

## Stress ulcer prophylaxis in the intensive care unit

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**S**tress-related mucosal disease (SRMD) is an acute, erosive gastritis representing conditions ranging from stress-related injury to stress ulcers (1, 2). Stress-related injury is superficial mucosal damage that presents primarily as erosions, whereas stress ulcers are deep, focal mucosal damage penetrating the submucosa with high risk for gastrointestinal bleeding (2, 3). Mucosal damage has been reported to occur during the first 24 hours of hospital admission in 75% to 100% of intensive care unit (ICU) patients (4, 5). Clinically important gastrointestinal bleeding can cause hemodynamic instability and increase the need for red blood cell transfusions (1). Significant bleeding may also increase the length of stay in the ICU and mortality (1).

Initiation of acid suppression therapy (AST) for stress ulcer prophylaxis (SUP) in the ICU setting is well established, but the use of SUP in general medicine patients has not been deemed necessary since most experts consider the risk of clinically important bleeding outside of the ICU too low for continuation of SUP (3). The American Society of Health-System Pharmacists (ASHP) published the only available guidelines in 1999 for the use of SUP in medical, surgical, respiratory, and pediatric ICU patients. The guidelines do not recommend SUP in adult patients in non-ICU settings since most clinical trials discontinued prophylaxis without evidence of clinically important bleeding upon extubation or ICU discharge (5). Furthermore, it has been reported that the number needed to treat is >900 patients with low risk for clinically important bleeding to prevent a single episode of clinically significant gastrointestinal bleeding (6). Thus, continuation of SUP in the general medicine setting is not necessary unless patients have at least one independent risk factor increasing the risk of clinically important bleeding (6).

Interestingly, case reports have noted that 56% to 75% of general medicine patients begin inappropriate AST in the hospital (7). As many as 55% of patients continue AST once discharged without an appropriate indication (7). A retrospective chart review of medical and surgical ICU patients reported that 80% of patients transferred from the ICU continued to receive AST (60% was inappropriate AST), and 24.4% of those patients were discharged from the hospital with AST and no appropriate indication (7, 8).

### ETIOLOGY AND PATHOPHYSIOLOGY

The underlying cause of SRMD is hypoperfusion of the mucosa in the upper gastrointestinal tract (3). Gastrointestinal microcirculation and the mucus layer normally maintain the integrity of the gastric mucosa by providing nourishment; eliminating hydrogen ions, oxygen radicals, and other toxic substances; and increasing bicarbonate secretion to neutralize hydrogen ions (2, 3, 6). SRMD occurs when the mucosal barrier is compromised and can no longer block the detrimental effects of hydrogen ions and oxygen radicals (3). Thus, antacids, sucralfate, histamine<sub>2</sub>-receptor antagonists (H<sub>2</sub>RAs), and proton pump inhibitors (PPIs) are utilized to prevent mucosal damage from acid produced by gastric cells or by inhibiting acid secretion (1).

### RISK FACTORS

Several risk factors are associated with the development of SRMD, and ASHP guidelines recommend SUP for ICU patients with risk factors (5). The *Table* provides the risk factors as provided by ASHP and a literature review noting a landmark trial by Cook et al (9). Several studies based on surgical and medical ICU patients suggest that as the number of risk factors increases, the frequency of clinically important bleeding increases (5). Specifically, two risk factors have been found to be independent predictors of clinically important bleeding—coagulopathy and mechanical ventilation (9)—while others are potential risk factors for SRMD (1–3). ASHP recommends initiating SUP if at least one independent risk factor or at least two other risk factors are present in the ICU setting.

### MEDICATIONS

AST is often used to prevent rebleeding caused by SRMD because acid impairs clot stability. According to the ASHP guidelines, the choice among AST for SUP should be made on an institution-specific basis for adult patients admitted to general medical and surgical ICUs (5). The choice should

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**Table. Risk factors associated with stress-related mucosal disease\***

Type	Risk factor
Independent	1. Coagulopathy (including medication-induced coagulopathy): platelet count <50,000 mm <sup>3</sup> , INR >1.5, or PTT >2× control value 2. Respiratory failure: mechanical ventilation ≥48 hours
Other	1. Spinal cord injuries 2. Multiple trauma <sup>†</sup> : trauma sustained to more than one body region 3. Hepatic failure <sup>†</sup> : total bilirubin level >5 mg/dL, AST >150 U/L (3× ULN), or ALT >150 U/L (3× ULN). 4. Thermal injuries >35% of body surface area 5. Partial hepatectomy 6. Head injury with Glasgow coma score of ≤10 or inability to obey simple commands 7. Hepatic or renal transplantation 8. History of gastric ulceration or bleeding during year before admission 9. Sepsis/septic shock <sup>†</sup> : vasopressor support and/or positive microbiologic cultures/suspected infection 10. Intensive care unit stay >1 week 11. Occult or overt bleeding >6 days 12. Corticosteroid therapy

\*From American Society of Health-System Pharmacists guidelines (5).

<sup>†</sup>Modified from ASHP guidelines.

ALT indicates alanine aminotransferase; AST, aspartate aminotransferase; INR, international normalized ratio; PTT, partial thromboplastin time; ULN, upper limit of normal.

consider concerns regarding administration, adverse drug reactions (ADRs), and total costs (6). The medications currently used for SUP are antacids, sucralfate, H<sub>2</sub>RAs, and PPIs.

### Antacids

Antacids neutralize the acidic contents of the stomach (1). Antacids require administration every 1 to 2 hours to maintain pH levels acceptable to decrease SRMD, which is labor intensive (3). Another disadvantage associated with high doses of antacids is the increase in ADRs, such as aspiration pneumonia and toxicity due to electrolyte accumulation (1).

### Sucralfate

Sucralfate is composed of aluminum hydroxide sulfate salts surrounding a core of sucrose molecules. Sucralfate adheres to epithelial cells to coat the gastric mucosa and creates a thin, protective layer between the mucosa and gastric acid in the stomach lumen (1, 3). One advantage of sucralfate is that it does not interact with other medications in the bloodstream since it is not a systemic drug. Sucralfate can be administered through a nasogastric tube but is labor intensive, as it requires dosing every 6 hours (3). Sucralfate has the potential to decrease the absorption of medications administered concurrently such as fluoroquinolones, tetracycline, ranitidine, ketoconazole, and digoxin (3). Thus, it is recommended to administer other

medications at least 2 hours apart to minimize drug interactions. Another possible disadvantage of sucralfate is that it should be avoided in patients with significant renal dysfunction due to potential aluminum accumulation and toxicity with repeated doses and prolonged use (3).

### H<sub>2</sub>RAs

H<sub>2</sub>RAs work by inhibiting histamine-stimulated acid secretion by reversible, competitive inhibition of H<sub>2</sub> receptors of the parietal cells (1, 3). Among the available H<sub>2</sub>RAs, cimetidine is the least potent, ranitidine is in the middle, and famotidine is the most potent. H<sub>2</sub>RAs can be administered orally and intravenously by intermittent bolus administration and continuous infusions. One disadvantage is a lack of potency of H<sub>2</sub>RAs, since gastrin and acetylcholine can stimulate acid secretion at different receptor sites on the parietal cells, leading to incomplete acid suppression (3). Other disadvantages are multiple dosing requirements due to the short duration of action of H<sub>2</sub>RAs and the development of tolerance as soon as 72 hours after H<sub>2</sub>RA administration (1, 3). Drug interactions can occur with H<sub>2</sub>RAs due to the inhibition of cytochrome P450 enzymes, with cimetidine causing more drug interactions than ranitidine (3). H<sub>2</sub>RAs have to be dose adjusted in patients with renal dysfunction (1).

### PPIs

PPIs inhibit the hydrogen-potassium-adenosinetriphosphatase enzyme at the secretory surface of the parietal cell (1). Inhibiting the final step in acid production leads to a longer duration of acid suppression than that of H<sub>2</sub>RAs (3). Esomeprazole, omeprazole, lansoprazole, rabeprazole, and pantoprazole are available in the USA. Esomeprazole and omeprazole may interfere with the cytochrome system, whereas rabeprazole and pantoprazole have minimal significant drug interactions. Some advantages of PPIs are that they have a rapid onset of action, longer duration of action, and a lack of observed tolerance (3). A disadvantage is the limited data on intravenous PPI utilization in SUP (1).

### ADVERSE DRUG REACTIONS

Most ADRs due to SUP occur in <1% of the adult population when given on a short-term basis (defined as <2 weeks) (5). Hospitalized patients may experience delirium and thrombocytopenia when receiving an H<sub>2</sub>RA (7). The frequency of ADRs may increase in renally impaired, elderly, and malnourished patients (5, 7). Central nervous system disturbances caused by H<sub>2</sub>RAs and electrolyte accumulation due to antacids are seen more frequently in these patient populations (5, 6). PPIs and H<sub>2</sub>RAs have recently been associated with an increase in risk of developing community- and hospital-acquired *Clostridium*

*difficile*-associated disease (10); the risk increases with prolonged duration of therapy (7). Another ADR observed with PPI and H<sub>2</sub>RA use is pneumonia (6).

### LITERATURE REVIEW: COMPARISON OF AST FOR SUP H<sub>2</sub>RAs versus sucralfate and antacids

H<sub>2</sub>RAs have generally been found to be better in reducing the incidence of clinically significant bleeding when compared with placebo, antacids, and sucralfate (1). A study by Kingsley et al (11) showed a higher bleeding rate in patients receiving antacids versus cimetidine, 8.8% versus 4.8%, respectively. A multicenter randomized controlled trial by Cook et al (12) in 1998 enrolled 1200 patients requiring mechanical ventilation for 48 hours. Patients were assigned to receive either nasogastric sucralfate (1 g every 6 hours) and intravenous placebo or intravenous ranitidine (50 mg every 8 hours). Ten (1.7%) of the 596 patients in the ranitidine group and 23 (3.8%) of 604 patients in the sucralfate group developed clinically important bleeding (relative risk, 0.44; 95% confidence interval, 0.21–0.92;  $P = 0.02$ ). There was no statistically significant difference between the groups in the rate of ventilator-associated pneumonia (19.1% vs 16.2%), mortality (23.5% vs 22.8%), or the duration of ICU stay (median 9 days in both groups). The authors concluded that approximately 48 critically ill patients undergoing mechanical ventilation need to receive prophylaxis with ranitidine rather than sucralfate to prevent one clinically important upper gastrointestinal hemorrhage.

In contrast, an earlier randomized controlled trial by Grau et al (13) in 1993 compared the efficacy of cimetidine and sucralfate in preventing gastrointestinal bleeding in the general medicine population. A total of 144 patients with the presence of risk factors for SRMD listed in the Table were enrolled in the study; 74 patients were randomized to receive cimetidine 800 mg by mouth at bedtime versus sucralfate 1 g by mouth every 6 hours. Bleeding was observed in two patients (2.7%) in the cimetidine group and two patients (2.8%) in the sucralfate group, but bleeding was more severe in the sucralfate group than in the cimetidine group. Based upon the results of this trial, the investigators concluded that both drugs had similar safety profiles and were well tolerated, but the easier administration of cimetidine in a single bedtime dose, in conjunction with its relatively low cost (25% less than sucralfate) argues in favor of using cimetidine to prevent gastrointestinal bleeding in seriously ill patients admitted to general hospital wards.

### PPIs versus H<sub>2</sub>RAs

Some studies have suggested the superiority of oral PPIs over H<sub>2</sub>RAs for SUP, but few studies have examined intravenous PPIs.

Levy et al (14) compared omeprazole with ranitidine in patients with risk factors for stress ulcer–related bleeding. Thirty-five patients were randomized to receive ranitidine (50-mg bolus followed by a 50-mg intravenous infusion every 8 hours), and 32 patients were randomized to receive omeprazole (40-mg capsule administered orally or nasogastrically once a day). The results of this study found significantly more clinically important bleeding

in the ranitidine group than in the omeprazole group (31% vs 6%,  $P < 0.05$ ). No statistically significant difference was found in the rate of nosocomial pneumonia between groups. One major limitation of the study is that more risk factors for SRMD were present at baseline in the ranitidine group than in the omeprazole group (2.7 vs 1.9,  $P < 0.05$ ) in this small patient population. The authors concluded that omeprazole is safe, effective, and clinically feasible for SUP in ICU patients.

Phillips et al (15) compared omeprazole suspension ( $n = 33$ ; 20 mg daily) administered via nasogastric tube versus continuous intravenous infusion ranitidine ( $n = 25$ ; 150 or 200 mg daily) in patients with at least two risk factors for stress ulcer–related bleeding. Clinically significant gastrointestinal bleeding occurred in 3% of patients receiving omeprazole versus 16% of those receiving ranitidine ( $P < 0.05$ ). Examining the costs of acquisition and administration for the medications in each group, the authors found that ranitidine was more expensive at \$20.32 per day versus omeprazole at \$12.85 per day. Pneumonia occurred in 16% of ranitidine patients versus 18% of omeprazole patients, a difference that was not statistically significant. The results of this trial independently reaffirm the findings by Levy et al, and the investigators concluded that omeprazole is superior in efficacy, safety, and cost when compared with continuous infusion intravenous ranitidine.

A subsequent trial compared the efficacy of three drugs for SUP: 150 mg daily of continuously infused ranitidine, sucralfate 1 g every 6 hours via nasogastric tube, and omeprazole 40 mg intravenously every 12 hours in 108 patients admitted to a general ICU with at least one risk factor for stress-related gastrointestinal bleeding (16). Gastrointestinal bleeding occurred in 10.5% of patients in the ranitidine group ( $n = 38$ ), 9.3% of those in the sucralfate group ( $n = 32$ ), and none of those in the omeprazole group ( $n = 38$ ;  $P = 0.1$ ). The incidence of nosocomial pneumonia was not statistically significantly different between the groups (10.5% vs 9.3% vs 13.1%, respectively;  $P = 0.2$ ). Mortality was also not statistically different between the three groups. This study suggests the superiority of omeprazole compared with ranitidine and sucralfate in preventing gastrointestinal hemorrhage; however, a statistically significant difference was not found in this small, single-center trial.

### USE AT BAYLOR UNIVERSITY MEDICAL CENTER

A 1-month retrospective chart review evaluated the use of SUP in ICU patients at Baylor University Medical Center (BUMC) to elucidate and further characterize the use of AST in our patient population. Eighty-seven patients were randomly selected and followed for their entire hospital admission. Sixty-six percent of patients were on AST without any indication or risk for SRMD, and 52% of patients were inappropriately transferred to a medicine floor with AST. The percentage of inappropriate initiation of AST in the ICU at BUMC is consistent with the studies by Nardino et al (17) and Zink et al (18). Overall, the percentages of proper discontinuation and continuation of AST at the time of discharge were high, with a total of 81% of AST appropriately discontinued at discharge and 67% of AST appropriately continued at time of discharge.

Appropriate discontinuation of AST at discharge was slightly higher at BUMC than what's been reported in the literature.

Sixteen patients (20%) may have experienced an ADR due to AST. Three patients experienced *C. difficile*-associated disease, 10 patients experienced altered mental state, six patients experienced pneumonia, and two patients experienced thrombocytopenia. Most of the patients who experienced one of these adverse events were also on AST prior to admission. Over half of the medication expenditures related to SUP use were for inappropriate AST, specifically unnecessary intravenous PPI use.

## CONCLUSION

SRMD can lead to significant morbidity in ICU patients. Based upon the limited clinical evidence to date, SUP should be promptly initiated if at least one independent risk factor or at least two other risk factors for SRMD are present during the patient's admission to the ICU. SUP in the general medicine setting has not been proven necessary by clinical trials unless the patient has at least one independent risk factor that increases the risk of clinically important bleeding. However, the data available to support these recommendations are not strong. PPIs appear to reduce overall gastrointestinal bleeding when compared to H<sub>2</sub>RAs, antacids, and sucralfate; however, there is insufficient evidence to prove they improve survival. The retrospective review of SUP in the ICU conducted at our institution revealed that 66% of patients were initiated on SUP, and 52% of patients reviewed were transferred out of the ICU setting on AST inappropriately. The use of unnecessary AST can lead to potential ADRs as well as an increase in medication costs for the patient and health care system. Health care professionals can play an important role in minimizing the inappropriate use of AST and maintaining optimal patient care by carefully scrutinizing the need for AST once a patient has left the ICU setting.

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