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Pathophysiology and prophylaxis of stress ulcer in intensive care unit patients

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Abstract Gastrointestinal complications frequently occur in patients admitted to the intensive care unit. Of these, ulceration and bleeding related to stress-related mucosal disease (SRMD) can lengthen hospitalization and increase mortality. The purpose of this review is to discuss the many risk factors and underlying illnesses that have a role in the pathophysiology of SRMD and evaluate the evidence pertaining to SRMD prophylaxis in the intensive care unit population. Suppressing acid production is fundamental to preventing stress-related mucosal ulceration and clinically important gastrointestinal bleeding. Traditional prophylactic options for SRMD in critically ill patients include antacids, sucralfate, histamine$_2$-receptor antagonists (H_2RAs), and proton pump inhibitors. Many clinicians prescribe intermittent infusions of H_2RAs for stress ulcer prophylaxis, a practice that has not been approved for this indication and may not provide the necessary degree or duration of acid suppression required to prevent stress ulcer–related bleeding. New data suggest that proton pump inhibitors suppress acid production more completely in critically ill patients, but more studies are required to assess their clinical effectiveness and safety for this indication. The prophylactic regimen chosen to prevent stress ulcer bleeding should take into account the risk factors and underlying disease state of individual patients to provide the best therapy to those most likely to benefit.
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1. Introduction

An estimated 4.4 million patients are admitted to intensive care units (ICUs) each year. Of these, about 12%, or 500 000 patients, die in the ICU [1]. Gastrointestinal (GI) complications (eg, gastric and intestinal motor dysfunction as well as stress-related mucosal disease [SRMD]) frequently occur in these patients and adversely affect patient outcomes. Gastrointestinal motor dysfunction may predispose patients to impaired enteral nutrition and pulmonary aspiration of gastric contents [2]. Stress-related mucosal damage—an acute erosive gastritis—occurs in many critically ill patients in ICUs and may develop within 24 hours of admission [3]. The incidence of clinically important GI bleeding, defined as overt bleeding complicated by hemodynamic instability, decrease in hemoglobin, and/or need for

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blood transfusion, from SRMD in the ICU population was 1.5% in a prospective study of 2252 patients [4]. In addition, the morbidity associated with this type of severe ulceration and bleeding can increase the length of stay in the ICU by up to 8 days, and mortality is as much as 4-fold higher than it is in ICU patients without this complication [5].

2. Pathophysiology and pathogenesis of SRMD

Several factors have a role in the pathogenesis of SRMD, including gastric acid secretion, mucosal ischemia (as a result of splanchnic hypoperfusion), and reflux of upper intestinal contents into the stomach (Fig. 1) [6,7]. Gastric hypoperfusion leads to an imbalance between oxygen supply and demand that may induce mucosal damage. Moreover, reperfusion after prolonged hypoperfusion may itself result in nonocclusive mesenteric ischemia and mucosal damage. As a result of ischemia, there is also a reduced ability to neutralize hydrogen ions, which can contribute to cell death and ulceration. Protective processes such as mucous production may also be impaired, further promoting SRMD [6,8]. In animal studies, Ritchie [6] showed that elevated gastric acid levels, bile salts, and ischemia must all be present for gastric lesions to form, whereas none of these factors alone or in combination with each other led to ulceration.

In stress ulceration, homeostasis of the gastric mucosa is disrupted as are the cellular defense mechanisms that normally protect against a highly acidic gastric milieu. Cellular defense is primarily mediated by gastric prostaglandins, which, in animal models, have been shown to prevent ulcer formation and accelerate the healing process. This seems to occur partly because prostaglandins reduce acid secretion. More importantly, they have been shown to exert a direct cytoprotective effect against agents that kill mucosal cells on contact [9]. Thus, prevention of acid injury and stress ulceration might be achieved by therapies that reduce acid secretion or enhance protective mechanisms.

The endoscopic signs of SRMD include multiple subepithelial petechiae progressing to superficial erosions, and in some cases, discrete ulceration, particularly in the gastric fundus [8]. Microscopically, these lesions are characterized by focal loss of the superficial epithelium, coagulation necrosis of the mucosa, and hemorrhage [10]. These lesions do not usually perforate and tend to bleed from superficial mucosal capillaries [11]. Because of the diffused nature of the lesions, stress ulcers are not generally amenable to endoscopic therapy.

2.1. Splanchnic hypoperfusion

Critical illness that warrants admission to an ICU (eg, trauma, severe shock, burns, sepsis) can contribute to splanchnic hypoperfusion, which has a major role in the pathogenesis of SRMD. Significant decreases in visceral blood flow can occur even when systemic circulation is maintained, and conventional measures of systemic tissue oxygenation may not accurately reflect regional GI oxygenation [12,13]. Intramucosal pH, which can be measured using gastric tonometry, is a marker of the adequacy of oxygenation in the upper GI tract and is used in experimental settings to assess the magnitude of splanchnic ischemia [12].

2.2. Underlying illness

Critical illness is often characterized by hypotension and hypovolemia, which can directly contribute to gastric hypoperfusion. In addition, critically ill patients often exhibit inflammatory responses involving the release of cytokines that can also result in hypoperfusion [8].

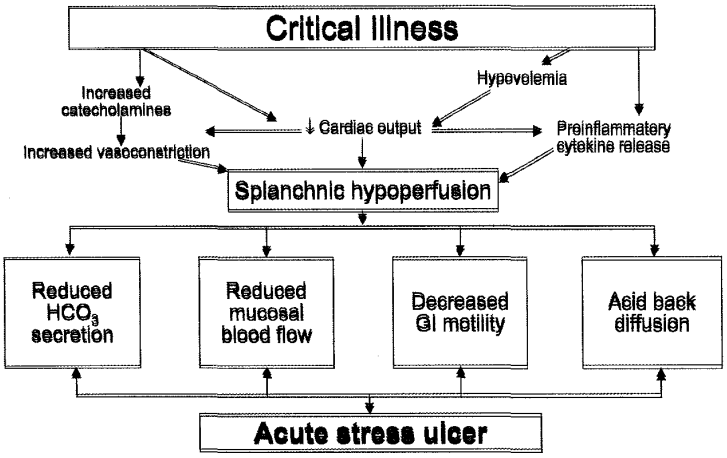

Fig. 1 Pathophysiology of stress ulcers. Adapted from *Chest* 2001;119:1222; *Hosp Pract* 1980;15:93.

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2.3. Mechanical ventilation

Mechanical ventilation can influence systemic hemodynamics, especially with potentially injurious ventilator strategies such as high tidal volumes or high positive end-expiratory pressure (PEEP). High PEEP decreases venous return and reduces preload, which in turn may reduce cardiac output (CO) [14] and result in splanchnic hypoperfusion. PEEP promotes plasma-renin-angiotensin-aldosterone activity, as well as catecholamine release, which may also contribute to splanchnic hypoperfusion [8,15,16].

Mesenteric blood flow and CO were found to significantly decrease with increasing levels of PEEP in rats randomized to PEEP vs control [15]. An inverse relationship between increasing plasma catecholamine levels and decreases in CO was observed in dogs treated with graded doses of PEEP [14]. Effects on the sympathetic nervous system have also been validated in human beings. In a study of 10 healthy males receiving continuous positive-pressure breathing, muscle sympathetic nerve activity rapidly increased, as did measurements of vasopressin and plasma renin activity as compared to control [17]. In addition, mechanical ventilation with large tidal volumes and high end-expiratory pressures have been shown in animals to promote release of pulmonary cytokines, which can enter the systemic circulation from the lungs, potentially causing splanchnic hypoperfusion [8,18,19].

Despite these data showing that PEEP can negatively influence blood flow, the effect of PEEP on GI bleeding in the ICU setting remains unknown.

2.4. Medications used in the ICU

Medications administered to patients in the ICU can have deleterious effects on GI function, especially when compounded with the effects of mechanical ventilation. Opiates and sedatives, such as benzodiazepines, can decrease gut motility and impair venous return [20]. Other agents that may contribute to GI complications include vasopressors and antibiotics [2,8,21]. Theoretically, any drug resulting in hypotension, decreased heart rate, or CO can in turn reduce mesenteric blood flow and put a critically ill patient at risk of developing SRMD [15].

2.4.1. *Helicobacter pylori*

Helicobacter pylori has been implicated as the causative agent in the pathogenesis of chronic gastritis and peptic ulcer. Its relationship to stress ulceration and GI bleeding, however, is not well documented. The relatively few studies exploring this association yielded conflicting results. A prospective epidemiologic survey of critically ill patients in an ICU found a significantly higher rate of seropositivity for *H pylori* in the ICU group than in the control group (67% vs 39%, $P < .001$) [3]. The relationship between *H pylori* status and GI bleeding was not significant, but there was a trend toward increasing seropositivity with increasing bleeding severity—from 50% seropositivity among patients with occult bleeding to 100% seropositivity among those with clinically significant bleeding [3]. In a prospective cohort analysis, 50 consecutive patients admitted to the ICU requiring mechanical ventilation were screened for *H pylori* infection using the laser-assisted ratio analyzer urea breath test and underwent endoscopy to assess mucosal injury. Of the 29 patients who developed minor mucosal disease, 34.5% were infected with *H pylori*. On the contrary, of the 15 patients that presented with major mucosal disease, 80% were infected, supporting the theory that the severity of mucosal injury is correlated with *H pylori* infection [22].

Yamamoto et al [23] inoculated a group of test animals with *H pylori*. After these, control animals were subjected to stress treatment; ulcer formation and bleeding occurred regardless of whether the animals were or were not infected with *H pylori*. However, after 30 minutes of treatment, the bleeding rate and index were significantly higher in the infected group than in the uninfected group ($P = .036$ and $P = .038$, respectively). The ulcer index was also higher in the infected group. It was determined that *H pylori* infection lowers the threshold for gastric mucosal injuries in the early phase of stress exposure, but suppresses the formation of mucosal lesions in the late phase [23].

In contrast, another study found no association between *H pylori* infection and GI bleeding. This study was conducted prospectively over 1 year in patients with and without evidence of GI bleeding admitted to the ICU after cardiac surgery. All patients received stress ulcer prophylaxis with ranitidine. Results showed that *H pylori* infection was not significantly more prevalent in patients with upper GI bleeding than in those without bleeding [24]. Only a limited association was found in another study. Among 874 critically ill patients admitted to an ICU and followed for 6 weeks, 76 (8.7%) developed stress gastritis [25]. Anti–*H pylori* immunoglobulin A was found to be an independent risk factor for stress gastritis, but not anti–*H pylori* immunoglobulin G, possibly suggesting that only a subset of individuals with chronic *H pylori* infection is at risk for stress gastritis [25].

3. Complications associated with SRMD

Mortality rates increase proportionately with the incidence and severity of SRMD. In 2 prospective multicenter studies, Cook et al [4,5] found significant differences in mortality between clinically important GI bleeding and nonbleeding patients (Fig. 2). In these studies, patients who bled as a result of SRMD had mortality rates of 49% and 46%. In contrast, mortality rates for nonbleeding patients were 9% and 21% ($P < .001$ and $P < .0001$, respectively) [4,5]. These findings are consistent with those of a study that evaluated the effectiveness of cimetidine in prevention and treatment of stress-induced GI lesions. In this study, mortality was significantly correlated with severity of GI mucosal injury: mortality rates were 57% in patients with

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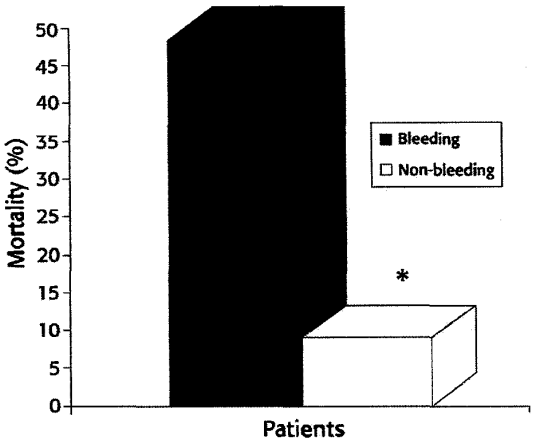

Fig. 2 Differences in mortality between bleeding (n = 33) and nonbleeding (n = 2219) patients. Asterisk indicates $P < .001$. Adapted from *N Engl J Med* 1994;330:377.

endoscopically evident ulcers and/or bleeding and 24% in patients with nonhemorrhagic erosions or normal mucosa ($P < .03$) [26]. Because it is possible to identify patients who are at the greatest risk for bleeding, strategies should logically focus on the prevention of SRMD and bleeding, rather than on its treatment after the fact. Such an approach may minimize complications associated with SRMD and, ideally, improve outcomes.

3.1. Impact of GI bleeding on ICU patients

Clinically important GI bleeding may cause hemodynamic instability or require red blood cell transfusions. The attendant risks of transfusion include infection and potential for immunosuppression, as well as possible blood-related incompatibilities [27]. As noted earlier, there is a potential for an increased length of stay in the ICU among patients with significant bleeding compared to nonbleeders, as well as a statistically significant increase in mortality.

4. Risk factors for stress ulcer–related bleeding

As noted, critically ill patients admitted to ICUs are at risk for developing stress ulceration and subsequent bleeding as a result of both underlying disease and therapeutic interventions. Prophylaxis against stress ulcers can significantly minimize bleeding, but such therapy may be costly and can have adverse effects. Therefore, it is important to identify risk factors that would substantiate the need for prophylaxis and target interventions to those at highest risk. A study involving more that 2200 patients admitted to ICUs (primarily postcardiovascular surgery) evaluated potential risk factors for stress ulcer–related bleeding [4]. Prophylactic therapy was withheld in all except 674 patients; these patients had received drugs that increased their risk of bleeding, had a history of peptic ulcer or gastritis, were undergoing high-risk surgery, or required prophylaxis for other reasons (eg, head injury, trauma) [4]. The only independent risk factors for clinically important stress ulcer bleeding determined by the study were respiratory failure requiring more than 48 hours of mechanical ventilation (odds ratio, 15.6) and coagulopathy (odds ratio, 4.3) [4]. Among 847 patients who had one or both of these risk factors, 31 (3.7%) developed clinically important bleeding, whereas among 1405 patients who had neither risk factors, only 2 (0.1%) developed significant bleeding [4].

Hastings et al [28] randomly assigned 100 patients at risk of developing stress ulcers and bleeding to receive antacid prophylaxis or no prophylaxis. An analysis of the patients reported 6 risk factors for acute GI bleeding: respiratory failure, extraabdominal sepsis, peritonitis, jaundice, renal failure, and hypotension. Notably, the frequency of bleeding increased with the number of risk factors present in both treated and untreated groups (Fig. 3) [28]. Results of this study demonstrated that there is a distinct association between acute GI ulceration and bleeding, and presence of risk factors [28].

The predictive value of risk factors for GI bleeding was also validated in another study of patients with illnesses or conditions requiring admission to an ICU [29]. In this study, the risk factors considered included surgery, burns, major trauma, established liver or renal disease, respiratory failure requiring mechanical ventilation, sepsis, and hypotension

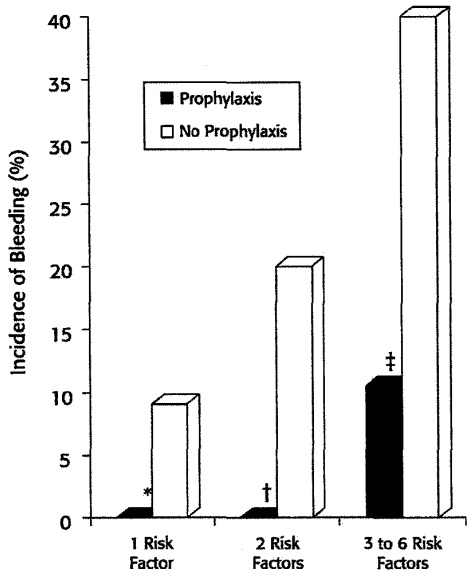

Fig. 3 The incidence of bleeding by number of risk factors in patients receiving and not receiving antacid prophylaxis. Asterisk indicates $P < .01$; dagger, $P < .025$; double dagger, $P < .005$. Adapted from *N Engl J Med* 1978;298:1041.

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[29]. The authors demonstrated that the probability for massive GI bleeding from stress ulceration increased as the number of risk factors rose and as the intramucosal pH fell, implying mucosal hypoperfusion. Gastrointestinal bleeding was, in fact, seen only in patients whose intramucosal pH had fallen below the lower limit of normality (7.24). Thus, the combination of risk factors and intramucosal pH were the best predictors of bleeding [29]. It is important to note that none of the risk factors discussed have been conclusively demonstrated to be the direct cause of stress ulcer–related bleeding; rather, they may be surrogate markers for severity of illness. All of the studies described strongly suggest that identifying risk factors can provide a valid predictive tool for GI bleeding that will allow clinicians to prescribe prophylactic treatment to the patients most likely to benefit [4,29]. The risk factors associated with increased risk of stress ulcer–related bleeding are summarized in Table 1.

5. Stress ulcer prophylaxis options

Prevention of stress-related bleeding is clearly the most effective strategy for patients at risk for SRMD in the ICU. This can be accomplished by preventing gastric ischemia or acid injury. Although high acid concentrations are not the only factor that contributes to SRMD, controlling acid production in at-risk patients seems to be protective against bleeding episodes [9]. A metaanalysis of clinical trials by Cook et al [30] reported that various prophylactic therapies such as antacids, sucralfate, and histamine$_2$ receptor antagonists (H_2RAs) reduced the incidence of overt or clinically important bleeding compared to no prophylaxis. Thus, agents that protect gastric mucosa from acid, either by minimizing injury from produced acid or by inhibiting acid secretion, have an important role in the prevention of bleeding due to SRMD.

5.1. Antacids

Antacids work by directly buffering or neutralizing the acidic contents of the stomach. In the study already referred to above, Hastings et al [28] found that in critically ill patients at risk for GI ulceration and bleeding, the frequency of bleeding was significantly reduced when antacid therapy was titrated to keep the pH above 3.5. Results showed that 2 patients (4%) in the antacid group bled compared with 12 patients (25%) in the group receiving no prophylaxis ($P < .005$). However, the fact that these agents need to be given every 1 or 2 hours to achieve adequate acid neutralization makes their use cumbersome. Moreover, administration of high doses of antacids may increase the risks of aspiration pneumonia and toxicity related to cation accumulation (particularly in patients with renal dysfunction).

Table 1 Risk factors for SRMD

Risk factor
Respiratory failure
Coagulopathy
Hypotension
Sepsis
Hepatic failure
Renal failure
Surgery
Burns
Major trauma

Adapted from *Gastroenterology* 1983;85:613; *N Engl J Med* 1978; 298:1041; *N Engl J Med* 1994;330:377.

5.2. Sucralfate

Sucralfate protects the gastric mucosa from acid by adhering to epithelial cells and forming a protective barrier, but has no acid-neutralizing activity. Used in prevention of SRMD, it has been shown to be more effective than no prophylaxis in decreasing overt bleeding, but no more effective than placebo, antacids, and H_2RAs in reducing clinically important bleeding rates [27,30]. The interest in sucralfate increased after a clinical trial, and a metaanalysis reported a trend toward a lower incidence of pneumonia with sucralfate than with agents that suppress acid [30,31]. However, a large randomized study of 1200 ICU patients reported no difference in the incidence of nosocomial pneumonia between patients receiving intravenous ranitidine 50 mg every 8 hours and those receiving sucralfate suspension 1 g via nasogastric tube every 6 hours. In the ranitidine group, 114 (19%) of 596 patients had ventilator-associated pneumonia compared with 98 (16%) of 604 patients in the sucralfate group. More importantly, clinically important GI bleeding was higher in the sucralfate group than in the ranitidine group, 3.8% and 1.7%, respectively ($P = .02$) [32].

5.3. H_2-receptor blockade

H_2RAs inhibit histamine-stimulated acid secretion by blocking H_2-receptor sites of the parietal cell in a highly selective manner; they have little or no effect on histamine receptors not involved with gastric secretion [9]. H_2RAs have been found to be significantly better than placebo, antacids, and sucralfate in reducing the incidence of clinically significant bleeding (Fig. 4) [32].

5.3.1. Continuous infusion vs bolus injection

Maintaining the pH between 3.5 and 4.5 is a surrogate endpoint accepted by many and should be the minimum goal of prophylactic therapy [11]. Effective prophylaxis requires selection of not only the proper drug and dose, but the appropriate method of administration. A continuous intravenous infusion of cimetidine (50-100 mg/h) was evaluated in a double-blind placebo-controlled study to determine its effectiveness in preventing upper GI hemorrhage [33]. Results showed that intragastric pH (>4.0 in both groups at baseline) declined over time in the placebo group

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