ABSTRACT

Background: The term stress-related mucosal disease (SRMD) represents a continuum of conditions ranging from stress-related injury (superficial mucosal damage) to stress ulcers (focal deep mucosal damage). Caused by mucosal ischemia, SRMD is most commonly seen in critically ill patients in the intensive care unit (ICU). Prophylaxis of stress ulcers may reduce major bleeding but has not yet been shown to improve survival.

Objectives: This article reviews currently available agents for the prophylaxis of SRMD and discusses their uses and potential adverse effects.

Methods: Relevant articles in the English-language literature were identified through a MEDLINE search (1968–2003) using the key words stress-related mucosal disease, stress-related injury, ulcer, prophylaxis, intensive care unit, and upper gastrointestinal bleeding.

Results: The most widely used drugs for stress-related injury are the intravenous histamine₂-receptor antagonists. These drugs raise gastric pH but are associated with the development of tolerance and possible drug interactions and neurologic manifestations. Sucralfate, which can be administered by the nasogastric route, can protect the gastric mucosa without raising pH, but may decrease the absorption of concomitantly administered oral medications. The prostaglandin misoprostol has not been shown to be of benefit in the prophylaxis of SRMD. Antacids lower the risk of gastrointestinal bleeding, but large volumes of antacids are required and treatment is labor intensive. Proton pump inhibitors (PPIs) are the most potent acid-suppressive pharmacologic agents available. Esomeprazole, lansoprazole, omeprazole, pantoprazole, and rabeprazole substantially raise gastric pH for up to 24 hours after a single dose. The availability of an intravenous formulation of pantoprazole may help improve the treatment of SRMD in ICU patients, particularly those receiving mechanical ventilation. Tolerance does not develop, and few adverse effects have been reported.

Conclusions: Recent studies of PPIs have shown promising results in high-risk patients, making this class of drugs an option for the prophylaxis of SRMD. (Clin Ther. 2004;26:197–213) Copyright © 2004 Excerpta Medica, Inc.

Key words: ulcer, prophylaxis, gastric mucosa, intensive care unit, enzyme inhibitors.
INTRODUCTION
The association between severe physiologic stress and gastrointestinal (GI) ulceration is well established.1,2 The pathogenesis of stress-related mucosal disease (SRMD) has not been described completely, but there is strong evidence that hypoperfusion of the upper GI tract is the major cause.1–4 Aggressive management of the underlying disease is the most important factor in the prevention of stress ulceration.1,5,6 Improving understanding and classification of the different types of stress injury will facilitate communication and aid in the diagnosis, prognosis, and therapeutic management of SRMD. Elucidating the mechanism of injury will help develop interventions that may lead to a reduction in mortality.

Various medications are currently used to reduce the incidence of stress-related GI bleeding. This article reviews currently available agents for the prophylaxis of SRMD and discusses their uses and potential adverse effects. Relevant English-language publications were identified through a search of MEDLINE (1968–2003) using the terms stress-related mucosal disease, stress-related injury, ulcer, prophylaxis, intensive care unit, and upper gastrointestinal bleeding.

STRESS-RELATED MUCOSAL DISEASE
Terminology
The terminology of SRMD is often confusing, with stress ulcer, stress gastritis, stress erosions, and stress lesions used interchangeably. However, there are important differences between these entities. For clarity, this review distinguishes between stress-related injury (SRI) and stress ulcers, which lie along the continuum of manifestations of SRMD. As illustrated in Figure 1, SRI involves superficial mucosal damage (primarily erosions), whereas stress ulcers involve focal deep mucosal damage and carry a high risk for bleeding. Both SRI and stress ulcers are found in physiologically stressed patients, particularly those requiring mechanical ventilation.1,2,7

Pathogenesis
The gastric mucosa is exposed to a very low intraluminal pH. Under normal physiologic conditions, the integrity of this tissue depends on a balance between aggressive factors (ie, gastric acid secretion, enzyme secretion, infection) and countervailing mucosal defense mechanisms.3,5 Studies in animal models have shown that mucosal defense is intimately related to adequate microcirculation through tissues of the upper GI tract.5 This circulation provides nutrients and removes waste products, particularly oxygen free radicals. In a rat model, Itoh and Guth5 found that oxygen-derived free radicals, particularly O$_{2}^-$, appear to play an important role in the formation of gastric lesions produced by ischemia plus hydrochloric acid.

In another study in rats, Yasue and Guth9 found that even without intragastric hydrochloric acid, sys-
tic ischemia followed by retransfusion of shed blood caused histologic mucosal injury in the corpus and antrum. They also found that a limited period of ischemia alone (systemic hypotension for 20 minutes without retransfusion) resulted in no more histologic lesions than occurred in controls not subjected to hemorrhage. These investigators reported that a longer period of ischemia caused more lesions and that reperfusion (retransfusion) was a critical factor in lesion development. In a canine model, Chung et al found that local ischemia and congestion preceded the development of gross mucosal ulcerations.

These studies point to a multifactorial etiology for stress ulcers in which the breakdown of mucosal defenses—usually by ischemia and reperfusion—allows aggressive physiologic processes, particularly gastric acid secretion, to produce injury and ulceration.

Location

SRMD is typically seen in the acid-producing areas of the stomach (ie, the corpus and fundus), unlike outpatient peptic ulcers, which are more common in the antrum or duodenal bulb. In rabbits and rats, Menguy and Masters found that with respect to the maintenance of energy metabolism, the antral mucosa tolerated the partial ischemia of hemorrhagic shock and the complete ischemia of total severance of the gastric vascular connections far better than did the corpus mucosa. Leung et al reported that gastric lesions began to appear when blood pressure fell to 33% of baseline during hemorrhagic shock in rats. At blood pressures 80% below baseline, a mean (SD) of 26.8% (4.5) of the total corpus area developed lesions, compared with 5.3% (1.4) of the antral area (P < 0.05, both regions vs control animals). With rare exceptions, corpus mucosal lesions were larger than antral mucosal lesions at all levels of hypotension.

It is believed that low-grade mucosal ischemia occurs during sepsis and multiple organ failure because of changes in blood volume and redistribution of blood flow. In a study in critically ill, normotensive, septic, ventilated patients, Spirt et al used endoscopic reflectance spectrophotometry to measure blood flow as an index of hemoglobin saturation and oxygen concentration. Control values were derived from patients undergoing routine endoscopy for the evaluation of symptoms of gastroesophageal reflux disease. The septic intensive care unit (ICU) patients had a 50% to 60% reduction in upper GI mucosal blood flow compared with controls.

Mortality

SRMD differs from outpatient peptic ulcer disease in many respects, including the location and number of lesions, risk factors, pathophysiology, prognosis, recurrence, management, and therapy. One study reported a mortality rate of 46% in critically ill patients with GI bleeding, compared with 21% in patients without bleeding (P < 0.001). Several studies have confirmed this high mortality rate. However, the SRMD lesions remit when the patient recovers and, in a healthy host, do not recur.

Risk Factors

A multicenter study in 2252 patients reported that the 2 strongest risk factors for stress-related GI bleeding were respiratory failure (odds ratio [OR], 15.6) and coagulopathy (OR, 4.3). The risk increases with increasing number of days of mechanical ventilation and length of ICU stay. Other factors conferring high risk for both SRI and stress ulcers include recent major surgery, major trauma, severe burns, head trauma, hepatic or renal disease at admission, sepsis, and hypotension.

Stress-Related Injury

The results of most studies indicate that 75% to 100% of patients in the ICU have abnormalities of the gastric mucosa within hours after admission and that samples of gastric juice test positive for blood in 35% to 100% of critically ill patients. However, occult blood in the gastric juice does not predict impending hemorrhage. The mucosal changes of SRI mainly involve small erosions (Figure 2) that do not usually lead to hemodynamically significant GI bleeding. When bleeding does occur in patients with SRI, there is usually a concomitant coagulopathy. Clinically apparent bleeding occurs in ~20% of patients, whereas hemodynamically significant bleeding probably occurs in <5% of patients. Erosions associated with SRI are not caused by hyperacidity, as affected patients have normal or slightly decreased gastric acid volume. If massive bleeding does occur, it is usually from a discrete stress ulcer rather than from diffuse SRI. These lesions tend to be superficial, and perforation is distinctly
uncommon, compared with an incidence of 1% to 2% in patients with gastric and duodenal ulcers.

**Stress Ulcers**

Stress ulcers differ from routine peptic ulcers. Peptic ulcer disease is relatively manageable; patients usually present with abdominal pain and epigastric discomfort and can receive treatment on an outpatient basis. A minority (≈10%) of outpatients with peptic ulcer disease develop complications (eg, bleeding, obstruction, perforation) requiring hospitalization. Stress ulcers (Figure 2), on the other hand, cause GI bleeding and are usually not associated with abdominal pain. Clinical bleeding often occurs between the third and seventh days after ICU admission.

In a 1987 review, Zuckerman and Shuman reported that ICU patients with stress ulcer bleeding had a mortality rate of 50% to 77%, compared with 9% to 22% in ICU patients without bleeding. In contrast to patients with SRI, patients with stress ulcers are at increased risk for hemodynamically significant GI hemorrhage, although this is rarely the cause of death. Death is usually the result of multiple organ failure and is probably related to hypoperfusion of the entire gut, promoting the translocation of bacteria and endotoxin. Although stress-related ulcers are a recognizable sign of this low-perfusion state, the prophylaxis of stress ulcers has not been shown to improve survival, even in the few trials in which the incidence of major bleeding appeared to have been favorably decreased.

**PROPHYLAXIS OF STRESS ULCERS**

The incidence of significant stress-related bleeding has decreased dramatically over the past several years, probably as a result of advances in the monitoring and support of critically ill patients, including optimization of hemodynamic status, tissue oxygenation, and treatment of sepsis. Nevertheless, the varying definitions of bleeding used in clinical studies tend to obscure the true incidence of stress-related bleeding. Criteria have ranged from guaiac-positive stool and guaiac-positive nasogastric aspirate to frank hematemesis, a drop in blood pressure, and the need for blood transfusion. The prevalence of acute stress-related GI bleeding is 1.5% to 6% in critically ill patients not receiving prophylaxis. The strongest predictors of bleeding in ICU patients are respiratory failure requiring prolonged mechanical ventilation and coagulopathy.

In a 1987 review, Zuckerman and Shuman reported that ICU patients with stress ulcer bleeding had a mortality rate of 50% to 77%, compared with 9% to 22% in ICU patients without bleeding. In contrast to patients with SRI, patients with stress ulcers are at increased risk for hemodynamically significant GI hemorrhage, although this is rarely the cause of death. Death is usually the result of multiple organ failure and is probably related to hypoperfusion of the entire gut, promoting the translocation of bacteria and endotoxin. Although stress-related ulcers are a recognizable sign of this low-perfusion state, the prophylaxis of stress ulcers has not been shown to improve survival, even in the few trials in which the incidence of major bleeding appeared to have been favorably decreased.

Taking the radical viewpoint, one might question whether there is a need for prophylaxis of stress-related GI bleeding, as bleeding from such lesions is usually not the cause of death and therapy has not been demonstrated to reduce mortality. There is considerable disagreement on this matter, but the consensus is that patients at very high risk for stress-related bleeding should receive prophylaxis (Table 1), and this is the standard of care in most ICUs. Moreover, a recent evidence-based review of clinical trials supported the use of prophylactic acid suppression in critically ill patients with coagulopathy or...
undergoing prolonged mechanical ventilation. The available evidence-based data do not support the use of any specific drug class over another for the prophylaxis of stress ulcer bleeding. Following is a discussion of the available agents and information pertinent to their use.

**Histamine2–Receptor Antagonists**

A variety of histamine2–receptor antagonists (H2RAs) can be used for the prophylaxis of stress ulcer bleeding in the ICU. The available H2RAs are not equally potent in blocking the actions of histamine on parietal cells. Cimetidine is the least potent, ranitidine and nizatidine are more potent, and famotidine is the most potent. Cimetidine, however, is the only H2RA with US Food and Drug Administration approval for the prevention of upper GI bleeding in the ICU. There are other differences between these medications and the methods of administering them that are discussed later in this article. Although H2RAs can effectively protect against SRI, they are only moderately effective in the prophylaxis of true stress ulcers. In their 1999 therapeutic guidelines on stress ulcer prophylaxis, the American Society of Health-System Pharmacists noted that the results of clinical trials of the efficacy of H2RAs in the prevention of stress ulcers fluctuate widely and provide no clear consensus (Table II).

**Routes of Administration**

Intermittent bolus administration and continuous infusion are the main modes of intravenous administration. Continuous infusion of H2RAs is superior to intermittent bolus administration in maintaining gastric pH at levels >4. However, no studies have demonstrated improved safety, more effective prophylaxis of ulcers, faster healing of existing ulcers, or a lower rebleeding rate with either method.21 Because some drug-related adverse effects associated with H2RAs are thought to result from high serum drug concentrations, maintaining steady blood concentrations within the therapeutic range may reduce the potential for these adverse effects. Continuous infusion avoids the peaks and troughs associated with bolus administration.

Oral therapy is also an option with H2RAs. The findings of a small study in 18 patients suggested that enteral administration of ranitidine 150 or 300 mg every 12 hours led to effective absorption of drug from the upper GI tract. With both doses, serum concentrations remained within or exceeded the therapeutic range after 12 hours in nearly 80% of ICU patients with clinically important risk factors for SRMD. Regardless of the route of administration or dosing interval, daily doses should be reduced in patients with renal insufficiency.

One major concern that requires further research is the development of tolerance to H2RAs, which has been reported to develop in the ICU within 48 hours after intravenous administration by both repeated bolus and continuous infusion. The resulting reduction in the antisecretory effect of H2RAs is not explained by altered pharmacokinetics.

**Cimetidine**

Cimetidine has been marketed in the United States for >25 years and has a well-established safety profile. Drug interactions, which occur more frequently than with other H2RAs, are the major concern with its use. Thrombocytopenia has also been associated with cimetidine use. Because it can cause neurologic manifestations and drug interactions, cimetidine should be used with caution in the ICU. A list of clinical trials of the efficacy of H2RAs in the prevention of stress ulcers fluctuate widely and provide no clear consensus (Table II).

### Table I. Factors associated with a high risk for stress-related bleeding.

<table>
<thead>
<tr>
<th>Very high risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prolonged mechanical ventilation*</td>
</tr>
<tr>
<td>Coagulopathy*</td>
</tr>
<tr>
<td>High risk</td>
</tr>
<tr>
<td>Sepsis†</td>
</tr>
<tr>
<td>Renal failure†</td>
</tr>
<tr>
<td>Hepatic failure†</td>
</tr>
<tr>
<td>Hypotension†</td>
</tr>
<tr>
<td>Trauma†</td>
</tr>
<tr>
<td>Severe burns†</td>
</tr>
<tr>
<td>Neurologic trauma†</td>
</tr>
<tr>
<td>Myocardial infarction†</td>
</tr>
<tr>
<td>Neurologic surgery†</td>
</tr>
<tr>
<td>Multiple organ failure†</td>
</tr>
<tr>
<td>Ileus‡</td>
</tr>
<tr>
<td>High-dose corticosteroids§</td>
</tr>
</tbody>
</table>

*Cook et al.16
†Beejay and Wolfe.3
‡Crill and Hak.37
§MacLaren et al.38
drugs known to interact with cimetidine is provided in Table III.55–58

Ranitidine

Ranitidine has 5 to 12 times greater antisecretory potency than cimetidine. However, there is no evidence of its superiority to cimetidine for the prevention of SRMD, and a meta-analysis of randomized studies indicated that ranitidine was no more effective than placebo in the prevention of GI bleeding in the ICU.59 Ranitidine is usually well tolerated; however, it can cause adverse central nervous system reactions, including agitation and restlessness, in ICU patients given the usual doses.48

Famotidine

Famotidine is the most potent H₂RA available in the United States.55 It is ≈8 to 10 times more

<table>
<thead>
<tr>
<th>Study/Treatments</th>
<th>No. of Patients</th>
<th>Bleeding Rate, %</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Martin et al41</td>
<td>H₂RA (cimetidine) 65</td>
<td>14</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Placebo 66</td>
<td></td>
<td>33</td>
<td></td>
</tr>
<tr>
<td>Zinner et al27</td>
<td>H₂RA (cimetidine) 100</td>
<td>14</td>
<td>NS vs no treatment</td>
</tr>
<tr>
<td>Antacid 100</td>
<td>5</td>
<td>&lt;0.005 vs no treatment</td>
<td></td>
</tr>
<tr>
<td>No treatment 100</td>
<td>20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weigelt et al42</td>
<td>H₂RA (cimetidine) 61</td>
<td>5</td>
<td>NA</td>
</tr>
<tr>
<td>Antacid 16</td>
<td>0</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Kingsley43</td>
<td>H₂RA (cimetidine) 124</td>
<td>4.8</td>
<td>NA</td>
</tr>
<tr>
<td>Antacid 125</td>
<td>8.8</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Ben-Menachem et al44</td>
<td>H₂RA (cimetidine) 100</td>
<td>5</td>
<td>NS vs placebo</td>
</tr>
<tr>
<td>Sacral fate 100</td>
<td>5</td>
<td>NS vs placebo</td>
<td></td>
</tr>
<tr>
<td>Placebo 100</td>
<td>6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cook et al45</td>
<td>H₂RA (ranitidine) 596</td>
<td>1.7</td>
<td>0.02 vs H₂RA</td>
</tr>
<tr>
<td>Sacral fate 604</td>
<td>3.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Levy et al45</td>
<td>H₂RA (ranitidine) 35</td>
<td>31</td>
<td>&lt;0.05 vs H₂RA</td>
</tr>
<tr>
<td>PPI (omeprazole) 32</td>
<td>6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Azevedo et al46</td>
<td>H₂RA (ranitidine) 38</td>
<td>10.5</td>
<td>NS vs H₂RA and</td>
</tr>
<tr>
<td>Sacral fate 32</td>
<td>9.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PPI (omeprazole) 38</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hastings et al32</td>
<td>Antacid 51</td>
<td>4</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Placebo 49</td>
<td>25</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

H₂RA = histamine₂–receptor antagonist; NA = not available; PPI = proton pump inhibitor.
potent than ranitidine. A lower volume of administration (10 mL/d) is required with famotidine compared with cimetidine and ranitidine (60–80 mL/d). This characteristic may be particularly useful in patients with congestive heart failure or those requiring fluid restriction. Twice-daily dosing (20 mg q12h) maintains the pH above 4 for most of the day,61 and higher doses (50 mg q24h) can maintain pH at this level for 24 hours.62 Drug interactions appear to be minimal with famotidine. Rare cases of thrombocytopenia have occurred,63 and there are reports of central nervous system reactions with its use.54 In controlled trials of famotidine, no drug interactions were observed with agents metabolized by the cytochrome P450 (CYP) enzyme system, including warfarin, theophylline, phenytoin, and diazepam.63

Proton Pump Inhibitors

Five proton pump inhibitors (PPIs) are available in the United States: omeprazole, esomeprazole, lansoprazole, rabeprazole, and pantoprazole.3,65 The most potent antisecretory agents available, these prodrugs block the final pathway for acid secretion by irreversibly inhibiting H⁺,K⁺-adenosine triphosphatase (ATPase, the proton pump) in gastric parietal cells.3 PPIs are capable of elevating or maintaining intragastric pH above 6.56,67 Studies have demonstrated that although an intragastric pH >4 may be adequate for preventing stress ulceration, a pH >6 may be necessary to maintain clotting in patients at risk for rebleeding of a peptic ulcer.68

PPIs are well tolerated and appear promising for the prophylaxis of SRMD, although the results of only 2 randomized clinical trials have been reported (Table II).45,46 One of these trials, which involved 67 patients, showed a significant reduction in bleeding with omeprazole compared with ranitidine (2/32 [6.3%] vs 11/35 [31.4%], respectively; P < 0.05),45 but this study was limited by a higher number of risk factors per patient in the H₂RA group and a higher rate of clinical bleeding than is generally reported in the literature. In the second trial, which involved 108 ICU patients,46 the rate of upper GI hemorrhage was 10.5% in the ranitidine group, compared with 0% in the omeprazole group (P = NS).

Omeprazole

Omeprazole was the first PPI approved in the United States. A single morning dose of omeprazole in healthy individuals maintains intragastric pH at ≥5 for up to 24 hours.69 After 15 to 24 hours, acid begins to return to the stomach, and omeprazole is cleared within 72 hours.70 The drug is given orally; no intravenous form is available in the United States. An early study using various doses of omeprazole reported that single intravenous doses of 10 to 80 mg produced dose-dependent and long-lasting inhibition of pentagastrin-stimulated gastric acid secretion.71 Omeprazole 40 mg IV given once daily significantly reduced intragastric pH after 5 days of treatment, although it was not sufficient to maintain intragastric pH above 4 in all patients during the first day of treatment.72 During the first 72 hours of treatment, a continuous infusion of omeprazole maintained pH above 4 for >95% of the time, with the maximal effect occurring between 3 and 5 days.70,73

In 2 prospective studies in 75 mechanically ventilated patients66 and 60 trauma patients,67 omeprazole suspension administered by nasogastric tube safely prevented clinically significant GI bleeding and maintained gastric pH at favorable levels. No cases of clinically important upper GI bleeding were observed. Although intravenous omeprazole was reported to

<table>
<thead>
<tr>
<th>Table III. Drug–drug interactions with cimetidine.55–58</th>
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</thead>
<tbody>
<tr>
<td>Coadministered cimetidine interferes with elimination of:</td>
</tr>
<tr>
<td>N-acetylprocainamide</td>
</tr>
<tr>
<td>Procainamide</td>
</tr>
<tr>
<td>Coadministered cimetidine interferes with absorption of:</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
</tr>
<tr>
<td>Chlordiazepoxide</td>
</tr>
<tr>
<td>Diazepam</td>
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<tr>
<td>Fentanyl</td>
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<tr>
<td>Lidocaine</td>
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<tr>
<td>Meperidine</td>
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<tr>
<td>Metronidazole</td>
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<tr>
<td>Midazolam</td>
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<tr>
<td>Nifedipine</td>
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<tr>
<td>Phenyltoin</td>
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<tr>
<td>Propofol</td>
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<tr>
<td>Propranolol</td>
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<tr>
<td>Quinidine</td>
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<td>Theophylline</td>
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<tr>
<td>Triazolam</td>
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<tr>
<td>Tricyclic antidepressants</td>
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<tr>
<td>Warfarin</td>
</tr>
</tbody>
</table>

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prevent gastric acid stimulation by parenteral nutrition with amino acids, it failed to maintain intragastric pH above 4.7. Development of tolerance to omeprazole does not appear to occur. Although efficacy and safety studies are currently under way, oral omeprazole is not approved for the prophylaxis of stress ulcers. Omeprazole is known to interact with certain drugs. For example, it can prolong the elimination of diazepam, warfarin, and phenytoin, which are metabolized by oxidation in the liver. Interactions have also been reported with certain drugs metabolized by the CYP system, such as cyclosporine (Table IV).

Esomeprazole
Esomeprazole, the S-isomer of omeprazole, is the most recently approved PPI in the United States. It is metabolized in the liver and may interfere with CYP2C19, the major metabolizing enzyme of the CYP system. No significant drug interactions between esomeprazole and phenytoin, warfarin, quinidine, clarithromycin, or amoxicillin have been demonstrated in clinical studies. Coadministration of esomeprazole and diazepam (a CYP2C19 substrate) resulted in a 45% decrease in the clearance of diazepam. Esomeprazole is well tolerated. The most common adverse events associated with its use are diarrhea (4.3%), headache (3.8%), and abdominal pain (3.8%).

Lansoprazole
Lansoprazole was the second PPI to become available in the United States. It is well tolerated, and its adverse effects are similar to those of other PPIs. The most commonly occurring adverse effects are headache and diarrhea.

Rabeprazole
Rabeprazole was the third PPI to become available. It has a rapid onset of H⁺,K⁺-ATPase inhibition. Like pantoprazole, rabeprazole has a minimal effect on the CYP enzyme system and has shown no potential for significant drug interactions.

Pantoprazole
Pantoprazole was the fourth PPI approved in the United States. It has the lowest potential for drug interactions of the PPIs. There is some evidence that pantoprazole may have pharmacologic properties leading to longer duration of antisecretory efficacy. PPIs inhibit acid production by binding to specific cysteine residues within the proton-transfer domain of actively secreting pumps. Whereas lansoprazole, omeprazole, and rabeprazole are capable of binding other cysteines on the proton pump that are unrelated to acid suppression, which may dilute the level of drug available for interaction with active enzymes and possibly contribute to unwanted systemic effects. Its unique binding characteristics may explain pantoprazole’s extended inhibitory action. Among the PPIs, pantoprazole has the lowest pH of activation and the highest stability under moderately acidic conditions. Consequently, pantoprazole is predicted to have high gastric selectivity and a low likelihood of interacting with ion pumps in cell types other than the parietal cell.

The fact that pantoprazole has no known drug interactions, probably because of its low affinity for CYP enzymes, makes it the most specific of the PPIs. This feature, in addition to its high potency and the availability of an intravenous form, makes it well suited for the prophylaxis of SRMD in the ICU.

Table IV. Drug–drug interactions with omeprazole and sucralfate.

| Coadministered omeprazole interferes with elimination of:  |
| Cyclosporine  |
| Diazepam  |
| Phenytoin  |
| Warfarin  |
| Coadministered sucralfate interferes with absorption of:  |
| Cimetidine  |
| Digoxin  |
| Fluoroquinolone antibiotics  |
| Ketoconazole  |
| L-thyroxine  |
| Phenytoin  |
| Quinidine  |
| Ranitidine  |
| Tetracycline  |
| Theophylline  |

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Intravenous Administration

The great majority of patients at risk for SRMD are found in the ICU. Many of these critically ill patients require mechanical ventilation; have acute gastro-paresis, ileus, or both; and cannot tolerate oral or nasogastric administration of medications. Therefore, their care may be improved by the use of intravenous forms of treatment for the prophylaxis of SRI or stress ulcers. In addition, because PPIs work at the cellular level, intravenous administration may provide the most efficient and rapid path for these drugs to reach their targets. The intravenous form of pantoprazole is equipotent to the oral form in suppressing acid secretion in critically ill patients.91 Inhibition of gastric acid secretion is dose dependent, and a dosage of 80 mg/d suppresses acid secretion by >90%.92 The availability of an intravenous formulation of pantoprazole will allow comparison of the prophylactic efficacy and safety of this PPI with H$_2$RAs in critically ill patients.93

Other Treatments

Sucralfate

Sucralfate consists of a core of sucrose molecules surrounded by aluminum hydroxide sulfate salts. It does not inhibit acid secretion or neutralize gastric acid; rather, it coats the gastric mucosa and forms a thin protective layer between the mucosa and the gastric acid in the lumen.26,94 Another mechanism of action may be the stimulation of mucosal defenses that trigger the release of prostaglandin E$_1$, which is cytoprotective.95,96 Sucralfate has comparable efficacy to antacids in the healing of ulcers.99 A meta-analysis of the efficacy of sucralfate compared with that of H$_2$RAs (9 studies) and antacids (8 studies) for the prophylaxis of stress ulcers indicated that sucralfate was at least as effective as the other agents.97 Sucralfate is not a systemic drug and therefore has advantages over some other agents in that it does not interact with other drugs in the bloodstream. A major drawback to the use of sucralfate is that it may decrease the absorption of other concomitantly administered oral medications such as cimetidine and ranitidine (Table IV).94 Therefore, sucralfate should be administered separately from these other drugs; administering the other medication 2 hours before sucralfate may eliminate drug interactions.94 Aluminum toxicity has occurred in patients with chronic renal failure given sucralfate.94 Toxic elevations in plasma aluminum levels have been reported in critically ill patients requiring continuous veno-venous hemofiltration who were receiving sucralfate for the prophylaxis of stress ulceration.99 A liquid form of sucralfate is available that can be adminis-tered via nasogastric tube.

Prostaglandins

The only commercially available prostaglandin for the prophylaxis of GI ulcers is misoprostol, a synthetic prostaglandin E$_1$ analogue. This medication protects the mucosa and diminishes gastric acid secretion.99 Very few studies have evaluated prostaglandin analogues for the prophylaxis of stress-related bleeding in the ICU. One study comparing misoprostol with antacid titration found no difference between treatment groups in lesion scores at endoscopy based on a standard scale or in the inci-dence of serious adverse effects.99 The rate of diarrhea was >22% in both groups, considerably higher than that seen with other prophylactic agents for stress ulcers.

Somatostatin Analogues

Somatostatin exerts a powerful tonic inhibitory effect on acid secretion. There is a local feedback mechanism by which intraluminal acid stimulates somatostatin, which in turn attenuates acid secretion.100 Somatostatin is the main inhibitor of gastrin in vivo. There are no clinical data evaluating somato-stat-in analogues for the prophylaxis of SRMD. Therefore, they cannot be recommended for the prophylaxis of stress ulcers.

Antacids

Antacids work by neutralizing gastric acid and inactivating the proteolytic activity of pepsin. Both actions are achieved at a pH of 5. With frequent dosing and pH monitoring, both of which are labor intensive, antacids can maintain a luminal pH ≥3.5.32 A randomized study in ICU patients found that 2 of 51 patients (4%) receiving antacid prophylaxis and 12 of 49 patients (25%) not receiving antacid prophylaxis had stress-related bleeding.32 Patients with renal failure or hypotension were at particular risk for bleeding. More deaths occurred in patients receiving antacid prophylaxis than in those who were not receiving such prophylaxis (11 vs 7, respectively).
Care should be taken when raising the pH of the stomach and concomitantly increasing gastric volume through frequent dosing via nasogastric tube. This combination may increase the number of pathogenic flora, and the large volumes may increase the risk of aspiration.

**Antibiotics for Helicobacter pylori Eradication**

The role of Helicobacter pylori in SRMD is controversial. A prospective study included serologic analysis of samples from all consecutive patients over a 1-year period who showed significant upper GI bleeding (defined as hematemesis, melena, or grossly bloody nasogastric aspirate) after cardiac surgery. Patients with no evidence of GI hemorrhage after cardiac surgery were chosen as controls. *H pylori* was not found to be a risk factor for upper GI bleeding, whereas patients who required prolonged mechanical ventilation were at high risk.

Antibiotic treatment of *H pylori* infection in the ICU setting can be associated with such severe consequences as selection for resistant organisms, acquisition of methicillin-resistant *Staphylococcus aureus*, promotion of ventilator-associated pneumonia, and induction of *Clostridium difficile* colitis. Therefore, use of antibiotics for the eradication of *H pylori* in the acute setting is strongly discouraged until there is further evidence that the benefit of early treatment outweighs the risks.

**Continuous Nasogastric Feeding**

Enteral feeding is widely used in the prevention of SRMD and is the standard of care in burn units, although its efficacy has not been well established in clinical studies. Nonetheless, early enteral nutrition has been effective in preventing stress ulceration of the upper GI tract in severely burned patients. The mechanism behind this protective effect is unclear, although because most enteral feeding solutions have a high pH, the constant neutralization of gastric acidity has been proposed. The available evidence does not support this hypothesis, however. A more likely mechanism is that enteral feeding increases mucosal blood flow, as demonstrated in patients with chronic mesenteric ischemia.

Care should be taken when choosing prophylactic drug therapies to be administered with continuous enteral nutrition. Gastric feeding has been shown to reduce the effectiveness of sucralfate, whereas coadministration of enteral nutrition and ranitidine for the prophylaxis of stress ulcers has been associated with reduced bleeding rates.

**PROPHYLAXIS OF STRESS ULCERS AND NOSOCOMIAL PNEUMONIA**

One concern with the prophylaxis of stress ulcers is the reported risk of nosocomial pneumonia, which is the most common infection in mechanically ventilated patients. This complication was thought to be related to increased gastric pH followed by aspiration. Preserving gastric acidity with acidified enteral feeding solutions has reduced gastric colonization in critically ill patients. Alternatively, development of nosocomial pneumonia could be related to incomplete suppression of acid volume. Antacids and H2RAs have been associated with increased gastric colonization, primarily by gram-negative organisms, at gastric pH values >4. Gram-negative bacteria do not grow well in the stomach when the pH is <3.5.

Several early studies suggested that gastric colonization might be less frequent and less severe when ventilated patients were given sucralfate rather than antacids or H2RAs. It was thought that not raising the gastric pH might reduce the incidence of nosocomial pneumonia, as aspiration of organisms from the stomach is a major route to the pulmonary tree. In one of the earliest studies, which involved 130 mechanically ventilated patients, nosocomial pneumonia occurred in twice as many patients receiving antacids, an H2RA, or both compared with those receiving sucralfate only (95% CI, 0.89–4.58; *P* = NS). On stratification by single medication use, however, receipt of antacids alone was associated with a 23.0% incidence of pneumonia, compared with 5.9% with H2RAs alone (lower than the 11.5% incidence in the sucralfate group). The incidence of pneumonia was 46.2% in patients who received both antacids and H2RAs. It is unclear whether this increase in the incidence of pneumonia was the result of acid suppression or of increased gastric volume from frequent antacid administration. The mortality rate was 1.6 times higher in the groups that received antacids or H2RAs compared with the group that received sucralfate (95% CI, 0.99–2.5; *P* = NS). A more recent study in children receiving
ranitidine or sucralfate found that sucralfate did not significantly decrease the incidence of ventilator-associated pneumonia compared with ranitidine (7.5% vs 11.1%, respectively) or compared with no prophylaxis. In contrast, a meta-analysis of studies in adults found that the risk of nosocomial pneumonia was significantly increased in critically ill patients who received ranitidine compared with sucralfate ($P = 0.012$). Another meta-analysis found that pneumonia occurred significantly less frequently in patients given sucralfate compared with H$_2$RAs in 5 studies (typical OR, 0.498; 95% CI, 0.316–0.783) or antacids in 4 studies (typical OR, 0.402; 95% CI, 0.235–0.687). A later randomized controlled trial involving 244 patients reported that sucralfate reduced the risk for developing late-onset pneumonia (after 4 days) compared with an antacid (5%, 16%, and 21%, respectively; $P = 0.022$) by maintaining a significantly lower median gastric pH ($P < 0.001$) and significantly reducing gastric bacterial colonization ($P = 0.015$). In a study comparing omeprazole and ranitidine for stress ulcer prophylaxis, 14% of patients receiving ranitidine developed nosocomial pneumonia, compared with 3% of patients receiving omeprazole; this difference was not statistically significant.

## ADVERSE-EFFECT PROFILES

### Histamine$_2$-Receptor Antagonists

All H$_2$RAs are capable of crossing the blood–brain barrier and can be associated with neuropsychiatric symptoms such as agitation, confusion, lethargy, and disorientation. They also block H$_2$ receptors on leukocytes, inhibiting histamine-induced immune functions (eg, cytokine production) and interfering with immunosurveillance. Their anti-inflammatory properties may be related in some way to the increase in GI bacterial colonization associated with the use of H$_2$RAs. Most adverse effects of H$_2$RAs are dose dependent. As mentioned previously, drug interactions occur with some H$_2$RAs, with the notable exception of famotidine. Therefore, use of famotidine may be preferable in patients receiving concomitant medications. Up to 30% of patients treated with high-dose intravenous ranitidine had increases in serum aminotransferase levels, but only 10% were affected in this way at lower doses. Adverse effects are more pronounced in the presence of renal insufficiency.

### Proton Pump Inhibitors

Of the available PPIs, omeprazole has the highest drug-interaction potential (Table IV). All 5 PPIs significantly raise the pH of the gastric fluid, which can alter the chemistry, absorption, or pH-dependent release of oral medications. The interaction of PPIs with the CYP enzyme family is a potential source of adverse drug interactions. Omeprazole and, to a much lesser extent, lansoprazole have been shown to induce the activity of CYP enzymes, which could affect the metabolism of other compounds (eg, caffeine, theophylline, carbamazepine, warfarin, phenytoin, diazepam, mephenytoin, cyclosporine, bismuth, methotrexate, ketoconazole). Of the 5 PPIs, pantoprazole and rabeprazole have the lowest potential to induce CYP enzymes and therefore have a relatively lower risk for adverse effects.

### Sucralfate

Sucralfate can decrease the absorption of certain medications when they are coadministered (Table IV). Other adverse effects of sucralfate include constipation and GI or esophageal bezoar formation. However, the incidence of these adverse effects is low (<2%).

### Prostaglandins

Use of the synthetic prostaglandin E$_1$ analogue misoprostol is associated with diarrhea even at mod-
erate doses and has induced a flare of colitis in patients with inflammatory bowel disease. Prostaglandins cause diarrhea in nearly one third of patients, limiting their clinical usefulness.

Antacids

Antacids are associated with electrolyte abnormalities and changes in bowel motility. Magnesium-containing preparations create a predisposition to diarrhea and cannot be given to patients with renal insufficiency, whereas use of aluminum/calcium-containing preparations leads to constipation. Prolonged use of antacids may cause alkalosis.

CONCLUSIONS

Improving GI mucosal hemodynamics by aggressive treatment of the underlying disease is of paramount importance in the treatment of SRMD. Removal of mucosal irritants such as gastric acid is also crucial. An ideal agent would be easily administered, have minimal potential for drug interactions and adverse effects, and be available in an intravenous form.

Prostaglandins and somatostatin have no proven benefit in the prophylaxis of SRMD and cannot be recommended. Their use is associated with diarrhea. Use of somatostatin analogues can lead to electrolyte abnormalities and thyroid dysfunction. The use of antacids is labor intensive, and the large volumes involved may increase the risk of aspiration. There can be clinically significant electrolyte abnormalities, diarrhea, and constipation with the use of these agents, and prolonged use may cause alkalosis.

No study has demonstrated a greater benefit with antacids compared with H2RAs or PPIs. H2RAs do not completely suppress acid secretion, have the potential for the development of tolerance, and can have adverse effects; consequently, they are not ideal agents for the prophylaxis of stress ulcers. Antibiotic treatment of H pylori infection in the ICU setting can be associated with such severe consequences as selection for resistant organisms, acquisition of methicillin-resistant S aureus, promotion of ventilator-associated pneumonia, and induction of C difficile colitis.

The PPIs are the most potent of the available agents. Their efficacy and low incidence of adverse effects or drug interactions make them attractive candidates for the prophylaxis of SRMD, and preliminary studies have shown promise in this area. One of the primary factors limiting this application has been the lack of a PPI that could be administered intravenously, although an intravenous formulation of pantoprazole is now available.

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