

# **CE** Stress-related Mucosal Disease in the Intensive Care Unit

## An Update on Prophylaxis

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### ABSTRACT

Gastric ulcers have been known to develop in critically ill patients secondary to physiological stress since the 19th century. It is only relatively recently that stress ulcer prophylaxis has become an established routine practice in the intensive care unit. Numerous terms have been used to describe stress ulcers, but stress-related mucosal disease (SRMD) is commonly used. Significant morbidity and mortality in critically ill patients is caused by SRMD and related bleedings, but the incidence depends on the definition of bleeding. Pathophysiology of SRMD is multifactorial and involves a complex set of in-

teractions that causes a breakdown of mucosal proactive defenses, leading to ulceration. Critically ill patients are at an increased risk for developing SRMD and subsequent bleeding secondary to several risk factors. To minimize stress-related mucosal bleeding, several regimens have been used. This article presents an update on the incidence, pathophysiology, risk factors, and prophylaxis of SRMD.

**Keywords:** gastrointestinal bleeding, intensive care unit, stress-related mucosal bleeding, stress-related mucosal disease, stress ulcer prophylaxis

Since the 1800s, erosions and gastric ulcers have been known to develop, secondary to physiological stress, in critically ill patients.<sup>1</sup> However, it was not until the early 1970s that studies began to appear suggesting that gastric acid may be the cause of stress ulcer development in this population.<sup>2,3</sup> In the 1980s, the incidence of stress-ulcer—related bleeding was decreased by therapies that increased gastric pH. Hence, stress ulcer prophylaxis became established as a routine practice in most intensive care units (ICUs).

Numerous terms have been used to describe stress-related gastric damage in critically ill patients, including stress ulcers/ulceration, stress erosions, stress gastritis, hemorrhagic gastritis, erosive gastritis, and stress-related mucosal disease (SRMD).<sup>4</sup> All these terms imply a physiological stress that causes damage to the gastric mucosa. For the purposes of this review, the term SRMD will be used to describe this

condition. This article presents an overview of the incidence, risk factors, pathophysiology, and prevention of SRMD.

### Definitions

Just as the terms used to describe SRMD were confusing, so were the definitions of clinically important bleeding in the 1990s' medical literature (eg, guaiac-positive stool and nasogastric [NG] aspirate, frank hematemesis or melena without an accompanied decrease in hemoglobin level, a drop in blood pressure, or a need for blood transfusion).<sup>1,5,6</sup> However, in 1994, a landmark trial by Cook et al<sup>7</sup> evaluated the potential risk of factors for gastrointestinal (GI) bleeding in critically ill patients. *Clinically*

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*important bleeding* was defined as overt bleeding (ie, hematemesis, gross blood or “coffee grounds” material in NG aspirate, hematochezia, or melena) complicated by one of the following within 24 hours after the onset of bleeding: a spontaneous decrease of more than 20 mm Hg in systolic blood pressure; an increase of more than 20 beats per minute in the heart rate, or a decrease of more than 10 mm Hg in the systolic blood pressure measured on sitting up; or a decrease of more than 2 g/dL in the hemoglobin level and subsequent blood transfusion, after which the hemoglobin level did not increase by a value defined as the number of units of blood transfused minus 2 g/dL.

## Epidemiology

SRMD is known to be a significant cause of morbidity and mortality in critically ill patients in the ICU. The morbidity due to SRMD and associated stress-related bleeding can increase the length of stay in the ICU from 4 to 8 days.<sup>8</sup> Mortality rate ranges from 50% to 77% in critically ill patients who develop stress-related mucosal bleeding during hospitalization, which can be as much as 4 times higher than it is in ICU patients without this complication. Although patients generally die from the underlying medical condition or multiple organ failure than from actual bleeding,<sup>3,7,9–11</sup> mortality rates have increased with the rise in the incidence and severity of SRMD.<sup>12</sup> However, bleeding is generally considered a marker of illness severity. Since it is possible to identify patients who are at the greatest risk for stress-related bleeding, prophylaxis of SRMD is a means to improve outcomes.

However, the prevalence of SRMD in critically ill patients largely depends on the definitions used to describe it. Endoscopic evidence of mucosal damage is seen in most patients within hours of admission to the ICU (74%–100%).<sup>5</sup> However, when *occult bleeding* (defined as guaiac-positive stools or NG aspirates) is used as an endpoint, the prevalence ranges from 15% to 50%.<sup>4</sup> Clinically *overt bleeding*, as previously defined, remains problematic, occurring in 5% to 25% of critically ill patients.<sup>4,7,13,14</sup> However, clinically overt bleeding does not predict an impending clinically important bleeding.<sup>10,15</sup>

The incidence of *clinically important* bleeding in adult patients has declined since the 1980s. Studies published before the 1999 publication of the American Society of Health-System Pharmacists therapeutic guidelines concerning stress ulcer prophylaxis reported

that the incidence of clinically important bleeding was 2% to 6% in patients not receiving prophylaxis.<sup>1,7,16</sup> However, prospective studies published since 1999 indicate that the risk for clinically important GI bleeding is dramatically decreasing, an effect that is probably a result of advances in the monitoring and support of critically ill patients, including the optimization of hemodynamic status, improved oxygenation of tissues, and treatment of sepsis.<sup>5,17</sup> In studies published since 2000, the incidence of clinically important bleeding has been reported to range between 0.1% and 4% with or without prophylaxis.<sup>7,18–20</sup>

Although the incidence of stress-related mucosal bleeding has decreased dramatically over the last 2 decades, prophylaxis still remains a key therapy for critically ill patients. However, patients with a low risk for clinically important bleeding may not derive benefits from prophylaxis. Cook and colleagues showed that among 847 patients with risk factors, 31 patients (3.7%) experienced clinically important bleeding, and among 1405 patients without risk factors, only two (0.1%) had clinically important bleeding.<sup>7</sup> One could even suggest whether there is a need for prophylaxis of stress-related mucosal bleeding, as therapy does not reduce mortality.<sup>1,19–22</sup> However, general medical consensus continues to support prophylaxis for patients who are considered to be at high risk for stress-related mucosal bleeding.<sup>1,7,23,24</sup>

## Pathophysiology of SRMD

The pathophysiology of SRMD is believed to be multifactorial and not completely understood. It involves a complex set of interactions that causes a breakdown of the mucosal protective defenses, allowing aggressive physiological factors to produce injury and ulceration.

A major factor in the development of SRMD is splanchnic hypoperfusion, which results from a number of stress-related effects that the body produces in response to critical illness (eg, hypotension and hypovolemia). These stress-related effects may include sympathetic nervous system activation, increased catecholamine release and vasoconstriction, hypovolemia, decreased cardiac output, and release of proinflammatory cytokines.<sup>11</sup> Initially, these effects are beneficial, shifting blood away from the GI tract and skin to locations where it is needed more, for example, the brain and muscle tissues.<sup>11</sup> As the initiating conditions persist, stress-related responses

damage the integrity of the gastric mucosa by reducing GI blood flow, oxygen delivery, and bicarbonate secretion.<sup>11</sup> As the permeability of the mucosal barrier is compromised, back-diffusion of hydrogen ions and pepsin further damages the mucosal epithelial layer.<sup>14</sup> Slowed mucosal blood flow impairs mucosal healing. Gastrointestinal motility is decreased following splanchnic hypoperfusion, delaying the removal of acidic material and other irritants from the stomach, which prolongs exposure of the poorly defended gastric mucosa to gastric acid, increasing the risk of ulceration.<sup>11,13</sup>

Another important factor involved in the development of SRMD is reperfusion injury. As blood flow is restored after long periods of hypoperfusion, elevated levels of nitric oxide synthetase lead to hyperemia, cell death, and an enhanced inflammatory response.<sup>11,13,14</sup> This results in further GI epithelial cell damage and ulceration.

Stress-related mucosal lesions are typically located in the acid-producing areas of the stomach (ie, upper body and fundus). However, these lesions rarely lead to hemodynamically significant GI bleeding. If bleeding does occur, it is generally seen in patients with concomitant coagulopathy.<sup>7</sup>

Endoscopically, lesions lie along a continuum where they can range from superficial erosions, known as stress-related injury, to stress ulcers. Associated with clinically significant bleeding, stress ulcers are deep focal lesions that penetrate the submucosa, generally occurring between the third and seventh day after ICU admission.<sup>5,9,7,15</sup> On the other hand, stress-related injury lesions have a low risk of clinically important bleeding.<sup>14</sup> Both stress-related injury and stress ulcers are found in physically stressed patients.<sup>1,6,25</sup>

**Risk Factors for Stress-related Mucosal Bleeding**

As previously mentioned, critically ill patients are at increased risk for developing SRMD and subsequent bleeding as a result of both underlying disease and therapeutic interventions. Several clinical conditions and medications place patients at risk for clinically important GI mucosal damage. In a multicenter observational study of 2252 patients, Cook et al<sup>7</sup> found that respiratory failure (mechanical ventilation for at least 48 hours) and coagulopathy (platelet count of <50 000 mm<sup>3</sup>, international normalized ratio of >1.5, partial thromboplastin time of >2

times the control value) were strong independent risk factors for stress-related mucosal bleeding. The frequency of bleeding was 3.7% if one or both of these risk factors were present, whereas patients without either of these complications had a bleeding risk of 0.1%. The risk factors for stress-related mucosal bleeding are summarized in Table 1. In addition, Pimentel et al<sup>17</sup> found that older patients and postoperative abdominal aortic aneurysm repair patients were also at significant risk for developing stress-related GI bleeding. As the number of risk factors increases, the risk for stress-related bleeding also increases.

**Prophylaxis of SRMD**

Several regimens have been used to prevent stress-related mucosal bleeding (Table 2).<sup>1,26-28</sup> Options for prophylaxis include antacids, sucralfate, histamine<sub>2</sub>-receptor antagonists (H<sub>2</sub>RAs), and proton pump inhibitors (PPIs). In a metaanalysis by Cook and colleagues,<sup>29</sup> various prophylactic therapies, including antacids, sucralfate, and H<sub>2</sub>RAs, were found to reduce the incidence of overt or clinically important bleeding compared with no prophylaxis. However, antacids are no longer considered a

**Table 1: Risk Factors for Stress-related Mucosal Bleeding**<sup>1-3,9,22,23</sup>

Respiratory failure requiring mechanical ventilation for more than 48 h*
Coagulopathy (international normalized ratio > 1.5 or platelet count < 50 000 mm <sup>3</sup> )*
Acute renal insufficiency
Acute hepatic failure
Sepsis syndrome
Hypotension
Severe head or spinal cord injury
Anticoagulation
History of gastrointestinal bleeding
Low intragastric pH
Thermal injury involving more than 35% of the body surface area
Major surgery (lasting more than 4 h)
Administration of high-dose corticosteroids (250 mg/d of steroids or equivalent hydrocortisone)
Enteral feedings

\*Independent risk factors for bleeding.

**Table 2: Common Medications Used for Prophylaxis of Stress-related Mucosal Disease<sup>1,26-28</sup>**

Medication	Route	Normal Renal Function	Renal Insufficiency	Comments
<b>Histamine<sub>2</sub>-receptor antagonists</b>				
Cimetidine	IV	50 mg/h continuous infusion	If CL <sub>cr</sub> < 30 mL/min: decrease dose to 25 mg/h	For patients requiring a more rapid elevation of gastric pH, continuous infusion may be preceded by a 300-mg loading dose administered as an IV infusion.
	po; NG tube	300 mg every 6 h	300 mg every 12 h orally or intravenously has been recommended	Some patients may require higher doses; this should be accomplished by administering 300 mg more frequently, but the daily dose should not exceed 2400 mg.
Famotidine	IV	1.7 mg/h continuous infusion	If CL <sub>cr</sub> < 30 mL/min: 0.85 mg/h by continuous infusion	
	po; NG tube; IV	20 mg every 12 h	If CL <sub>cr</sub> < 30 mL/min: decrease dose to 20 mg once daily	
<b>Sucrose-aluminum complex</b>				
Sucralfate	po; NG tube	1 g every 6 h	Use with caution in severe renal impairment	
<b>Proton pump inhibitors</b>				
			No adjustment necessary	
Esomeprazole	po; NG tube; IV	40 mg every day		
Lansoprazole	po; NG tube; IV	15 or 30 mg every day		
Omeprazole	po; NG tube; JT; DT	Two 40-mg doses separated by 6–8 h on the first day, then 20–40 mg daily		
Pantoprazole	po; NG tube; IV	40 mg every day		

Abbreviations: IV, intravenous; CL<sub>cr</sub>, creatinine clearance; po, per os (orally); NG, nasogastric; JT, jejunal tube; DT, duodenal tube.

viable therapeutic option because of the labor-intensive dosing frequency and potential side effects.<sup>1,11,24,29</sup> Another option is sucralfate. Although less widely used than H<sub>2</sub>RAs or PPIs, sucralfate is more effective than no prophylaxis in reducing overt bleeding and is associated with a decreased mortality.<sup>1,22,24,30</sup> Nonetheless, its effectiveness in reducing clinically important bleeding is more variable than that of antacids, H<sub>2</sub>RAs, or placebo.<sup>1,19,20,22,29,31</sup> H<sub>2</sub>RAs, however, are still considered first line of defense by many clinicians.<sup>29</sup> In a recent 2004 national survey of 2000 intensivists, H<sub>2</sub>RAs were chosen first

nearly 64% of the time, followed by PPIs (23.1%).<sup>29</sup> As more PPIs are introduced to the market, the percentage of clinicians prescribing them will likely increase.

### **Sucralfate**

Sucralfate is a basic nonabsorbable aluminum salt of saccharose octasulfate.<sup>6</sup> It is physicochemically an antacid, but it does not lead to a significant pH increase; rather, its mechanism of protection is multifactorial: (1) it forms a protective barrier on the surface of gastric mucosa; (2) it stimulates mucus and bicarbonate secretion; (3) it

stimulates epidermal growth factor and renewal; and (4) it improves mucosal blood flow and enhances prostaglandin release.<sup>4</sup> Through these actions, sucralfate strengthens the mucous barrier by improving the neutralization capacity of the mucous layer.<sup>6</sup>

Sucralfate is available as either a tablet or a suspension and can be administered through an NG tube. However, this may be labor intensive or result in a clogged tube.<sup>1,9,32</sup> Since sucralfate is not systemically absorbed, it may decrease the absorption of other concomitantly administered oral medications such as ciprofloxacin, theophylline, phenytoin, ranitidine, levothyroxine, ketoconazole, and digoxin.<sup>33</sup> To minimize this interaction, it is recommended that these drugs be administered 2 hours before sucralfate.<sup>34</sup> Sucralfate may also interact with enteral feedings, resulting in diminished efficacy or a clogged feeding tube.<sup>1</sup> Though not well studied, caution is recommended when combining enteral formulas containing casein and sucralfate.<sup>35</sup> When continuous tube feedings are used in conjunction with sucralfate, it is recommended that the feedings be held at least 30 minutes before and after the administration of sucralfate.<sup>1,35</sup> Bezoars have also been reported in patients treated with sucralfate.<sup>1</sup> Case reports suggest that sucralfate may contribute to bezoar formation, especially when given to patients with delayed gastric emptying in combination with enteral feedings. Sucralfate should not be administered through duodenal or jejunostomy feeding tubes because the medication would bypass its site of action. Other adverse effects associated with sucralfate include constipation and aluminum toxicity.<sup>5,6</sup> Toxic elevations in plasma aluminum levels have been reported in critically ill patients requiring continuous veno-venous hemofiltration who were receiving sucralfate. Sucralfate may also be associated with a lower incidence of nosocomial pneumonia secondary to lower incidence of gastric gram-negative colonization. The development of nosocomial pneumonia in critically ill patients has been linked to increased gastric pH. In theory, as gastric pH is raised, gram-negative bacteria proliferate in the stomach. Microaspiration of oropharyngeal or gastric contents in the presence of the endotracheal tube colonizes the trachea, often leading to pneumonia.<sup>36,37</sup> Sucralfate may offer an advantage over H<sub>2</sub>RAs and possibly PPIs for the prophylaxis of SRMD, as it has a lower incidence

of nosocomial pneumonia in comparison with antacids and H<sub>2</sub>RAs.<sup>29,36,38,39</sup> However, this advantage may be in doubt. Several recent studies have demonstrated no significant differences in the incidence of nosocomial pneumonia in critically ill patients when treated with sucralfate versus acid-suppression therapy or placebo.<sup>16,19-21,40</sup>

Acid suppression has become the primary therapy for patients at risk for stress-related mucosal bleeding. Treatment usually involves H<sub>2</sub>RAs, although the use of PPIs does appear to be increasing, despite a relative lack of published data supporting their use.<sup>14,24,41</sup>

### **Histamine<sub>2</sub>-receptor Antagonists**

H<sub>2</sub>RAs are the most widely used drugs for stress-related mucosal bleeding prophylaxis. They decrease gastric acid secretion through a reversible, competitive inhibition of histamine-stimulated acid secretion.<sup>9</sup> Four H<sub>2</sub>RAs are available in the United States for the prophylaxis of stress-related mucosal bleeding: cimetidine, ranitidine, famotidine, and nizatidine. Famotidine and ranitidine are the most often used within the ICU setting.<sup>24</sup>

Several clinical trials have evaluated the efficacy of H<sub>2</sub>RAs for the prevention of stress-related mucosal bleeding. In a metaanalysis, H<sub>2</sub>RAs were found to be significantly better than placebo in reducing the incidence of both overt and clinically important bleeding.<sup>29</sup> Cook et al<sup>21</sup> reported that H<sub>2</sub>RAs significantly lowered the incidence of clinically important bleeding in mechanically ventilated patients compared with sucralfate. Conversely, there have been several studies that have shown no significant differences in the reduction of clinically important bleeding using H<sub>2</sub>RAs compared with either placebo or sucralfate.<sup>16,19,20,22</sup>

Tolerance to H<sub>2</sub>RA acid inhibition develops as early as 72 hours after administration.<sup>9</sup> However, clinical significance of this has not been demonstrated. Administration of H<sub>2</sub>RAs by continuous infusion provides better control of gastric pH than bolus infusion. But this is not more effective in preventing clinically significant stress-related mucosal bleeding.<sup>15,21,29,40</sup> Administration through oral or NG tube is also equally effective in reducing the incidence of stress-related mucosal bleeds.<sup>15</sup>

H<sub>2</sub>RAs are usually very safe and the adverse effects are minor. Central nervous system toxicity (confusion, delirium, hallucinations, slurred speech, and headaches) has been observed in elderly patients and occurs primarily

with intravenous administration.<sup>15</sup> Hematologic toxicity, in the form of thrombocytopenia, is often attributed to H<sub>2</sub>RAs. However, it is difficult to assess whether H<sub>2</sub>RAs are the cause of thrombocytopenia in critically ill patients. Thrombocytopenia may be a marker of disease severity or secondary to another concurrent agent such as heparin, milrinone, or phenytoin.<sup>42</sup> Although there have been numerous published case reports of H<sub>2</sub>RA-associated thrombocytopenia, the rate of incidence is unknown and no direct correlation has been demonstrated.<sup>42</sup> If thrombocytopenia does occur, patients with mild thrombocytopenia (50 000–100 000 mm<sup>3</sup>) should continue therapy since the risk of bleeding is minimal. However, if the patient's platelet count is less than 50 000 mm<sup>3</sup>, the risk-to-benefit ratio favors therapy with an alternative agent, such as a PPI.<sup>42</sup>

Drug interactions can occur with H<sub>2</sub>RAs, particularly with cimetidine. Cimetidine interferes with cytochrome P450 metabolizing enzymes, decreasing the clearance of several drugs (eg, warfarin, ketoconazole, theophylline, phenytoin).<sup>1</sup> However, few of these interactions are clinically important when patients are well monitored.

### **Proton Pump Inhibitors**

Proton pump inhibitors (eg, lansoprazole, omeprazole, esomeprazole, pantoprazole, rabeprazole) are substituted benzimidazoles that inhibit gastric secretion in a dose-dependent manner. They are the most potent antisecretory agents available,<sup>5</sup> and can elevate or maintain intragastric pH above 6, which is necessary to maintain clotting in patients at risk for rebleeding or ulcer healing.<sup>14,43,44</sup> Under acidic conditions in parietal cells, PPIs irreversibly inhibit the final step in acid production (the transport of H<sup>+</sup> by the proton pump H<sup>+</sup>/K<sup>+</sup> ATPase), providing long-lasting suppression of acid secretion. Unlike H<sub>2</sub>RAs, PPIs inhibit both histamine-induced and vagally mediated gastric acid secretion. In addition, because PPIs are activated in the acidic compartments of parietal cells, they only inhibit actively secreting proton pumps.<sup>45</sup> Consequently, the maximum activity of PPIs does not occur for 2 days after starting therapy. However, this is not clinically significant, as SRMD occurs at the mucosal sites of most parietal cell activity. In addition, unlike in the case of H<sub>2</sub>RAs, patients do not develop tolerance to PPIs with continued use. Conversely,

rebound acid hypersecretion is common after discontinuation of PPI therapy.<sup>45</sup>

Available data on the use of PPIs for prevention of stress-related mucosal bleeding have been promising, although the number of comparative studies has been limited. Drawing conclusions regarding their efficacy has been difficult owing to methodological limitations such as lack of a control group or small sample size. However, 2 recent trials show that omeprazole is as effective as H<sub>2</sub>RAs in the prevention of stress-related mucosal bleeding when given either intravenously or as an immediate-release bicarbonate suspension.<sup>19,44</sup> Nevertheless, when compared to placebo, neither the H<sub>2</sub>RAs nor the PPIs were significantly different in reducing stress-related clinically important bleeding.<sup>19</sup> These findings are consistent with other trials in which prophylactic medications did not reduce the incidence of stress-related hemorrhage.<sup>20,22</sup>

Proton pump inhibitors can be administered through an NG tube into the stomach or jejunum in patients who are unable to take medications by mouth.<sup>5</sup> When oral medications are not tolerated, intravenous PPIs (esomeprazole, lansoprazole, and pantoprazole) are available as another option.

Furthermore, PPIs are well tolerated, with a low incidence of adverse drug effects. However, there have been reports that PPIs can cause abdominal pain, nausea, diarrhea, and headaches.<sup>1,46</sup> Furthermore, PPIs have recently been associated with an increased incidence of *Clostridium difficile* diarrhea. Dial et al<sup>47</sup> noted that PPI use independently predicted the development of *C difficile* diarrhea in hospitalized patients (adjusted odds ratio 2.1, 95% CI 1.2–3.5), but not with the use of H<sub>2</sub>RAs. In a case control study of 188 patients, *C difficile* diarrhea was associated with the use of PPIs (adjusted odds ratio 2.7, 95% CI 1.4–5.2).<sup>47</sup>

However, PPIs have the potential for drug interactions. PPIs are metabolized by hepatic cytochrome (CYP450) isoenzymes and therefore may interfere with the elimination of other drugs cleared by this route. Of the available PPIs, omeprazole has the highest potential for drug interaction.<sup>5</sup> Omeprazole inhibits several cytochrome enzymes, including CYP2C19, the major metabolizing enzyme of the CYP system. Omeprazole also interferes with the metabolism of cyclosporine, diazepam, phenytoin, and warfarin.<sup>5</sup> Omeprazole also induces the expression of CYP1A2, thereby increasing the metabolism of several antipsychotic drugs, tacrine, and

theophylline. Esomeprazole, the S-isomer of omeprazole, may interfere with the hepatic enzyme CYP2C19. However, no significant drug interactions have been demonstrated between esomeprazole and phenytoin, warfarin, quinidine, clarithromycin, or amoxicillin.<sup>5</sup> Importantly, esomeprazole decreases the metabolism of diazepam by 45% when given concomitantly. Pantoprazole has the lowest potential for drug interactions secondary to its low affinity for the CYP enzymes.<sup>11</sup> Lansoprazole, the second PPI to become available in the United States, may interfere with the metabolism of warfarin, as may rabeprazole.<sup>15</sup>

### Enteral Nutrition

Enteral feeding is widely used in the critically ill patient population because it offers many benefits.<sup>23,48</sup> It optimizes splanchnic distribution of blood flow and lessens macroscopic ulceration. Mucosal immunity may be supported via stimulation of gut-associated lymphoid tissue. However, with respect to SRMD prophylaxis, the efficacy of enteral feeding is controversial. Clinical trials have been inconsistent with regard to its ability to reduce GI bleeding. Studies have been confounded by poor study designs (eg, inadequate statistical power and concurrent use of pharmacologic prophylaxis) and small sample sizes.<sup>48</sup> While enteral nutrition offers many benefits to critically ill patients, it should not be used as the sole method of prophylaxis against SRMD.

### Discontinuation of Prophylaxis

Patients who are receiving stress-related prophylactic therapy should be assessed daily, and if their clinical condition improves, discontinuation should be considered. Since medications used to prevent stress-related mucosal bleeding do not decrease the overall mortality rate, clinicians should weigh the benefits, costs, and any potential adverse effects when contemplating length of therapy. Many clinicians discontinue stress-related ulcer prophylaxis when patients begin an oral diet or when they are transferred from the ICU.<sup>24,31</sup>

### Conclusion

SRMD continues to pose a significant threat to critically ill patients. Although the incidence of clinically important bleeding has diminished significantly over the last 2 decades, the consequences of bleeding can be devastating.<sup>7,18</sup> Therefore, critically ill patients at high risk for

GI hemorrhage still need to be started on appropriate prophylactic therapy.

Still, admission to the hospital or the ICU alone is not sufficient reason to begin SRMD prophylaxis. Only patients with respiratory failure requiring mechanical ventilation for more than 48 hours, renal insufficiency, and coagulopathy are at significant risk for such bleeding and are likely to benefit from prophylaxis.

The most appropriate prophylactic agent for treating SRMD remains to be determined. Sucralfate, which does not alter intragastric pH, was thought to offer an advantage by not promoting nosocomial pneumonia. However, studies have cast doubt on the association between acid-suppressive therapy and nosocomial pneumonia.

As for acid-suppressive therapy, H<sub>2</sub>RAs are the most widely used class of agents for SRMD prophylaxis. They have proven to be very effective in reducing the risk of both overt and clinically important bleeding in critically ill patients. But their position in the ICU is slipping as PPIs are increasing in acceptance. PPIs are at least as effective as H<sub>2</sub>RAs, as a limited number of clinical trials have demonstrated. But these trials were small, lacked an active comparator, varied in the number of risk factors, and used a different definition of clinically important bleeding than previously established.<sup>7,43,48-50</sup>

The incidence of stress-related mucosal bleeding is decreasing. As seen in recent clinical trials, prophylactic therapy did not alter the already low incidence of stress-related clinically important bleeding in high-risk ICU patients.<sup>19,20,22</sup> There may be a time when routine prophylactic therapy for SRMD will not be necessary. More studies are needed before we can say for certain that prophylactic therapy is no longer justified. Until then, we as healthcare professionals should continue to evaluate risk and assess the need for SRMD prophylaxis.

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Test writer: Jane Baron, CS, RN, ACNP

Contact hours: **2.0**

Category: A

Passing score: 8 correct (73%)

**CE Test Instructions**

To receive CE credit for this test (ID# CI1821), mark your answers on the form below, complete the enrollment information, and submit it with the \$12 processing fee (payable in US funds) to the American Association of Critical-Care Nurses (AACN). Answer forms must be postmarked by June 1, 2009. Within 3 to 4 weeks of AACN's receiving your test form, you will receive an AACN CE certificate.

The American Association of Critical-Care Nurses (AACN) is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation. AACN has been approved as a provider of continuing education in nursing by the State Boards of Nursing of Alabama (#ABNP0062), California (#01036), Florida (#FBN2464), Iowa (#332), and Louisiana (#ABN12). AACN programming meets the standards for most other states requiring mandatory continuing education credit for relicensure.

<b>CE Test Form</b>		Test ID#: CI1821 <b>FORM EXPIRES</b> <b>June 1, 2009</b> Fee: \$12																	
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# Stress-related Mucosal Disease in the Intensive Care Unit: An Update on Prophylaxis

### Objectives:

Upon completion of this article, the reader will be able to:

1. Review the incidence and risk factors for stress-related mucosal disease (SRMD).
2. Describe the pathophysiology of SRMD.
3. Identify 3 types of medications used in prophylaxis of SRMD, their actions and adverse effects.

**1. What complication is associated with clinically important bleeding?**

- a. A spontaneous decrease of less than 20 mm Hg of systolic blood pressure
- b. A decrease of fewer than 20 beats per minute in heart rate
- c. An increase of 10 mm Hg of systolic blood pressure upon sitting up
- d. An increase of more than 20 beats per minute in heart rate

**2. What is the mortality rate in critically ill patients with SRMD who develop stress-related mucosal bleeding during hospitalization?**

- a. 10% to 25%
- b. 25% to 50%
- c. 50% to 77%
- d. >90%

**3. What is the reported incidence of clinically important bleeding since 2000?**

- a. 0.1% to 4%
- b. 4% to 8%
- c. 10% to 25%
- d. >50%

**4. What is a major factor in the development of SRMD?**

- a. Splanchnic hypoperfusion
- b. Portal hypertension
- c. Pulmonary hypotension
- d. Vagal nerve overstimulation

**5. Which of the following are factors that contribute to damaging the gastric mucosa?**

- a. Increased gastrointestinal blood flow and diminished oxygen delivery
- b. Increased bicarbonate secretion and diminished gastrointestinal blood flow
- c. Decreased bicarbonate secretion and decreased oxygen delivery
- d. Increased gastrointestinal blood flow and diminished bicarbonate secretion

**6. What is reperfusion injury in the development of SRMD?**

- a. Blood flow is restored, increasing nitric oxide synthetase
- b. Blood flow is diminished, leading to increased bicarbonate secretion
- c. Blood flow is diminished, leading to diminished hydrogen ion levels
- d. Blood flow is restored, leading to increased peptin levels

**7. What are the 2 strong independent risk factors for stress-related mucosal bleeding?**

- a. Respiratory failure and coagulopathy
- b. Cardiac failure and sepsis
- c. Renal failure and low bicarbonate levels
- d. Hepatic failure and elevated ammonia levels

**8. Which of the following is a mechanism of protection of sucralfate?**

- a. Forms protective barrier on the surface of small-intestine mucosa
- b. Stimulates mucus and decreases bicarbonate production
- c. Stimulates epidermal growth factor and renewal
- d. Decreases prostaglandin release

**9. How do ranitidine and famotidine decrease gastric acid secretion?**

- a. They form a barrier on the surface of mucosa and enhance prostaglandin release.
- b. They inhibit histamine-stimulated acid secretion.
- c. They stimulate mucus and bicarbonate secretion.
- d. They stimulate epidermal growth factor and renewal.

**10. What is a potential adverse effect on elderly patients receiving intravenous histamine-2 receptor antagonist medications?**

- a. Gastric bleeding
- b. Tachycardia
- c. Hypertension
- d. Central nervous system toxicity

**11. When does maximum activity of proton pump inhibitors occur?**

- a. 24 hours after starting therapy
- b. 48 hours after starting therapy
- c. 6 hours after starting therapy
- d. 12 hours after starting therapy