Pathophysiology and prophylaxis of stress ulcer in intensive care unit patients

Neil Stollman MD a,*, David C. Metz MD b

a Division of Gastroenterology, Department of Medicine, University of California San Francisco, San Francisco, CA 94110, USA
b Division of Gastroenterology, Department of Medicine, University of Pennsylvania Health System, Philadelphia, PA 19104, USA

Received 12 May 2004; revised 24 August 2004; accepted 12 October 2004

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, histamine2-receptor antagonists (H2RAs), and proton pump inhibitors. Many clinicians prescribe intermittent infusions of H2RAs 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.

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 dys-
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 (e.g., 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.
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
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. 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.

**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.
5.1. Antacids

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 histamine2 receptor antagonists (H2RAs) 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).

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 H2RAs 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. H2-receptor blockade

H2RAs inhibit histamine-stimulated acid secretion by blocking H2-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]. H2RAs 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.
but not in the cimetidine group, and significantly less upper GI bleeding occurred in the cimetidine group (P = .009) [33]. This study clearly indicated that prophylaxis with continuously infused cimetidine is a valuable approach for preventing GI hemorrhage in patients with risk factors (eg, major surgery, trauma, burns, hypotension, sepsis, or organ failure) for stress-related mucosal bleeding [33].

Although cimetidine given by continuous intravenous infusion is currently the only regimen approved by the US Food and Drug Administration for prevention of stress-related mucosal bleeding, various H2-receptor antagonists are often given by intermittent infusion for this indication in clinical practice [34]. However, the ability of these agents, when given intermittently, to maintain the intragastric pH above 4.0 is questionable, given their relatively short half-lives [35]. One study compared bolus doses and continuous infusions of cimetidine in the maintenance of intragastric pH above 4.0 in critically ill patients with at least one major organ system failure or multiple traumas. Patients were randomized to receive cimetidine either in bolus doses (up to 300 mg IV every 6 hours) or by continuous intravenous infusion (up to 50 mg/h for 24 hours) [36]. Most patients (87%) receiving continuous infusions maintained their intragastric pH above 4.0. There was a strong (92.9% positive) correlation between serum levels of cimetidine and intragastric pH above 4.0. Thus, cimetidine given by continuous infusion proved to be effective in maintaining pH above 4.0, thereby potentially preventing stress ulceration (Fig. 5) [36]. It is important to note that although H2RAs dosed as a continuous infusion are more effective in raising gastric pH than H2RAs dosed intermittently, there are no comparative trials evaluating these dosing regimens on clinical outcomes. One can only surmise that more complete acid suppression leads to enhanced GI protection.

### 5.3.2. Risk of nosocomial pneumonia

In regard to the association of increased pH—as a consequence of H2RA administration for SRMD prophylaxis—with potential for nosocomial pneumonia, Navab and Steingrub [37] reported that the results of several studies were conflicting. They concluded that other factors such as intragastric volume, severity of illness, bile reflux, and infection contributed to the development of pneumonia and that the pathogenesis of pneumonia is multifactorial [37]. As noted earlier, a large, well-controlled, randomized trial failed to find a difference in the rate of nosocomial pneumonia when ranitidine was compared to sucralfate in critically ill patients [32].

#### 5.3.3. Limitations of H2RAs

A significant limitation of H2RAs is the tendency for tolerance to occur within a relatively short interval after initiation of therapy. Two studies in healthy subjects demonstrated that the H2 RA ranitidine rapidly lost anti-secretory effect after the first day of administration [38,39]. One study reported the development of tolerance despite dose escalations on days 2 and 3 [38]. The other study found that continuous infusions of ranitidine were superior to intermittent injections only on day 1 of treatment [39]. The latter observation may seem to contradict results of the previously cited study comparing continuously infused and bolus doses of cimetidine. However, that study did not extend beyond a 12-hour observation period; thus, the impact of tolerance was not detected [36].

Some H2RAs interfere with cytochrome P450 metabolizing enzymes, potentially leading to drug interactions. Cimetidine and, to a lesser extent, ranitidine inhibit P450 enzymes, which may facilitate accumulation and possibly toxicity of coadministered drugs. In addition, H2RAs require dosing adjustments in the setting of renal dysfunction [40]. Another clinical concern is thrombocytopenia that may be induced by H2RAs, but it remains a rare occurrence in the absence of another independent risk factor [41].

### 5.4. Proton pump inhibitors

Gastric acid is produced and regulated by mechanisms within the parietal cell [42]. Transport of H+ by the proton pump, H+K+-ATPase, is the underlying mediator and final step in the regulation of acid secretion [43]. Proton pump inhibitors (PPIs) inactivate this enzyme and inhibit gastric acid secretion by specific inhibition of H+K+-ATPase at the secretory surface of the parietal cell [43], regardless of whether the cell is stimulated by histamine, gastrin, or acetylcholine.

The efficacy and utility of PPIs have been established for several acid-related GI disorders, but they have not, as yet, been approved as prophylaxis for GI bleeding associated with stress ulceration. Small open-label trials have examined the use of oral PPIs administered as extemporaneously compounded suspensions in patients at risk for stress ulcer. No clinically significant bleeding was reported in these trials, but drawing conclusions regarding efficacy is difficult because of several methodological limitations of these studies, such as the lack of a comparator arm and the small
number of patients. In the first open-label study by Lasky et al [44], 60 mechanically ventilated trauma patients with an additional risk factor for stress ulcer development received omeprazole suspension 40 mg given twice on the first day, approximately 6 hours apart, followed by 20 mg/d. Baseline pH (a secondary outcome in this study) was 3.3 for patients enrolled in this study, with a mean gastric pH increase to 6.7 after administration of omeprazole [44]. The second prospective open-label study by Phillips et al [45] included patients admitted to a surgical ICU and to a burn unit requiring mechanical ventilation and with at least one additional risk factor for stress ulcer disease. Seventy-five eligible patients received omeprazole suspension 40 mg, followed by a second 40-mg dose 6 to 8 hours later, and thereafter 20 mg daily. Four hours postomeprazole administration, the gastric pH increased to 7.1. The mean pH was 6.8 after starting therapy, up from an initial mean baseline pH of 3.5 ($P < .001$) [45]. No bleeding was reported in either of these trials, but the number of patients enrolled is likely insufficient to adequately assess an outcome of such low incidence [44,45].

Few clinical studies have compared a PPI with an H2RA for prophylaxis of GI bleeding in patients at risk for stress ulceration. Levy et al [46] compared omeprazole with ranitidine in patients with risk factors for stress ulcer–related bleeding. Sixty-seven patients were randomized to receive either ranitidine (n = 32), as a 50-mg bolus followed by a 50-mg IV infusion every 8 hours, or omeprazole (n = 32), as a 40-mg capsule administered orally or nasogastrically once a day [46]. Results showed significantly more clinically significant bleeding in the ranitidine group than in the omeprazole group (31% vs 6%, $P < .05$). In addition, fewer patients receiving omeprazole developed nosocomial pneumonia (3% vs 14%), although the difference between groups was not significant [46]. It should be noted, however, that despite randomization, the ranitidine-treated patients had more risk factors present at baseline than the omeprazole group (2.7 vs 1.9, $P < .05$) [46]. The fact that PPIs are more potent pump inhibitors raises theoretical concerns that their more potent acid suppression may actually confer increased risk of ventilator-associated pneumonia, which is a more frequent and serious problem than stress ulcer bleeding.

Additional randomized trials in stress ulcer patients have been published in abstract form only. One study compared omeprazole suspension administered nasogastrically with continuously infused ranitidine (150 or 200 mg/d) in 58 patients with at least 2 risk factors for stress ulcer–related bleeding. Omeprazole was shown to be superior to ranitidine in efficacy, safety, and cost. Clinically significant GI bleeding occurred in 3% of patients receiving omeprazole (n = 33) vs 16% of those receiving ranitidine (n = 25; $P < .05$) [47]. Another trial compared the efficacy of ranitidine 150 mg/d via continuous infusion, sucralfate 1 g every 6 hours via nasogastric tube, and omeprazole 40 mg IV every 12 hours as prophylaxis for stress ulcers in 108 patients with at least one risk factor for stress ulcer bleeding. Gastrointestinal bleeding occurred in 10.5% of patients in the ranitidine group (n = 38), 9.3% of those in the sucralfate group (n = 32), and none of those in the omeprazole group (n = 38) [48]. These studies suggest the superiority of omeprazole for the prophylaxis of GI bleeding in high-risk patients, but await the scrutiny of full-text publication.

Unlike H2RAs, PPIs do not seem to develop tolerance with sustained therapy. Two studies comparing omeprazole with ranitidine found that omeprazole maintained a pH greater than 4.0 over 72-hour treatment periods [38,39]. In one of the studies, the dose of omeprazole required to maintain this degree of acid suppression actually decreased by 43% from the first to the third day of treatment [38]. These results seem to be supported by those of a pilot study by Morris [49]. This study included 202 critically ill patients at high risk for GI bleeding who were randomized to receive 1 of 5 different dosing regimens of intravenous pantoprazole administered intermittently or a standard regimen of cimetidine administered as a continuous infusion, with each regimen given at least 48 hours and up to 7 days. The time to achieve pH 4.0 or more was 4.3 hours for the pantoprazole groups compared to 4.5 hours for the cimetidine group. In all pantoprazole groups, the percentage of time that pH remained at or above 4.0 increased on day 2 compared with day 1 (Fig. 6). In contrast, this percentage actually decreased on day 2 in the cimetidine group, despite administration of continuous infusions. These data suggest that intermittent dosing with intravenous pantoprazole can rapidly achieve...
and maintain a pH of 4.0 or more in critically ill patients, implicating a rapid onset of action in the presence of a requisite number of activated parietal cells to provide efficacy comparable to cimetidine in the absence of tolerance [49].

5.4.1. Administration issues
Proton pump inhibitors are inactivated by gastric acid and thus must be given as enteric-coated granules in gelatin capsules or enteric-coated tablets [50]. This requirement poses an obstacle to PPI therapy in patients who cannot swallow capsules. Attempts have been made to deliver the granules orally with orange juice, with applesauce, or in an aqueous solution with bicarbonate as a suspending agent [50]. However, these extemporaneous formulations, primarily evaluated in healthy subjects, have the potential to clog enteral feeding tubes [51], have variable bioavailability [52], and require that patients have adequate absorptive capacity, which is often altered during critical illness [2,53]. The availability of an intravenous PPI formulation offers a potentially attractive alternative to oral PPI administration, but there is a need for published outcome data regarding the role of this route of administration. Overall, data on the use of PPIs for the prevention of stress-related bleeding in critically ill patients are limited; hence, further studies are required to clearly establish their efficacy and safety for this indication.

5.5. Enteral nutrition

Enteral nutrition offers many benefits to critically ill patients. It may provide protection from postoperative sepsis by supporting mucosal immunity and modulate progression from gut ischemia to the systemic inflammatory response syndrome. Studies of animals subjected to brief periods of mesenteric ischemia and reperfusion have found that enteral feeding, as compared to total parenteral nutrition, reduced mortality rate, abnormal gastric motility, and organ permeability [54,55]. With regards to stress ulcer prophylaxis, however, the efficacy of enteral nutrition is controversial. A review of studies evaluating enteral nutrition as stress ulcer prophylaxis found that the effects of intragastric or postpyloric enteral nutrition on gastric pH were variable, but that intramucosal pH was generally lowered—a condition that predisposes to GI hemorrhage [56]. In animals subjected to intestinal hypoperfusion, it was found that aggressive delivery of enteral nutrition soon after trauma increased oxidative demands and exacerbated intestinal hypoxia, with the potential of leading to intestinal ischemia [57].

Trials that evaluated enteral nutrition for reducing risk of GI bleeding produced conflicting results and were limited by design, size, varying definitions of bleeding, and inconsistencies surrounding enteral nutrition [58-60]. It seems that although early enteral nutrition offers benefits to critically ill patients and is generally desirable, it should not be used as the sole method of prophylaxis against stress ulcer–related bleeding. Enteral nutrition should probably not be started until hemodynamic perturbations have been corrected in the ICU.

An additional issue to consider is the potential impact of enteral nutrition on the efficacy of the stress ulcer prophylaxis regimen a patient is receiving. Recent data presented in abstract form suggest that a continuous infusion of intravenous cimetidine (300 mg bolus followed by 50 mg/h) may be less effective at maintaining pH 4 or more in ICU patients that are enterally fed compared to intravenous

Fig. 6  The effect of intravenous pantoprazole and continuous infusion cimetidine on intragastric pH (n = 202). Adapted from Crit Care Med 2002;30(suppl):A34.
pantoprazole. Cimetidine increased intragastric pH 4 or more for 76% of the time in patients in the fasting state, but only for 49% of the time once the patients were enterally fed. The opposite held true in the patients receiving pantoprazole (doses ranging from 40 mg QD to 80 mg TID) with an average pH of 4 or more for 69% and 89% of the time during the nothing by mouth period and fed period, respectively. Regardless of the dose infused, pantoprazole was more effective during the period for which the patients were fed [61].

6. Cost of prophylaxis

When evaluating the cost of regimens used for prevention of stress ulcer–related bleeding, it is important to recognize that acquisition cost is only one of several factors that need to be considered. Other factors include cost of preparing and administering the agent, as well as the potential for overuse, adverse effects, and risk of bleeding.

Evidence strongly suggests that stress ulcer prophylaxis should be limited to patients with established risk factors for clinically significant GI bleeding. Several institutions have developed guidelines for stress ulcer prophylaxis in an effort to improve quality and cost of patient care. Two medical centers that instituted such guidelines evaluated their impact on drug costs and frequency of major GI bleeding. One study found that limiting stress ulcer prophylaxis to patients with established risk factors resulted in significantly fewer patients receiving prophylaxis and a significant reduction (80% decrease) in drug costs, without altering frequency of GI bleeding [62]. The other study implemented the guidelines in 2 phases—a 2-month preintervention surveillance and a 2-month postintervention drug use evaluation. The investigators found that mean duration of prophylaxis and mean medication costs were both reduced from phase 1 to phase 2 (8.69 ± 8.04 days and $36.19 ± 38.29 vs 6.31 ± 6.65 days and $24.92 ± 27.36, respectively), resulting in an overall decrease in the cost of hospitalization (Fig. 7). They also noted that when clinically significant bleeding did occur, it resulted in extended hospital stays and a concomitant increase in overall costs [63].

7. Conclusions

The etiology of SRMD is multifactorial, but 2 conditions that seem to be necessary are intraluminal acid and gastric mucosal ischemia. Therefore, prophylaxis and treatment require maintenance of perfusion and protection against acid damage through elevation of gastric pH. Underlying disease and risk factors including surgery, burns, trauma, respiratory failure requiring mechanical ventilation, and coagulopathy predispose patients to SRMD. Gastrointestinal bleeding exacerbates the underlying illness and results in an increase in morbidity and mortality. Therefore, in high-risk patients, the emphasis should be on prevention of SRMD rather than on treatment of complications.

Several approaches can be taken to prevent SRMD. First, it is extremely important to restore hemodynamic stability to maximize mesenteric perfusion and avoid ischemia. Second, suppressing acid production pharmacologically is fundamental to preventing stress-related ulceration and potential GI bleeding. If intraluminal pH is kept at or above 3.5, bleeding from stress ulcers can be minimized. Because pH titration is not common in clinical practice, it is important to be knowledgeable about the medical literature, which can assist us in choosing the appropriate pharmacologic agent. Although H2RAs have demonstrated superiority over placebo, antacids, and sucralfate in preventing clinically significant stress-related GI hemorrhage, their effectiveness at raising intragastric pH may be limited as tolerance...
quickly develops. Proton pump inhibitors have been shown to suppress acid production more effectively than H2RAs, but data on their role in SRMD prophylaxis are limited, and they have not, as yet, received approval for this indication. They do possess theoretical advantages over H2RAs. In contrast to H2RAs, PPIs lack tolerance, and thus are effective for longer periods in critically ill patients. Further, they are clearly more potent antisecretory agents.

The largest disadvantage at the present time is the fact that there are currently limited published data assessing the role of PPIs in the prevention of stress-related bleeding. Enteral nutrition improves splanchnic blood flow, but trials have been inconsistent with regard to its use in stress ulcer prophylaxis and yielded conflicting results on its ability to reduce GI bleeding. It should therefore not be used as sole therapy for stress-ulcer prophylaxis.

Choosing an appropriate prophylactic regimen to prevent complications associated with stress ulcers requires that the clinician carefully evaluate the available data. Studies performed so far that seek to determine the best means of prevention have been characterized by conflicting outcomes and have several limitations that need to be considered.

Acid suppression is an established preventive measure; however, they are clearly more potent antisecretory agents. The largest disadvantage at the present time is the fact that there are currently limited published data assessing the role of PPIs in the prevention of stress-related bleeding. Enteral nutrition improves splanchnic blood flow, but trials have been inconsistent with regard to its use in stress ulcer prophylaxis and yielded conflicting results on its ability to reduce GI bleeding. It should therefore not be used as sole therapy for stress-ulcer prophylaxis.

Acknowledgment

This work is supported by Wyeth Pharmaceuticals, Philadelphia, PA, with editorial support provided by Accel Medical Education, New York, NY.

References

Stress ulcer prophylaxis


