Helicobacter pylori in the critically ill patient
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Chapter 1

INTRODUCTION AND OUTLINE OF THE THESIS

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Chapter 1

**General introduction**

Insight in the pathogenesis of gastric and duodenal ulcer disease has changed considerably over the last 20 years. With the dictum ‘no acid, no ulcer’ Karl Schwarz in 1910 introduced the hypothesis that gastric acid was the most important factor for the development of ‘peptic’ ulcer disease [1]. Antacids were used for treatment of peptic ulcer disease since 1915 [2]. In 1966, the role of the histamine receptor in acid production was reported [3]. According to these insights treatment changed after histamine-2-receptor antagonists (H₂RA) became available [4]. More effective acid reduction was possible since the first proton pump inhibitor became commercially available in 1990 [5]. In the 1980’s an acid independent cause of ulcer disease was described. A spiral shaped micro-organism, *Helicobacter pylori*, was found to be the cause of most duodenal and gastric ulcers [6]. Therefore, eradication of *H. pylori* is the goal of therapy in ulcer disease nowadays [7]. The presence of spiral bacteria in the canine stomach was first reported in 1893 [8]. Later reports describing the presence of these micro-organisms in the human stomach were published in 1906 [9], 1938 [10], 1975 [11] and 1979 [12]. The definite role of *H. pylori* in the pathogenesis of gastric ulcer disease was determined in 1983 by Warren and Marshall [13].

Stress ulceration in the critically ill has a less turbulent history. Mucosal ischaemia is thought to be the final common pathway of many conditions leading to stress ulcerations [14,15]. Nevertheless, reduction of acid production by H₂RA or antacids, to reduce back diffusion of acid, is often used to prevent and treat stress ulcerations [16]. The role of *H. pylori* in the pathogenesis of stress ulceration is unknown. The prevalence, pathogenesis and the possible role of *H. pylori* in stress ulcerations in the critically ill patient are subject of this thesis.

**Definition of stress ulceration**

The description of stress ulcerations has a long history. The first reports of ulcerations in the upper gastrointestinal tract in patients with excessive burns were by Swan in 1823 [17] and by Curling in 1842 [18]. In 1853, Virchow related mucosal ulceration to hypoxaemia and hypoperfusion [19]. The presence of ulcers in a postoperative patient was reported by Billroth in 1867 [20]. Furthermore, in 1932 Cushing described mucosal ulcerations in head trauma patients [21]. Since that time the term ‘stress ulcer’ was used. The introduction of antibiotics and improvement in surgical techniques reduced the mortality of severely ill patients. The prolonged survival of severely ill patients resulted in complications that were infrequently faced before.
Stress ulceration was reported frequently since the 1950's [22]. Despite the widely used term 'stress ulceration', there is no universally accepted definition. Usually stress ulcerations are defined as multiple superficial mucosal erosions of the stomach in critically ill patients [23,24]. Deeper ulcers may develop from these superficial erosions [25,26] and may lead to stress ulcer related bleeding (SURB). The true prevalence of stress ulcerations remains unknown because in most studies endoscopy is not routinely performed [27]. The incidence of upper gastrointestinal bleeding as a surrogate for SURB has been studied more extensively [27]. Upper gastrointestinal bleeding is usually defined as clinically important when overt bleeding is accompanied by (a) a decrease in blood pressure of 20 mm Hg within 24 hours of onset of bleeding or (b) a decrease in blood pressure of 10 mm Hg and an increase in heart rate of 20 beats per minute on orthostatic change or (c) a decrease in haemoglobin level of 1.2 mmol/L and transfusion of 2 units of blood within 24 hours or when gastric surgery is required [16]. However, other definitions are used as well [28,29] and this variability in definition should be considered when studies are compared.

**Prevalence of stress ulceration, upper gastrointestinal bleeding and stress ulcer related bleeding**

Routine endoscopy in selected patient groups reveals mucosal lesions in the majority of critically ill patients. Brown described mucosal lesions in 91% of the patients after head trauma [30]. In surgical patients a prevalence of 82% was found [31]. A spectrum of lesions can be found from haemorrhagic gastritis to erosions and ulcerations. Lucas and co-workers showed progression from petechiae to erosions and bleeding [25]. These findings were confirmed by Eddleston [26] who found mucosal lesions and haemorrhagic gastritis which developed into erosions and ulcerations in 88.9% of placebo and 37.5% of treated patients. Only a minority of the lesions will cause overt or significant bleeding. The incidence of upper gastrointestinal bleeding in critically ill patients varies from 0.6 to 8.9% [27,32-35] and has shown a significant decline in prevalence from 12 to 5% over the last years caused by an improvement in general intensive care treatment and possibly by stress ulcer prophylaxis [35-37]. Upper gastrointestinal bleeding may be due to other causes than stress ulceration. Bleeding from esophagitis, tumours and varices may be confused with SURB when upper gastrointestinal endoscopy is not performed. Therefore, the exact frequency of SURB remains unknown in most studies, but is probably lower than the incidence of UGIB.
Pathogenesis

The pathogenesis of stress ulceration in critically ill patients is complex and multifactorial [38,39]. Ischaemia leads to intramucosal acidosis which, at present, can only be measured by tonometry [40,41]. Fiddian-Green demonstrated that 30% of post-cardiac surgery patients have mucosal acidosis using gastric tonometry [40]. Intramucosal acidosis determined by gastric tonometry is related to impaired gastric mucosal blood flow [42]. It was also shown that gastric intramucosal acidosis was a risk factor for upper gastrointestinal bleeding [40]. Mucosal cell ischaemia and hypoxia lead to cell dysfunction and ultimately mucosal lesions [43,44]. During hypovolaemic shock vasoconstriction of the splanchnic circulation leads to submucosal shunting [45,46] and ischaemia of the intestinal mucosa [47-49]. These effects will continue for hours, even after sufficient volume replacement [50]. Active vasodilation restores blood flow to the splanchnic area which may be beneficial for the ischaemic mucosa [51-53]. However, reperfusion induces free oxygen radical production which may further increase mucosal damage [54]. Degranulation of mast cells plays an important role in reperfusion injury and precedes tissue damage [55,56].

Since the 1960's the presence of sepsis at the time of onset of bleeding was reported [57,58]. The reduction in gastric mucosal blood flow in septic shock is more prominent than in hypovolaemic shock. Richardson and Sales described a decrease in mucosal blood flow of 62% during septic shock where the cardiac output decreased by 12% [14]. They and others found that endotoxins and vasoactive molecules produced during septic shock like histamine, serotonin and (nor)adrenaline, impaired splanchnic blood flow more extensively than the vasoconstriction without endotoxins in other forms of shock [14,46,59]. In addition, endotoxins exert a direct toxic effect on the mitochondria of mucosal cells [60]. As a result, oxygen extraction and utilisation impairs leading to mucosal injury [61]. Moreover, activated leukocytes in sepsis will adhere to the vascular endothelium by the selectine family of adhesion molecules which further impairs microcirculation by plugging and luminal obstruction [62]. It was shown that prevention of capillary luminal obstruction by anti-platelet aggregators inhibits the development of stress ulcers in rats [63]. To sepsis related coagulopathy may increase the risk of bleeding from the mucosal lesions that have developed by ischaemia. Gastric acid facilitates stress ulcer formation in the presence of ischaemia. The ischaemic mucosa will allow back diffusion of acid which creates further mucosal injury [64]. Therefore acid reduction by H2RA and antacids is used for prevention and treatment of stress ulceration [16]. However 20-50% of critically ill patients treated with H2RA reaches a gastric acid pH above 4
[65,66]. Moreover, this treatment may not be necessary in all patients as in approximately 45% of critically ill patients hyposecretion of gastric acid is present [67]. These results indicate that gastric acid can not be the only factor leading to stress ulceration and related bleeding.

Possible role of *Helicobacter pylori* in the pathogenesis of stress ulceration

A strong causal relation exists between *H. pylori* and gastric and duodenal ulcer disease in patients who are not critically ill [68-70]. It may be questioned whether such a relationship also exists for *H. pylori* and stress ulceration in the critically ill patient. *H. pylori* infection leads to inflammation and gastric mucosal injury [71]. Moreover, gastric permeability as determined by the sucrose loading test, is increased by *H. pylori* infection [72]. Paré and colleagues hypothesised that gastric mucosa with *H. pylori* associated inflammation may be vulnerable for a second event, for instance ischaemia [73]. Studies concerning *H. pylori* in critically ill patients are scarce. The prevalence of *H. pylori* in critically ill patients has been studied using serological assessment of antibodies [33,74] showing that 55 to 67% of critically ill patients were infected, a frequency that is slightly higher than found in the general population [33,74]. However, since serology does not reliably test active *H. pylori* infection [75] the exact prevalence of *H. pylori* in critically ill patients remains unknown. Until now, only one study on the role of *H. pylori* in upper gastrointestinal bleeding in critically ill patients has been described, by Ellison and co-workers [33]. These authors found a higher level of IgA antibodies against *H. pylori* in patients with upper gastrointestinal bleeding compared to patients without such bleeding. That study does not prove a causal relationship between *H. pylori* and stress ulceration although a weak correlation was found between the presence of *H. pylori* IgA-antibodies and upper gastrointestinal bleeding. Neither antibody detection in serum nor other diagnostic tests for the detection of *H. pylori* infection have been validated in critically ill patients. Part of this thesis is dedicated to the validation of diagnostic tests for the detection of *H. pylori* in critically ill patients. Furthermore, it remains unknown whether some *H. pylori* strains more often induce stress ulceration than others as is the case in duodenal ulcer disease. *Cag-A* positive strains are more cytotoxic and duodenal ulcer disease is in approximately 96% associated with infection of a *CAG-A* positive *H. pylori* [76]. Studies describing the detection of *Cag A* positive *H. pylori* strains have not been performed in critically ill patients.
Stress ulcer prevention

Pharmacological prevention of stress ulcer has been performed by pirenzepine, antacids, H₂RA, sucralfate and proton pump inhibitors (PPI). The aim of acid suppressive drugs is to reduce back diffusion of acid in ischaemic mucosa and thus prevention of further damage [77]. Both antacids and H₂RA have shown to be effective in stress ulcer prophylaxis [16]. Omeprazole has not been studied conclusively concerning the prevention of stress ulceration [78-80]. However, in rats omeprazole prevented stress ulcerations in a dose related manner [81]. Sucralfate is associated with a lower incidence of pneumonia compared to antacids. Moreover, it is associated with a reduced mortality rate relative to antacids and to H₂RA [16]. Studies comparing sucralfate with placebo are scarce [82]. In a recent study a higher incidence of upper gastrointestinal bleeding occurred during prophylaxis with sucralfate compared to prophylaxis with H₂RA [27]. Therefore, H₂RA currently are the drugs of choice in cases where acid suppression is used to reduce stress ulceration and related bleeding in defined groups of patients at risk. Side effects, however, should be considered when these drugs are prescribed. H₂RA interact with the cells of the immune system in the gut [83]. Moreover, mRNA for histamine was detected in the immune cells of the gastric lamina propria and not in the parietal cells as was shown using in situ hybridisation [84]. Clinically, H₂RA are associated with an increased infection rate [85,86], but also with a favourable immunomodulatory action [87].

Obviously, the best way to prevent mucosal damage is to prevent ischaemia and vasoconstriction of the splanchnic circulation. Inotropes do not necessarily improve splanchnic perfusion [88,89]. In contrast, it is hypothesised that critically ill patients may benefit from the routine use of vasodilators [34]. In animal studies vasodilators improve splanchnic perfusion by reducing vasoconstriction, thereby preventing stress ulcers [51,52,53].

Infection, endotoxaemia and sepsis all lead to vasoconstriction and mucosal damage. Infection prevention should therefore receive the highest possible attention in the intensive care unit. Selective decontamination of the digestive tract (SDD) is an effective way to prevent primary and secondary endogenous infection [90,91]. In addition to SDD a high standard of hygiene should prevent exogenous infections. It was shown in animal studies that gut decontamination decreased the incidence of stress ulceration [92,73]. In this thesis the hypothesis is made that H. pylori plays a role in stress ulcer formation and suppression of this micro-organism by SDD may therefore contribute to the prevention of stress ulceration.

To reduce the systemic inflammatory response in critically ill patients, corti-
costeroids may be used. The use of corticosteroids is not a risk factor for stress ulceration [32] and may even reduce stress ulcer formation [15]. Dexamethason reduces inducible nitric oxide synthetase (iNOS) production, which exerts toxic effects on mucosal cells [93,94,95]. Enteral feeding improves mucosal blood flow effectively [96]. In addition, gastric pH increases during continuous enteral feeding which may reduce ulcer formation [97]. Sander and co-workers showed that orally fed rats were less susceptible to stress ulcer formation than parenterally fed rats [98]. Moreover, a well functioning stomach protects against backdiffusion of H⁺ ions, pepsin and bile acids into the gastric mucosa [99].

**Aim of the thesis**

Currently it is unknown whether *H. pylori* plays a role in the pathogenesis of stress ulceration in critically ill patients. Until now research on stress ulcer formation has focussed on splanchnic ischaemia. The important role of *H. pylori* in gastric and duodenal ulcer disease in patients outside the intensive care have raised the question whether *H. pylori* is a factor in the formation of stress ulceration in critically ill patients.

**Outline of the thesis**

The incidence of gastrointestinal disease and stress ulceration in critically ill patients is described in chapter 2. The frequency of gastroenterological interventions and the incidence of endoscopically detected stress ulcerations in a mixed population of intensive care patients are studied. Literature concerning the incidence of stress ulceration in the specific group of patients after cardiac surgery is reviewed in chapter 3. Moreover, the efficacy of pharmacological stress ulcer prophylaxis in this group of patients is determined from this literature review. Chapter 4 describes the validation of both the Laser Assisted Ratio Analyser ¹³C-urea breath test and serological antibody detection for the diagnosis of *H. pylori* infection for use in mechanically ventilated patients. In chapter 5 the usefulness of the faecal *H. pylori* antigen test in critically ill patients is determined. Chapter 6 describes the gastric mucosal barrier function in critically ill patients studied by the sucrose loading test. Sucrose excretion in the urine is determined in patients with and without *H. pylori* infection. In addition, the severity of intensive care disease is related to sucrose excretion. In chapter 7 the incidence of *H. pylori* infection in critically ill patients and the suppression of this infection by intensive care treatment and selective decontamination of the digestive tract (SDD) are described. In chapter 8 the role of SDD antibiotics in the suppression of
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*H. pylori* infection during intensive care treatment is determined. In vitro studies determined the susceptibility for the SDD antibiotics. Chapter 9 describes the relation between *H. pylori* infection and gastric and duodenal mucosal injury. The endoscopically detected mucosal injury score (EMIS) in critically ill patients is related to *H. pylori* infection determined by the LARA-¹³C urea breath test. In chapter 10 the prevalence of *H. pylori* infection in intensive care nurses is studied. It is hypothesised that *H. pylori* infection is an occupational hazard. The incidence of *H. pylori* infection is studied in intensive care nurses from a unit where *H. pylori* is effectively suppressed compared to a unit where antibiotics which suppress *H. pylori* are not routinely used.
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