be converted to ¹³CO₂ in case of active *H. pylori* infection. The test is positive when ¹³C/¹²C ratio is above a cut-off level as determined by ROC analysis in a large international multicenter registration study [12]. The included patients were tested by LARA-¹³C-UBT instantaneously after admission to the intensive care unit, before antibiotics were administered.

Serology
Blood was drawn for antibody detection immediately after intensive care admission. IgG antibodies against *H. pylori* were detected 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 [14]. Sensitivity of this test compared to urea breath test in ambulant patients was 98.7%, specificity
and positive predicting value were both 100\% and negative predicting value was 98.6\% [14].

**Histopathology**

Biopsies were taken when coagulopathy was not present. For histopathology two biopsies from the antral region and two from the corpus were taken. Biopsies were fixed in formaline. Hematoxylin-eosin stains were used for *H. pylori* detection. When *H. pylori* was not detected in this stain a modified Giemsa stain was used in addition.

**Statistical analysis**

Sample size was determined by Lehr’s formula [15] for 80\% power and two sided 5\% significance. The prevalence of *H. pylori* infection was estimated for this determination. *H. pylori* infection prevalence was estimated to be 30\% in the patients with minor mucosal injury [11]. *H. pylori* infection was estimated to be present in 65\% of the patients with major mucosal injury [11]. With these assumptions the minimal sample size was determined to be 35. A comparison of means was performed using the T-test. A comparison of categorical data was performed by the Chi Square test. Variables significantly associated with major mucosal injury were analysed following a multiple regression. All statistical analyses were made using the SPSS statistical analyser release 8.0.0 (SPSS inc., USA, 1997). A p value < 0.05 was considered to be statistically significant.

**Table 1**

Mucosal injury score according to Brown as determined by endoscopy (EMIS).

<table>
<thead>
<tr>
<th>Grade 0</th>
<th>normal mucosa</th>
<th>Minor mucosal injury</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>1 to 5 erosions or submucosal haemorrhages</td>
<td>Major mucosal injury</td>
</tr>
<tr>
<td>Grade 2</td>
<td>6 to 20 erosions or haemorrhages</td>
<td></td>
</tr>
<tr>
<td>Grade 3</td>
<td>more than 20 erosions or haemorrhages</td>
<td></td>
</tr>
</tbody>
</table>
Results

Fifty consecutive patients were included. Patients were not eligible because of improperly collected breath samples (n=4) or interference of a high oxygen fraction of the expired air with the LARA (n=1). In one patient the breath sample was not processed because this patient appeared to have open tuberculosis. Therefore the LARA-\(^{13}\)C-UBT results of 44 patients were used for analysis. In half of the patients (22/44) the LARA-\(^{13}\)C-UBT was positive (50%), indicating active \(H.\) pylori infection, and in the other 22 the LARA-\(^{13}\)C-UBT was negative. Demography of the 44 eligible patients are presented in table 2. The results of the endoscopy are summarised in table 3. Twenty nine out of 44 patients (66%) had an endoscopic mucosal injury score (EMIS) greater than 0, indicating mucosal injury. Of the patients with minor mucosal injury (EMIS 0 or 1), 34.4% (10/29) had a positive LARA-\(^{13}\)C-urea breath test indicating \(H.\) pylori infection. In patients with major mucosal injury (EMIS 2 or 3) a significant higher prevalence of \(H.\) pylori infection (12/15 or 80%, \(p=0.004\)) was found. In 14% of patients with a negative LARA-\(^{13}\)C-urea breath test the EMIS was greater than 2, whereas 55% of the patients with \(H.\) pylori infection had an EMIS of greater than 2 (\(p=0.004\)). The relative risk for \(H.\) pylori infection and other factors that may cause mucosal injury, such as non-steroidal anti-inflammatory drugs (NSAID), are summarised in table 3. In all patients IgG antibodies against \(H.\) pylori were determined. Twenty nine patients had a positive \(H.\) pylori serology and 15 patients had a negative serology. Major mucosal injury as determined by EMIS of 2 or 3 was found in 34.4% of the patients with a positive serology and in 33.3% of the patients with a negative serology (table 4). In 18 patients biopsy specimens were taken, the other patients had coagulopathy. The histopathology specimens of 4 out of these 18 patients detected \(H.\) pylori. However, all 4 patients had minor mucosal injury. All patients with a positive histopathology also had a positive LARA-\(^{13}\)C-urea breath test and a positive \(H.\) pylori serology. Forty percent of the patients with EMIS 2 or 3 used NSAID's compared to 15.4% in the patients with EMIS 0 or 1 (all 100 mg acetylsalicylic acid once daily). This difference was not statistically significant (\(p=0.08\)). In \(H.\) pylori positive patients 31.8% used NSAID's compared to 15% of \(H.\) pylori negative patients (all 100 mg acetosal once daily; \(p=0.17\)). All variables that are summarised in table 2 and 3 were analysed by multiple regression. \(H.\) pylori infection indicated by a positive LARA-\(^{13}\)C-urea breath test was the only factor significantly related to mucosal injury (\(p=0.019\)).
### Table 2

Demography of eligible patients. UBT: LARA-13C-urea breath test; EMIS: endoscopically detected mucosal injury score; APACHE: acute physiology and chronic health evaluation; SAPS: simplified acute physiology score; MPM: mortality prediction model; ICU: intensive care unit.

<table>
<thead>
<tr>
<th>N= 44</th>
<th>UBT positive</th>
<th>UBT negative</th>
<th>0 or 1</th>
<th>2 or 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (range, yr.)</td>
<td>72 (36-85)</td>
<td>61 (31-84)</td>
<td>65.3 (31-85)</td>
<td>69.1 (36-85)</td>
</tr>
<tr>
<td>M/F (%)</td>
<td>64/36</td>
<td>64/36</td>
<td>58.6/41.4</td>
<td>73.3/26.7</td>
</tr>
<tr>
<td>APACHE II</td>
<td>25.1</td>
<td>25.9</td>
<td>25.4</td>
<td>25.7</td>
</tr>
<tr>
<td>APACHE II predicted mortality</td>
<td>0.53</td>
<td>0.52</td>
<td>0.51</td>
<td>0.56</td>
</tr>
<tr>
<td>SAPS II</td>
<td>55.0</td>
<td>54.8</td>
<td>54.0</td>
<td>56.6</td>
</tr>
<tr>
<td>SAPS II predicted mortality</td>
<td>0.54</td>
<td>0.54</td>
<td>0.53</td>
<td>0.56</td>
</tr>
<tr>
<td>MPM 0</td>
<td>0.53</td>
<td>0.46</td>
<td>0.48</td>
<td>0.55</td>
</tr>
<tr>
<td>MPM 24</td>
<td>0.54</td>
<td>0.47</td>
<td>0.50</td>
<td>0.53</td>
</tr>
<tr>
<td>Observed ICU mortality (%)</td>
<td>27.3</td>
<td>31.8</td>
<td>34.5</td>
<td>20.0</td>
</tr>
<tr>
<td>Total (n)</td>
<td>22</td>
<td>22</td>
<td>29</td>
<td>15</td>
</tr>
</tbody>
</table>
### Table 3
**Risk factors for gastric and duodenal mucosal injury.**

<table>
<thead>
<tr>
<th>Risk factor:</th>
<th>EMIS 0 or 1</th>
<th>EMIS 2 or 3</th>
<th>Relative Risk: (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lowest ABP in first hour (mmHg)</td>
<td>93.2</td>
<td>99.8</td>
<td>P=NS</td>
</tr>
<tr>
<td>Lowest ABP in first 24 hours (mmHg)</td>
<td>79.5</td>
<td>83.8</td>
<td>P=NS</td>
</tr>
<tr>
<td>Dopamine dose (µg/kg/min)</td>
<td>7.3</td>
<td>4.8</td>
<td>P=NS</td>
</tr>
<tr>
<td>Diagnosis (n):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sepsis</td>
<td>3</td>
<td>1</td>
<td>0.714</td>
</tr>
<tr>
<td>Cardiogenic shock</td>
<td>15</td>
<td>11</td>
<td>1.89 (0.72 – 5.0)</td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>6</td>
<td>3</td>
<td>0.972</td>
</tr>
<tr>
<td>Other</td>
<td>5</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>NSAID’s before admission (%)*</td>
<td>15.4%</td>
<td>40%</td>
<td>2.07 (0.98 – 4.4)</td>
</tr>
<tr>
<td>Ulcer history (n)</td>
<td>1/29</td>
<td>1/15</td>
<td>1.50 (0.35 – 6.4)</td>
</tr>
<tr>
<td>H. pylori pos. by Urea breath test (%)</td>
<td>34.4</td>
<td>80</td>
<td>4.00 (1.3 – 12.2)</td>
</tr>
</tbody>
</table>

**ABP:** arterial blood pressure; **NSAID:** Non-steroidal anti-inflammatory drugs; **EMIS:** endoscopically detected mucosal injury score

* all patients used aspirin 100 mg once daily

### Table 4
**Distribution of mucosal injury among mechanically ventilated intensive care patients in relation to the LARA-13C-urea breath test (UBT) and serological assessment (serol.) of anti-** *H. pylori* **antibodies. EMIS: endoscopically detected mucosal injury score.**

<table>
<thead>
<tr>
<th>UBT positive</th>
<th>UBT negative</th>
<th>Serol. positive</th>
<th>Serol. Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>EMIS 0</td>
<td>7</td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td>EMIS 1</td>
<td>3</td>
<td>11</td>
<td>9</td>
</tr>
<tr>
<td>EMIS 2</td>
<td>6</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>EMIS 3</td>
<td>6</td>
<td>2</td>
<td>4</td>
</tr>
</tbody>
</table>
**Discussion**

Gastric mucosal injury in critically ill patients represents an endoscopical spectrum ranging from intramucosal haemorrhages to erosions and ulcerations. The prevalence of gastric or duodenal mucosal injury in this study appeared to be 65.9% which was lower compared to previous studies [3,4]. The incidence of upper gastrointestinal bleedings in critically ill patients was 0.6 to 9% in previous studies [5-8]. Apparently, the high incidence of gastric mucosal injury leads to a clinical relevant bleeding (UGIB) in only a minority of patients. The intramucosal haemorrhages may progress to erosions and ulcerations with or without bleeding [16,17]. Mechanical ventilation and coagulopathy are two known independent risk factors for the development of UGIB in critically ill patients [3]. Ischaemia is an important factor for the development of gastric mucosal damage in critically ill patients. However, the pathogenesis is complex and several other causative factors such as sepsis and endotoxaemia may play a role in the development of gastric mucosal injury [18]. The present study identifies *H. pylori* as an independent risk factor for upper gastrointestinal mucosal injury. The 66% prevalence of mucosal injury in critically ill patients is higher than can be found in healthy volunteers. It is also shown that gastric mucosal injury is more extensive in mechanically ventilated critically ill patients with active *H. pylori* infection compared to those without the infection. Obviously, gastric mucosal injury induced by *H. pylori* is enhanced by severe disease. About the precise mechanism for this change in interaction between host and microbe one can only speculate. The observed lesions that are related to *H. pylori* infection are in all probability the same as the so called stress ulcerations. The potential role of *H. pylori* in stress ulceration was first hypothesised by Paré in 1993 [19]. However, assessment of *H. pylori* in critically ill patients was reported since 1996 in preliminary studies [20-22]. The presence of *H. pylori* antibodies in critically ill patients has been associated with a slightly increased incidence of upper gastrointestinal bleeding compared to patients without *H. pylori* antibodies [7,20,21]. However, serological detection of *H. pylori* has never been validated in critically ill patients. Serological detection of *H. pylori* may reveal false negative tests in critically ill patients due to blood loss and haemodilution [23]. Furthermore, serology does not necessarily indicate active *H. pylori* infection and reveals a relative high number of false positive test results since the widespread *H. pylori* eradication attempts. In the present study a *H. pylori* positive serological test result did not correlate with the presence of gastric or duodenal mucosal injury. This may be due to aforementioned factors. The fact that LARA-13C-urea breath test correlates with the EMIS and serology does not, is additional evidence that only active *H.
infection is obligatory for the development of gastric mucosal injury. This hypothesis is also supported by the sub-group of 7 H. pylori negative patients (by LARA-13C-urea breath test) with a positive serology, indicating a suppressed or recently eradicated H. pylori infection. Six of them had minor gastric mucosal injury whereas only one of them had major mucosal injury. It is known that mucosal ischaemia is an important factor for the development of mucosal injury [24,25]. Whether mucosal ischaemia is equally distributed among our H. pylori positive and our H. pylori negative group is not known. Mucosal ischaemia can not be determined routinely. Gastric tonometry is currently the best tool to determine gastric mucosal ischaemia but was not performed in the present study. Indirect information about the circulation was collected by the lowest blood pressure in the first hour and in the first 24 hours as well as the need for inotropic support. However, these measurements did not give specific information about the splanchnic circulation and were not significantly related to EMIS (table 2). In all patients aggressive fluid resuscitation and vasodilators were routinely used in an attempt to counteract vasoconstriction in the splanchnic circulation. Furthermore the APACHE II, SAPS II and MPM scores where determined and did not differ between the two groups. Another determinant of mucosal injury, NSAID use, was not equally distributed between the groups with minor and major mucosal injury. In all patients NSAID use appeared to be aspirin 100 mg once daily, a relatively low dose. The relative risk of this medication for EMIS was 2.07 but in a multiple regression analysis NSAID use was not significantly related to EMIS.

Sepsis is frequently associated with mucosal injury as endotoxaemia and an enhanced inflammatory state lead to activation and adherence of leukocytes [26]. Leukostasis leads to impairment of the micro-circulation and therefore mucosal damage [27]. In our study, the diagnosis of sepsis was not associated with mucosal injury (table 3).

The association of active H. pylori infection with the presence of gastrointestinal mucosal injury in critically ill patients raises the question whether suppression of H. pylori will diminish the mucosal injury. Prospective studies concerning the effect of H. pylori suppression in critically ill patients and the impact on stress ulcer formation have not been performed. In the present study we have shown that in 6 out of 7 patients with suppressed or eradicated H. pylori infection only minor mucosal injury was present. In an other study we have shown that in patients treated with selective decontamination of the digestive tract H. pylori was effectively suppressed and this was associated with a low incidence of stress ulcer related bleeding [11]. It may be possible however, that other factors than H. pylori suppression have attributed to the low incidence of stress ulcer related bleeding. Further prospective
Helicobacter pylori in the critically ill patient

studies to determine the role of *H. pylori* suppression in the prevention of stress ulcer related bleeding are needed.

In conclusion, we demonstrated that upper gastrointestinal mucosal injury develops in 66% of unselected patients admitted to a mixed surgical and medical intensive care unit. The strongest risk factor for the presence of major mucosal injury was *H. pylori* infection and to a lesser extent aspirin use. Whether *H. pylori* suppression may lead to a reduced incidence of stress ulceration and related bleeding should be the focus of future studies.
References

1 Curling T.B. On acute ulceration of the duodenum, in cases of burn. Medico-Chir Trans (Lond) 1842;25:260-281.
13 Van der Voort PHJ, van der Hulst RWM, Zandstra DF, Geraedts AAM, Tytgat GNJ. Detection of Helicobacter pylori in mechanically


