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 interactions 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. 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. 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). 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 (e.g., 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). However, in 1994, a landmark trial by Cook et al evaluated the potential risk of factors for gastrointestinal (GI) bleeding in critically ill patients. Clinically...
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. 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, mortality rates have increased with the rise in the incidence and severity of SRMD. 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%). However, when occult bleeding (defined as guaiac-positive stools or NG aspirates) is used as an endpoint, the prevalence ranges from 15% to 50%. Clinically overt bleeding, as previously defined, remains problematic, occurring in 5% to 25% of critically ill patients. However, clinically overt bleeding does not predict an impending clinically important bleeding.

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. 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. 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.

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. One could even suggest whether there is a need for prophylaxis of stress-related mucosal bleeding, as therapy does not reduce mortality. However, general medical consensus continues to support prophylaxis for patients who are considered to be at high risk for stress-related mucosal bleeding.

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. 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. 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. As the permeability of the mucosal barrier is compromised, back-diffusion of hydrogen ions and pepsin further damages the mucosal epithelial layer. 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.

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. 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.

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. On the other hand, stress-related injury lesions have a low risk of clinically important bleeding. Both stress-related injury and stress ulcers are found in physically stressed patients.

### 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 2232 patients, Cook et al found that respiratory failure (mechanical ventilation for at least 48 hours) and coagulopathy (platelet count of <50 000 mm$^3$, 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 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). Options for prophylaxis include antacids, sucralfate, histamine2-receptor antagonists (H$_2$RAs), and proton pump inhibitors (PPIs). In a metaanalysis by Cook and colleagues, various prophylactic therapies, including antacids, sucralfate, and H$_2$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

<table>
<thead>
<tr>
<th>Risk Factor</th>
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<tbody>
<tr>
<td>Respiratory failure requiring mechanical ventilation for more than 48 h*</td>
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<tr>
<td>Coagulopathy (international normalized ratio &gt; 1.5 or platelet count &lt; 50 000 mm$^3$)*</td>
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<tr>
<td>Acute renal insufficiency</td>
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<tr>
<td>Acute hepatic failure</td>
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<tr>
<td>Sepsis syndrome</td>
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<tr>
<td>Hypotension</td>
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<tr>
<td>Severe head or spinal cord injury</td>
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<tr>
<td>Anticoagulation</td>
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<tr>
<td>History of gastrointestinal bleeding</td>
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<tr>
<td>Low intragastric pH</td>
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<tr>
<td>Thermal injury involving more than 35% of the body surface area</td>
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<td>Major surgery (lasting more than 4 h)</td>
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<tr>
<td>Administration of high-dose corticosteroids (250 mg/d of steroids or equivalent hydrocortisone)</td>
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<tr>
<td>Enteral feedings</td>
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*Independent risk factors for bleeding.
Another option is sucralfate. Although less widely used than H2RAs or PPIs, sucralfate is more effective than no prophylaxis in reducing overt bleeding and is associated with a decreased mortality. Nonetheless, its effectiveness in reducing clinically important bleeding is more variable than that of antacids, H2RAs, or placebo. H2RAs, however, are still considered first line of defense by many clinicians. In a recent 2004 national survey of 2000 intensivists, H2RAs were chosen first nearly 64% of the time, followed by PPIs (23.1%). 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. 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...
containing casein and sucralfate.35 When con-
ommended when combining enteral formulas
terated 2 hours before sucralfate.34 Sucralfate
recommended that these drugs be adminis-
terated, often leading to
Microaspiration of oropharyngeal or gastric
contents in the presence of the endotracheal
Microaspiration of oropharyngeal or gastric
doesn’t systemically absorbed, it may
decrease the absorption of other concomi-
tantly administered oral medications such as
ciprofloxacin, theophylline, phenytoin, raniti-
dine, levothyroxine, ketoconazole, and
digoxin.13 To minimize this interaction, it is
recommended that these drugs be adminis-
ted 2 hours before sucralfate.14 Sucralfate
may also interact with enteral feedings, result-
ing in diminished efficacy or a clogged feeding
tube.9 Though not well studied, caution is rec-
commended when combining enteral formulas
containing casein and sucralfate.37 When con-
tinuous 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.1,13 Be-
zoars have also been reported in patients
treated with sucralfate.4 Case reports suggest
that sucralfate may contribute to bezoar for-
mation, especially when given to patients with
delayed gastric emptying in combination with
enteral feedings. Sucralfate should not be ad-
ministered 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.1,6 Toxic elevations in
plasma aluminum levels have been reported in
critically ill patients requiring continuous
veno-venous hemofiltration who were receiv-
ing sucralfate. Sucralfate may also be associ-
ated with a lower incidence of nosocomial
pneumonia secondary to lower incidence of
gastric gram-negative colonization. The devel-
opment 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.1,37 Sucralfate may offer an advan-
tage over H2RAs and possibly PPIs for the
prophylaxis of SRMD, as it has a lower incidence
of nosocomial pneumonia in comparison with
antacids and H2RAs.19,20,21,22 However, this ad-
vantage may be in doubt. Several recent studies
have demonstrated no significant differences in
the incidence of nosocomial pneumonia in criti-
cally ill patients when treated with sucralfate ver-
sus acid-suppression therapy or placebo.16,19,21,22

Acid suppression has become the primary
therapy for patients at risk for stress-related
mucosal bleeding. Treatment usually involves
H2RAs, although the use of PPIs does appear
to be increasing, despite a relative lack of pub-
dished data supporting their use.14,24,41

Histamine, receptor Antagonists

H2RAs 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.7 Four H2RAs are
available in the United States for the prophy-
laxis of stress-related mucosal bleeding: cime-
tidine, ranitidine, famotidine, and nizatidine.
Famotidine and ranitidine are the most often
used within the ICU setting.24

Several clinical trials have evaluated the ef-
cicacy of H2RAs for the prevention of stress-
related mucosal bleeding. In a metaanalysis,
H2RAs were found to be significantly better
than placebo in reducing the incidence of both
over and clinically important bleeding.29
Cook et al31 reported that H2RAs 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 clin-
ically important bleeding using H2RAs com-
pared with either placebo or sucralfate.16,19,20,22

Tolerance to H2RA acid inhibition develops
as early as 72 hours after administration.9
However, clinical significance of this has not
been demonstrated. Administration of H2RAs
by continuous infusion provides better control
of gastric pH than bolus infusion. But this is
not more effective in preventing clinically sig-
ificant stress-related mucosal bleeding.15,21,22,28
Administration through oral or NG tube is
equal in efficacy in reducing the incidence
of stress-related mucosal bleeds.15

H2RAs are usually very safe and the adverse
effects are minor. Central nervous system
toxicity (confusion, delirium, hallucinations,
slurred speech, and headaches) has been ob-
served in elderly patients and occurs primarily
with intravenous administration." Hematologic toxicity, in the form of thrombocytopenia, is often attributed to H\textsubscript{2}RAs. However, it is difficult to assess whether H\textsubscript{2}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.\textsuperscript{42} Although there have been numerous published case reports of H\textsubscript{2}RA-associated thrombocytopenia, the rate of incidence is unknown and no direct correlation has been demonstrated.\textsuperscript{42} If thrombocytopenia does occur, patients with mild thrombocytopenia (50 000–100 000 mm\textsuperscript{3}) should continue therapy since the risk of bleeding is minimal. However, if the patient’s platelet count is less than 50 000 mm\textsuperscript{3}, the risk-to-benefit ratio favors therapy with an alternative agent, such as a PPI.\textsuperscript{42}

Drug interactions can occur with H\textsubscript{2}RAs, particularly with cimetidine. Cimetidine interferes with cytochrome P450 metabolizing enzymes, decreasing the clearance of several drugs (eg, warfarin, ketoconazole, theophylline, phenytoin).\textsuperscript{1} 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,\textsuperscript{1} and can elevate or maintain intragastric pH above 6, which is necessary to maintain clotting in patients at risk for rebleeding or ulcer healing.\textsuperscript{14,43,44} Under acidic conditions in parietal cells, PPIs irreversibly inhibit the final step in acid production (the transport of H\textsuperscript{+} by the proton pump H\textsuperscript{+}/K\textsuperscript{+} ATPase), providing long-lasting suppression of acid secretion. Unlike H\textsubscript{2}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.\textsuperscript{45} 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\textsubscript{2}RAs, patients do not develop tolerance to PPIs with continued use. Conversely, rebound acid hypersecretion is common after discontinuation of PPI therapy.\textsuperscript{45}

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\textsubscript{2}RAs in the prevention of stress-related mucosal bleeding when given either intravenously or as an immediate-release bicarbonate suspension.\textsuperscript{19,44} Nevertheless, when compared to placebo, neither the H\textsubscript{2}RAs nor the PPIs were significantly different in reducing stress-related clinically important bleeding.\textsuperscript{19} These findings are consistent with other trials in which prophylactic medications did not reduce the incidence of stress-related hemorrhage.\textsuperscript{20,22}

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.\textsuperscript{5} 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.\textsuperscript{1,46} Furthermore, PPIs have recently been associated with an increased incidence of Clostridium difficile diarrhea. Dial et al\textsuperscript{47} 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\textsubscript{2}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).\textsuperscript{47}

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.\textsuperscript{1} 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.\textsuperscript{1} Omeprazole also induces the expression of CYP1A2, thereby increasing the metabolism of several antipsychotic drugs, tacrine, and
CYP enzymes. Lansoprazole, the second PPI to undergo metabolism by CYP2C19. However, no significant drug interactions have been demonstrated between esomeprazole and phenytoin, warfarin, quinidine, clarithromycin, or amoxicillin. 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. Lansoprazole, the second PPI to become available in the United States, may interfere with the metabolism of warfarin, as may rabeprazole.

**Enteral Nutrition**

Enteral feeding is widely used in the critically ill patient population because it offers many benefits. 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. 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.

**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. 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, H2RAs 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 H2RAs, 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.

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. 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.

**References**