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Which ICU patients need stress ulcer prophylaxis?

ABSTRACT

Critically ill patients are at an increased risk for developing stress ulcers of the mucosa of the upper gastrointestinal (GI) tract. Bleeding from stress ulcers was previously associated with a longer stay in the intensive care unit and an increased risk of death. Thus, most patients admitted to the intensive care unit receive stress ulcer prophylaxis. However, there is a growing concern that acid-suppression drugs may be associated with increased frequency of nosocomial pneumonia and *Clostridioides difficile* infection. In this article, the authors address controversies regarding stress ulcer prophylaxis in critically ill patients and provide guidance for its appropriate use in this setting.

KEY POINTS

Although 75% of critically ill patients who do not receive stress ulcer prophylaxis develop stress ulcers, only a minority of these ulcers bleed.

Positive pressure ventilation for more than 48 hours and coagulopathy are two major independent predictors of clinically important GI bleeding in critically ill patients.

Although stress ulcer prophylaxis has not been shown to reduce mortality risk, it decreases the risk of clinically significant bleeding and does not increase risk of *C difficile* infection or pneumonia.

The beneficial effects of stress ulcer prophylaxis on GI bleeding argue for its use in critically ill patients with risk factors for developing stress ulcers.

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Most critically ill patients are at an increased risk for developing erosions and ulceration of the mucosa of the gastrointestinal (GI) tract.[1] The exact physiology is not fully known, but postulated mechanisms include splanchnic and GI tract hypoperfusion, mucosal ischemia or disruption leading to decreased mucous secretion, and increased acid production with subsequent GI tract injury.[2] Although about 75% of critically ill patients who do not receive stress ulcer prophylaxis develop stress ulceration, only a minority of these ulcers bleed.[1,3–8]

Stress ulcers in critically ill patients can be divided into 3 categories, each with separate definitions and incidence rates (**Table 1**).[1,3–9] Earlier studies suggested an association between stress ulceration and an increase in mortality risk and length of stay in the intensive care unit (ICU),[4] which led to a significant emphasis on providing prophylaxis to most critically ill patients. But stress ulcer prophylaxis may not be benign, as reports of an association with increased risk of pneumonia and *Clostridioides difficile* infection spurred debate as to its role in critically ill patients.[1,10,11]

In this article, we address controversies regarding the use of stress ulcer prophylaxis in critically ill patients. We will discuss risk factors associated with the development of stress ulcers and GI bleeding in critical illness, review evidence comparing different prophylactic agents, and provide guidance for appropriate use of stress ulcer prophylaxis in this population.

TABLE 1
Categories, definition, and incidence of stress ulcers in critically ill patients

Category	Definition	Incidence
Stress ulceration with occult bleeding	Fecal samples with guaiac-positive test for blood	15%–50%
Stress ulceration with overt gastrointestinal bleeding	Hematemesis, bloody nasogastric tube aspirate, or melena	1.5%–8.5%
Stress ulceration with clinically important gastrointestinal bleeding	Overt gastrointestinal bleeding plus 1 or more of the following within 24 hours: • Decrease in systolic, mean arterial blood pressure, or diastolic blood pressure of ≥ 20 mm Hg • Orthostatic hypotension (systolic blood pressure > 10 mm Hg) or postural tachycardia (increase in pulse ≥ 20 beats/minute) • Drop in hemoglobin ≥ 2 g/dL • Received transfusion of ≥ 2 units of packed red blood cells • Need for vasopressors or invasive interventions (eg, endoscopy)	1%–3%

Based on information in references 1 and 3–9.

WHICH PATIENTS ARE AT INCREASED RISK?

Numerous risk factors are associated with the development of stress ulcers in ICU patients. Perhaps the biggest risks were identified in the Canadian Critical Care Trials Group,[3] a multicenter prospective cohort study of 2,252 critically ill patients. This study found that positive pressure ventilation for more than 48 hours (odds ratio [OR] 15.6, $P < .001$) and bleeding diathesis (OR 4.3, $P < .001$) are major independent predictors of clinically important GI bleeding in these patients.[3] The incidence of stress-related GI bleeding when these risk factors were present was 3.7% vs 0.1% in patients with no risk factors.[3] Subsequent studies have identified other risk factors associated with clinically important GI bleeding in critically ill patients (**Table 2**).[3,5,6,8,12] However, as no single variable is an independent predictor of clinically important GI bleeding, the decision to use prophylaxis should be tailored to the individual patient.

WHAT IS THE EFFECT OF STRESS ULCER PROPHYLAXIS ON OUTCOMES?

The effect of stress ulcer prophylaxis on mortality in patients in the ICU was evaluated in the Stress Ulcer Prophylaxis in the Intensive Care Unit (SUP-ICU) trial,[5] a multicenter European randomized controlled trial that included 3,298 ICU patients with at least 1 predefined risk factor for GI bleeding. Notably, 20% of these patients had coagulopathy, and 79% were receiving positive pressure ventilation.[5] Interestingly, 90-day mortality rates were similar between groups: 31.1% in the prophylaxis group vs 30.4% in the placebo group ($P = .76$).[5]

These results have been replicated in other studies and at least 2 meta-analyses,[13,14] stirring the debate as to whether stress ulcer prophylaxis is beneficial.[15] Advocates argue that despite similar 90-day mortality rates between the treatment and placebo groups, studies evaluating this question may be subject to type II error (a false-negative error of omission) because of a potentially real but small mortality benefit related to prophylaxis.[16] In addition, advocates point out that the rate of clinically significant GI bleeding was 41% lower in patients treated with proton pump inhibitors (PPIs) than in the placebo group (2.5% vs 4.2%), a finding that has been replicated in meta-analyses.[5,13,14]

It should be noted that in the intervention arm of the SUP-ICU trial, more patients in the PPI group required transfusion than in the placebo group (32.5% vs 29.6%).[5] Although the significance of this is unclear, we believe that the clear beneficial effect of stress ulcer prophylaxis on clinically significant GI bleeding argues for its continued use in select critically ill patients.

WHICH AGENT SHOULD I USE?

Agents used for stress ulcer prophylaxis include PPIs, histamine-2 receptor blockers, and sucralfate. The

choice should be tailored to the patient's needs, comorbidities, and potential risk factors for pneumonia and C *difficile* infection. A Cochrane meta-analysis of 18 studies (N = 1,636) reported that PPIs were more effective in suppressing gastric acid than histamine-2 receptor blockers (risk ratio [RR] 2.90, 95% confidence interval [CI] 1.83–4.58; absolute risk 4.8%, 95% CI 2.1–9.0].[17] A 2020 randomized controlled trial of critically ill patients receiving positive pressure ventilation (N = 26,982) showed a statistically significant decrease in GI bleeding in patients taking PPIs compared with those taking histamine-2 receptor blockers (1.3% vs 1.8%, *P* = .009).[18]

Although PPIs may be more effective than histamine-2 receptor blockers in preventing GI bleeding,[17,18] there has been a concern for increased risk of pneumonia and C *difficile* infection associated with PPIs. This concern was primarily based on a large, propensity-matched cohort study of patients on positive pressure ventilation for more than 24 hours (N = 35,312).[1] The study showed a higher incidence of pneumonia in patients treated with a PPI than in those treated with a histamine-2 receptor blocker (38.6% vs 27%, *P* < .001), and a higher incidence of C *difficile* infection with a PPI vs a histamine-2 receptor blocker (3.8% vs 2.2, *P* < .001).[1]

However, the PEPTIC trial (Proton Pump Inhibitors vs Histamine-2 Receptor Blockers for Ulcer Prophylaxis Treatment in the Intensive Care Unit)[18] largely dispelled this concern after finding no increase in C *difficile* infection (0.3% with a PPI vs 0.43% with a histamine-2 receptor blocker; RR 0.74, 95% CI 0.51–1.09) or in pneumonia (6.5% with a PPI vs 5.8% with a histamine-2 receptor blocker; RR 1.18, 95% CI 0.87–1.59). The PEPTIC trial results are supported by those of the SUP-ICU trial,[5] which found no increased incidence of infectious events (composite end point of nosocomial pneumonia or C *difficile* infection) between PPI and placebo (16.8 vs 16.9; RR 0.99, 95% CI 0.84–1.16).

In addition, data from 3 meta-analyses also did not show an increase in the risk of infectious complications (including C *difficile* infection and pneumonia) between PPIs and histamine-2 receptor blockers.[17,19,20] Given these data, we prefer an oral PPI to a histamine-2 receptor blocker when indicated in high-risk patients who can receive enteral nutrition to decrease their risk of clinically significant GI bleeding. **Table 3** shows dosing recommendations.[21] We do not use intravenous PPIs unless a patient is actively bleeding from a stress ulcer or cannot tolerate enteral nutrition, because intravenous PPI is significantly more expensive than oral PPI therapy.[22] In rare cases in which PPIs and histamine-2 receptor blockers cannot be used for prophylaxis (eg, because of drug intolerance or interactions), sucralfate may be considered as an alternative.

TABLE 2
Indications for stress ulcer prophylaxis in critically ill patients

Major risk factors (prophylaxis recommended)
Positive pressure ventilation > 48 hours, including extracorporeal life support
Coagulopathy (platelet count < 50 × 10^9/L, international normalized ratio > 1.5, activated partial thromboplastin time > 2 times normal)[a]
History of gastrointestinal ulceration or bleeding within past year
Acute traumatic brain or spinal cord injury
Major thermal injury (≥ 35% of total body surface area)
Minor risk factors (prophylaxis recommended if ≥ 2 minor criteria are present)
Sepsis
Intensive care unit stay > 1 week
Occult gastrointestinal bleeding for ≥ 6 days
Glucocorticoid therapy (> 250 mg of hydrocortisone or the equivalent)
Use of antiplatelet or nonsteroidal anti-inflammatory agents
Renal failure or renal replacement therapy
Hepatic failure
History of peptic ulcer disease
Extracorporeal life support
Organ transplantation

[a] Independent predictors of clinically important gastrointestinal bleeding in critically ill patients.

Based on information in references 3, 5, 6, 8, and 12.

DOES ENTERAL NUTRITION REDUCE THE RISK OF DEVELOPING STRESS ULCERS?

Emerging data show that the incidence of stress ulcers may be lower in patients receiving enteral nutrition in the ICU. In these patients, it is unclear whether stress ulcer prophylaxis is indicated. In a meta-analysis, Huang et al[23] concluded that prophylaxis provides no added benefit to patients receiving enteral nutrition. They found no statistically significant difference in the rate of GI bleeding. They reported that prophylaxis had no effect on overall mortality, duration of positive pressure ventilation, incidence of C *difficile* infection, or ICU length of stay.[23] Early enteral nutrition is recommended as it promotes gut integrity, decreases infectious morbidity, and may lower mortality risk.[24] Because there are no data from prospective randomized controlled trials on enteral nutrition as

TABLE 3
Dosing recommendations for stress ulcer prophylaxis

Route	Proton pump inhibitor	Histamine-2 receptor blocker	Sucralfate
Parenteral	Pantoprazole 40 mg/day Esomeprazole 40 mg/day	Famotidine 20 mg every 12 hours	
Enteral	Pantoprazole 40 mg/day Omeprazole 40 mg/day Lansoprazole 30 mg/day Esomeprazole 40 mg/day	Famotidine 20 mg every 12 hours Cimetidine 300 mg every 6 hours Ranitidine 150 mg every 12 hours	Sucralfate 1 g every 6 hours

Based on information in reference 21.

a sole means of stress ulcer prophylaxis, we believe that enteral feeding should not replace prophylaxis in high-risk critically ill patients.

WHAT IS THE OPTIMAL DURATION OF STRESS ULCER PROPHYLAXIS IN ICU PATIENTS?

The optimal duration of stress ulcer prophylaxis in ICU patients is unclear. While most experts agree that prophylaxis should be used if risk factors are present, there is limited agreement on when to stop it.[25] A practical approach would be to evaluate indicators associated with a high risk for developing stress ulcers. Once these stressors have been mitigated, prophylaxis could possibly be de-escalated. This approach, while not validated, may be reasonable given the low risk of bleeding from stress ulcers in non-ICU hospitalized patients (0.29%).[26]

THE BOTTOM LINE

In some critically ill patients, the risk of clinically significant GI bleeding is high. Stress ulcer prophylaxis does not reduce mortality rates. But on the other hand, it decreases the risk of clinically significant bleeding and does not increase the risk of *C difficile* infection or pneumonia. Based on these findings, we believe that prophylaxis should be considered in critically ill patients with risk factors for stress ulcers. Frequent reassessment and de-escalation of therapy are warranted when the patient is at lower risk for bleeding.

DISCLOSURES

Dr. Bass has disclosed consulting for AbbVie Pharmaceuticals. The other authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

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