Stress ulcers in the intensive care unit: Diagnosis, management, and prevention

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INTRODUCTION

Stress ulcerations are common in intensive care unit (ICU) patients, some of which can cause hemorrhage. As a consequence, many critically ill patients require prophylaxis for primary prevention of bleeding from stress ulceration or treatment for stress ulcer-related bleeding.

The incidence, pathophysiology, risk factors, diagnostic evaluation, management, and prevention of stress ulceration in the ICU are discussed in this topic review. Diagnosis and treatment of bleeding from peptic ulcers **not** due to hospitalization are discussed separately. (See "Approach to acute upper gastrointestinal bleeding in adults" and "Overview of the treatment of bleeding peptic ulcers".)

DEFINITION

Stress ulceration is defined as ulceration of the upper gastrointestinal (GI) tract (esophagus, stomach, duodenum) that occurs **due to** hospitalization. Hemorrhage from stress ulceration is secondary GI bleeding (ie, nosocomial GI bleeding), which is distinct from primary GI bleeding (ie, GI bleeding that **results in** hospitalization). Primary prevention of GI bleeding from stress ulcers is known as stress ulcer prophylaxis (SUP).

Stress ulceration may be further sub-classified as the following [1]:

- Stress ulceration that is asymptomatic – Ulceration without bleeding.

- Stress ulceration with occult bleeding – Gastric or fecal samples with guaiac-positive testing for blood.
- Stress ulceration with overt bleeding – Hematemesis, frank blood or coffee-grounds in nasogastric aspirate, and/or melena.
- Stress ulceration with clinically important bleeding – Overt bleeding plus one or more of the following:
  - Decrease in systolic or diastolic blood pressure ≥20 mmHg within 24 hours before or after bleeding
  - Orthostatic increase in pulse ≥20 beats per minute and decrease in systolic BP >10 mmHg
  - Decrease in hemoglobin >2 g/dL over 24 hour period or transfusion of ≥2 units pack red blood cells within 24 hours after bleeding starts
  - Need for vasopressor support and/or invasive interventions (eg, endoscopy)

While the definition of overt and clinically-important bleeding is important for research purposes, the definition varies from study to study and from a practical aspect in the intensive care unit (ICU), it is somewhat artificial since all forms of GI bleeding in the ICU are important and need addressing.

INCIDENCE

Published incidence rates vary with the definition of stress ulceration (see 'Definition' above), the presence of risk factors, and the prophylaxis prescribed. While estimates of asymptomatic stress ulceration in critically ill patients not receiving prophylaxis is likely high (eg, >75 percent), rates are decrementally lower for stress ulceration with occult bleeding (eg, 15 to 50 percent), stress ulceration with overt bleeding (eg, 1.5 to 8.5 percent), and stress ulceration with clinically significant bleeding (eg, 1 to 3 percent) [2-9]. Stress ulceration resulting in perforation occurs in fewer than 1 percent of intensive care unit (ICU) patients [10].

Overt gastrointestinal (GI) bleeding due to stress ulceration is associated with increased mortality. In a prospective cohort study, mortality was higher among ICU patients with clinically important GI bleeding than among those without bleeding (49 versus 9 percent) [2]. Another study used four different statistical models to adjust for confounders and found that overt GI

bleeding was associated with increased mortality using three of the models (relative risk ranged from 1.8 to 4.9) [5].

PATHOPHYSIOLOGY

Stress ulcerations usually occur in the fundus and body of the stomach, but sometimes develop in the antrum, duodenum, or distal esophagus. They tend to be shallow and cause oozing of blood from superficial capillary beds. Deeper lesions may also occur, which can erode into the submucosa and cause massive hemorrhage or perforation [11].

In most patients, stress ulceration generally begins in the proximal regions of the stomach within hours of major trauma or serious illness but only a small percentage go on to develop overt clinical bleeding. In contrast, stress ulcerations that develop later (eg, after the first few days of hospitalization) tend to be deeper and more distal (eg, antrum, duodenum) [12,13].

It is uncertain if early and late stress ulcerations have the same pathophysiology. However, both types probably result from an imbalance between mucosal protection and gastric acid production.

- Impaired mucosal protection – The stomach is normally protected by a glycoprotein mucous layer that forms a physical barrier to hydrogen ion diffusion and traps bicarbonate. The bicarbonate neutralizes gastric acid adjacent to the stomach wall. This barrier may be denuded by increased concentrations of refluxed bile salts or uremic toxins, which are common in critically ill patients [14,15]. In addition, its synthesis may be decreased when there is poor gut perfusion caused by hypovolemia, shock, sepsis, or trauma [16,17].

- Hypersecretion of acid – Hypersecretion of acid due to excessive gastrin stimulation of parietal cells has been detected in patients with head trauma [18-20]. This abnormality is probably not a factor in all ICU patients, since acid secretion tends to be normal or subnormal in most other patients.

RISK FACTORS

Several risk factors have been associated with an increased risk of stress ulceration (table 1). The two most common major risk factors for the development of clinically important gastrointestinal (GI) bleeding from stress ulceration were identified in a multicenter prospective cohort study of 2252 intensive care unit (ICU) patients as [2]:

- Mechanical ventilation for more than 48 hours (odds ratio [OR] 15.6)
- Coagulopathy (OR 4.3; eg, thrombocytopenia [platelet count <50,000 per m^3], elevated international normalized ratio [INR] >1.5, or a partial thromboplastin time [PTT] >2 times the control value)

The incidence of clinically important GI bleeding among patients with one or both of these risk factors was 3.7 percent, compared with 0.1 percent among patients with neither risk factor.

Other studies have suggested that patients with chronic liver disease may also be among the highest risk groups, although this may be due to the association with coagulopathy [21].

Smaller studies have reported additional risk factors for stress ulceration, including the following [4,7,11,22-24]:

- Shock
- Sepsis
- Hepatic failure
- Renal failure and renal replacement therapy
- History of peptic ulcer disease
- History of upper GI bleeding
- Three or more coexisting diseases
- Extracorporeal life support
- Multiple trauma, head trauma, spinal trauma
- Burns over 35 percent of total body surface area
- Organ transplantation
- Antiplatelet agents
- Nonsteroidal antiinflammatory drugs (NSAIDs)

Other risk factors with limited or conflicting evidence include the following:

- **Glucocorticoid therapy** – Glucocorticoid therapy is commonly cited as an indication for stress ulcer prophylaxis [25]. However, glucocorticoid therapy alone has not been conclusively shown to be a risk factor for stress ulceration [2] but may increase the risk when combined with other risk factors for GI ulceration. (See "Major side effects of systemic glucocorticoids", section on 'Gastrointestinal effects'.)
- ***Helicobacter pylori*** – *H. pylori* infection may also contribute to stress ulceration, but the evidence is limited and conflicting. A case-control study of 50 ICU patients found that patients with GI bleeding were more likely to have *H. pylori* infection than patients without

acute GI bleeding (36 versus 16 percent) [26]. Another observational study of 99 ICU patients found that patients with *H. pylori* infection were more likely to have GI bleeding than patients without *H. pylori* infection (23 versus 13 percent), although the difference did not reach statistical significance [27].

- **Enteral nutrition** – The impact of enteral nutrition on the risk of bleeding is also unclear. While some data suggest that enteral nutrition decreases the risk of bleeding [28-30], other data suggest that the administration of prophylaxis in those who are being enterally fed may be ineffective or possibly harmful when enteral feeding is administered simultaneously with GI prophylaxis [31]. However, many of these studies are fundamentally flawed and further study is required before firm conclusions can be made regarding enteral nutrition and the risk of bleeding from stress ulceration. We also believe that enteral nutrition should not influence the decision to administer stress ulcer prophylaxis but may be used to facilitate the duration of prophylaxis. (See 'Prophylaxis' below.)

  - In one post-hoc study performed using data from a randomized trial, enteral nutrition independently reduced the risk of overt GI bleeding (relative risk 0.30, 95% CI, 0.13-0.67) in 1077 critically ill patients who were mechanically ventilated for more than 48 hours [30]. Another observational study of 526 patients in a burn ICU found that the incidence of overt GI bleeding was lower among patients who received early enteral nutrition alone than among patients who received a histamine-2 receptor antagonist (H2 blocker) without early enteral nutrition (3 versus 8 percent) [29]. These results suggest a protective effect of enteral feeding against the risk of GI bleeding.

  - One systematic review of 17 trials reported that while the administration of H2 blockers in patients who were not being enterally fed reduced the rate of GI bleeding (OR 0.47, 95% CI 0.29-0.76), this effect was lost in patients who were being enterally fed (OR 1.26, 95% CI 0.43-3.7) [31]. However, the administration of GI prophylaxis in patients who were enterally fed was associated with an increased mortality (OR 1.89, 95% CI 1.04-3.44) and increased rate of hospital acquired pneumonia (HAP; OR 2.81, 95% CI 1.20-6.56). However, the analysis was limited since it included patients who were both at high risk and at low risk for stress ulceration and none of the included studies prospectively examined the effects of enteral nutrition on the risk of ulcer prophylaxis. Another meta-analysis of seven studies reported that compared with placebo or no prophylaxis, patients receiving enteral feeding and on GI prophylaxis had similar rates of GI bleeding, mortality and *Clostridioides difficile* infection but an increased risk of nosocomial pneumonia (relative risk 1.53, 95% CI 1.04-2.27) [32].

DIAGNOSTIC EVALUATION AND MANAGEMENT

Clinical presentation — Stress ulcers should be suspected in critically ill patients who present with the following:

- Hematemesis (eg, positive occult blood testing, coffee grounds or frank blood observed in nasogastric aspirate)
- Melena
- Anemia noted on routine laboratory testing
- Hypotension or shock

Patients rarely present with the manifestations of esophageal perforation (eg, chest pain, respiratory distress, mediastinal air, pleural effusion). (See "Overview of gastrointestinal tract perforation", section on 'Clinical features'.)

Additional details on the clinical manifestations and evaluation of patients with suspected peptic ulcer disease is provided separately. (See "Peptic ulcer disease: Clinical manifestations and diagnosis".)

Diagnostic evaluation — In cases with occult bleeding, the diagnosis is an assumptive one and most experts do not perform diagnostic endoscopy. However, follow-up of such patients for evidence of resolution is important. Once the critical illness has resolved, patients during recovery who continue to show evidence of bleeding or who have another indication should undergo endoscopy (eg, upper gastrointestinal [GI] symptoms, continued positivity for fecal blood or screening is not up to date).

For those with overt and/or clinically significant bleeding, endoscopy may be indicated, when feasible. The decision to perform endoscopy is individualized and is more likely to be indicated when the results are likely to affect decision-making and/or a potentially treatable lesion is suspected. During endoscopy, the diagnosis is typically confirmed by the visualization of superficial erosions in the gastric mucosa. They are usually shallow, well-demarcated, and primarily involve the superficial layers of the gastric epithelium. However, deeper ulcerations may also be noted. (See "Approach to acute upper gastrointestinal bleeding in adults" and "Peptic ulcer disease: Clinical manifestations and diagnosis", section on 'Diagnosis'.)

Complications — Stress ulceration is associated with hemorrhage but can also be associated with more serious complications including perforation, hemorrhagic shock, and death. An increased length of ICU stay by four or more days has also been reported in patients with stress ulceration [5].

Treatment — For critically ill patients who have occult bleeding, most experts treat using a strategy of observation or increased surveillance (eg, daily hemoglobin, fecal and gastric occult blood testing) and optimization of prophylactic agents.

Critically ill patients with overt bleeding from stress ulcers are treated using similar principles to patients with ulceration that is not stress-induced, the details of which are discussed separately. (See "Approach to acute upper gastrointestinal bleeding in adults".)

PROPHYLAXIS

The administration of stress ulcer prophylaxis (SUP) is an area of topical debate. While in the past, nearly every patient admitted to the intensive care unit (ICU) was treated with a prophylactic agent, data and guidelines now support SUP in select patients, in particular, patients assessed to be at high risk of bleeding.

High-risk patients — Based upon randomized trials that demonstrate reduced bleeding rates, we and other guideline groups agree that SUP should be administered to critically ill patients who are assessed as high risk for gastrointestinal (GI) bleeding [33]. Although it is unclear what constitutes "high risk", we and others believe this includes patients with any one of the following characteristics:

- Bleeding diathesis (eg, platelet count <50,000 per m^3, an international normalized ratio [INR] >1.5, or a partial thromboplastin time [PTT] >2 times the control value)
- Mechanical ventilation for >48 hours especially those who are not being enterally fed
- Chronic liver disease
- History of GI ulceration or GI bleeding within the past year
- Traumatic brain injury, traumatic spinal cord injury, or burn injury
- Two or more of the following minor criteria: sepsis, an ICU stay more than one week, occult GI bleeding for six or more days, or glucocorticoid therapy (more than 250 mg hydrocortisone or the equivalent)
- On nonsteroidal antiinflammatory or antiplatelet agents

This approach is based upon the rationale that the risk in this population is high enough to justify prophylaxis (see 'Risk factors' above) and data from randomized trials that support a reduction in the rate of clinically relevant bleeding in high-risk critically ill patients treated with

prophylactic agents when compared with patients who do not receive prophylaxis (see 'Efficacy' below). Although patients with traumatic brain, spinal cord, or burn injury were typically excluded from most randomized trials, most experts administer SUP as the risk is considered high in these patients.

Until the impact of enteral nutrition on the risk of bleeding is clarified, we believe that the evidence is insufficient to justify withholding SUP from patients who are at high risk for GI bleeding even if they are receiving enteral nutrition. The impact of enteral nutrition on the risk of GI bleeding is discussed above. (See 'Risk factors' above.)

Choosing an agent — The optimal SUP agent is unknown and substantial variation exists in practice over agent selection in critically ill patients. Our practice is the following:

- For critically ill patients who are able to receive enteral medications and in whom SUP is indicated, an oral proton pump inhibitor (PPI) is preferred rather than an alternative prophylactic agent (eg, histamine-2 receptor antagonist [H2 blocker], sucralfate, or antacids). This preference is based upon randomized trials and meta-analyses which report that PPIs are more effective than other agents. For patients in whom an oral PPI is not tolerated, an oral H2 blocker is an appropriate alternative. (See 'Efficacy' below and 'Pharmacologic agents' below.)

  In the United States, pantoprazole is the most common PPI prescribed in the ICU for SUP, although there are no comparative data among PPIs to suggest one is superior to another. Similarly, there are no data comparing H2 blockers with one another. In reality, within a chosen class of prophylactic agents, many clinicians prescribe an agent that is determined by the hospital or pharmacy policy [34].

- For critically ill patients who cannot receive enteral medications, an intravenous (IV) H2 blocker or IV PPI can be administered. While an IV PPI is preferred, some clinicians administer IV H2 blockers (usually famotidine) based upon their lower cost and an increase in efficacy of PPIs over H2 blockers that is uncertain, especially when the baseline risk of stress ulcer-related GI bleeding is on the lower end of the range (1 to 8 percent).

- In rare cases where PPIs or H2 blockers cannot be administered, sucralfate is a suitable oral alternative. Antacids or prostanoids are rarely, if ever, used.

For most experts, the choice of SUP agent depends upon the balance between efficacy and potential harm, as well as cost.

- Efficacy versus potential harm – Evidence indicates that although prophylactic agents, in particular H2 blockers and PPIs, effectively reduce the rate of GI bleeding in critically ill patients, they may also be associated with an increased rate of nosocomial infections. However, data supporting an infectious adverse risk associated with acid suppressants are conflicting and many of the studies had several flaws. Thus, we believe that the benefits of SUP in critically ill patients who are at high risk of bleeding outweigh the potential risk of adverse effect. (See 'Efficacy' below and 'Potential harms' below.)

- Cost – Choosing less expensive prophylactic agents can diminish the cost of SUP. One analysis found that prophylaxis with an oral PPI may be more cost-effective than intravenous agents due to the lower cost of oral medications and fewer treatment failures in the oral PPI group [35].

Choosing an agent in patients with **active** gastrointestinal bleeding requires a different approach and is discussed separately. (See "Approach to acute upper gastrointestinal bleeding in adults", section on 'Medications'.)

Efficacy — Most clinical trials have demonstrated that compared with placebo or no prophylaxis PPIs, H2 blockers, sucralfate, and antacids reduce the frequency of overt GI bleeding in critically ill patients but do not appear to have a mortality benefit [4,6,36-45]. On balance, evidence favors PPIs based upon meta-analyses that report possible superiority of PPIs in the reduction of clinically important GI bleeding compared with H2 blockers. However, the evidence is limited because many of the studies were imprecise or had other significant methodologic flaws. Patients with trauma, severe burns, or spinal injury were typically excluded from major trials and the administration of SUP in those populations is based upon a risk that is considered high enough to justify prophylaxis (table 1). (See 'High-risk patients' above and 'Risk factors' above.)

- **PPI versus placebo** – In the largest trial (SUP-ICU) of 3298 critically ill patients at risk of GI bleeding, three-quarters of whom were mechanically ventilated, the PPI, pantoprazole, was compared with placebo. While the 90 day mortality was no different (30 versus 31 percent), rates of clinically important GI bleeding were lower in patients treated with pantoprazole (2.5 versus 4.2 percent) [6]. However, the study was not adequately powered to detect a significant difference in the rate of bleeding events; mortality remained unaffected at one year [44]. A post-hoc analysis of this trial suggested a possible increased 90-day mortality in severely ill patients who were on pantoprazole but the data were flawed and further research is needed to draw firm conclusions [46]. A network meta-analysis of 57 trials, that did not include SUP-ICU provided moderate quality evidence that PPIs reduced the rate of GI bleeding when compared with placebo or no prophylaxis (odds

ratio [OR] 0.2, 95% CI 0.1-0.6) but PPIs had no impact on mortality [47]. The same network analysis ranked PPIs as the most effective followed by H2 blockers, sucralfate, and placebo. Results from another randomized trial of pantoprazole compared with placebo (REVISE) are pending [48]. Another 2020 meta-analysis of 72 trials including 12,600 patients also reported similar results [49]. Rates of upper GI bleeding were reduced in patients considered at high risk for bleeding by PPIs when compared with placebo (OR 0.61, 95% CI 0.42-0.89).

- **PPI versus H2 blockers** – Several meta-analyses report a reduction in the rate of GI bleeding with PPIs when compared with H2 blockers [42,45,47,50-52]. In a Cochrane meta-analysis of 18 studies (1636 participants), PPIs more often prevented upper GI bleeding in ICU patients compared with H2 blockers (risk ratio [RR] 2.90, 95% CI 1.83-4.58; low certainty of evidence; absolute risk 4.8 percent) [42]. In a large randomized crossover trial of ICU patients who were mechanically ventilated, patients receiving PPIs had a significant reduction in the rate of upper GI bleeding compared with patients receiving H2 blockers (1.3 versus 1.8 percent) [53]. There was a nonstatistical difference in mortality (18.3 for PPI versus 17.5 percent for H2 blockers; RR 1.05, 95% CI 1.00-1.10; absolute risk difference 0.93 percentage points), suggesting that the remote possibility of harm from PPIs has not been confidently ruled out. However, study interpretation may be limited by crossover in the use of the assigned medication (4 percent in the PPI group received an H2 blocker and 20 percent received a PPI in the H2 blocker group). In a 2020 network meta-analysis (NMA) of 74 trials (which included the above randomized trial), PPIs resulted in a reduction of clinically important GI bleeding compared with H2 blockers (RR 0.69, 95% CI 0.29-0.66) without an effect on mortality [45]. The risk reduction was highest in patients at high risk of bleeding. However, this NMA could not confidently rule out a possible increased risk of mortality with PPIs.

- **Other comparisons** – A 2018 NMA provided moderate quality evidence of reduced rates of clinically significant bleeding for the following comparisons [47]:

  - PPIs compared with sucralfate (OR 0.3, 95% CI 0.1-0.7)
  - H2 blockers compared with placebo (OR 0.64, 95% CI 0.32-1.30)
  - H2 blockers compared with sucralfate (OR 0.80, 95% CI 0.46-1.40)

  Another 2020 NMA of 72 trials including 12,600 patients also reported reduced rates of upper GI bleeding in H2 blockers when compared with placebo (OR 0.46, 95% CI 0.27-0.79; moderate certainty) [49].

Older meta-analyses reported lower rates of overt GI bleeding in critically ill patients receiving H2 blockers compared with antacids (OR 0.56, 95% CI 0.33-0.97) [37] and similar rates of GI bleeding when sucralfate was compared with antacids (OR 0.73, 95% CI 0.54-0.97), although sucralfate was associated with a reduced mortality [36]. There are a lack of moderate or high quality trials comparing PPIs to antacids and sucralfate to placebo in critically ill patients.

Potential harms — Older data suggested that prophylactic agents which increase gastric pH (PPI, H2 blockers, antacids) may increase the frequency of nosocomial pneumonia and, possibly, of *C. difficile* infection (CDI). However, many of those trials failed to account for appropriate confounding variables and newer data suggest no increased risk. Data that suggest a possible increase in mortality from PPIs have also been suggested but require further study; these data are discussed above (see 'Efficacy' above). Other adverse effects are rare.

- **Nosocomial pneumonia** – Randomized trials and meta-analyses report conflicting data on the impact of SUP, on the rate of nosocomial pneumonia [6,36,41,42,47,49-51,54-60]. However, many of the older studies had methodologic flaws, in particular, a lack of control for confounding variables that predispose to pneumonia (eg, age, mechanical ventilation), variability in the estimated baseline risk for and definition of pneumonia, and influence of enteral nutrition. Furthermore, newer data suggest no convincing difference in the rates of pneumonia with SUP. Thus, we and many intensivists believe that the risk of pneumonia is not sufficient to justify withholding SUP to patients at high risk of GI bleeding.

  Studies that report no increased risk of pneumonia include the following:

  - PPI versus placebo – In a 2018 trial (SUP-ICU) of 3298 critically ill patients at risk of GI bleeding that compared pantoprazole with placebo, no difference in the rates of pneumonia was reported [6]. However, the study was not adequately powered to detect a difference in the risk of infections.

  - PPI versus H2 blockers – In a 2018 meta-analysis of 18 studies (1636 critically ill patients), that did not include SUP-ICU, PPI use had no impact on the rate of pneumonia compared with H2 blockers [42].

  - H2 blockers versus sucralfate – A randomized trial of 1200 mechanically ventilated patients reported similar rates of ventilator-associated pneumonia when an intravenous H2 blocker (ranitidine) was compared with sucralfate (19 versus 16 percent; RR 1.18, 95% CI 0.92-1.51) [54].

- Sucralfate versus placebo – A network meta-analysis of 57 trials demonstrated no increase in the risk of pneumonia when sucralfate was compared with placebo (OR 1.09, 95% CI 0.72-1.66; low quality evidence) [47].

The strongest evidence in support of an increased risk of pneumonia comes from one 2018 network meta-analysis (NMA) of 57 trials [47] which did not include SUP-ICU that demonstrated an increase in the risk of pneumonia when:

- PPIs were compared with H2 blockers (OR 1.27, 95% CI 0.96-1.68; moderate-quality evidence), sucralfate (OR 1.65, 95% CI 1.20-2.27), and placebo (OR 1.52, 95% CI 0.95-2.42; 3.1 percent absolute increase).
- H2 blockers were compared with placebo (OR 1.19, 95% CI 0.80-1.78; moderate-quality evidence).
- H2 blockers were compared with sucralfate (OR 1.30, 95% CI 0.08-1.58; low-quality evidence).

A subsequent 2020 NMA of 72 trials including 12,600 patients also reported increased rates of pneumonia in patients receiving H2 blockers or PPIs when compared with placebo (OR for PPI 1.39, 95% CI 0.98-2.10, absolute increase risk 5 percent; OR 1.26 for H2 blockers, 95% CI 0.89-1.85, absolute increase risk 3.4 percent; low certainty) [49].

The role of gastric acid suppression in the development of community acquired and hospital-acquired pneumonia in non-critically ill patients is discussed in detail separately. (See "Proton pump inhibitors: Overview of use and adverse effects in the treatment of acid related disorders", section on 'Pneumonia'.)

- ***C. difficile* infection** – Data to suggest that PPIs and H2 blockers are associated with an increased risk of CDI are weak and conflicting [6,21,41,53,60-67]. Favoring no increased risk is a large randomized trial (SUP-ICU) of critically ill patients at high risk of bleeding that reported no difference in the CDI rates when the PPI, pantoprazole, was compared with placebo, although the study was not adequately powered to detect a difference in the risk of CDI [6]. Another large randomized trial reported no difference in the incidence of *C. difficile* infection when PPIs were compared with H2 Blockers, although study interpretation may be limited due to significant crossover in the use of the assigned medication [53]. In contrast, only indirect evidence from retrospective studies, most of which were **community**-based, have suggested an increased risk of CDI in patients receiving SUP [60-67].

The role of gastric acid suppression in the development of community-acquired CDI is discussed in detail separately. (See "Clostridioides difficile infection in adults: Epidemiology, microbiology, and pathophysiology", section on 'Gastric acid suppression' and "Proton pump inhibitors: Overview of use and adverse effects in the treatment of acid related disorders", section on 'Clostridioides difficile and other enteric infections'.)

- **Other adverse effects** – Additional potential adverse effects of gastric acid suppressants include intolerance, drug interactions or allergies, and thrombocytopenia, which are discussed in detail separately. (See "Proton pump inhibitors: Overview of use and adverse effects in the treatment of acid related disorders", section on 'Adverse effects'.)

Duration — Prophylaxis should be discontinued when the patient is no longer at risk for stress ulceration. However, criteria that indicate when it is safe to withhold SUP are lacking. Nonetheless, most experts consider discontinuing prophylaxis after discharge from the ICU (ie, the patient is no longer critically ill) unless risk factors (eg, coagulopathy, occult blood positivity) persist. This approach is based upon the rationale that although prophylaxis reduces the rate of nosocomial GI bleeding among non-critically ill patients when compared to no prophylaxis (OR 0.63), the baseline risk of bleeding in this population is low (0.29 percent) [68]. Despite the lower risk in non-critically ill hospitalized patients, several studies have demonstrated a high rate of ongoing SUP among patients who are discharged from the ICU [69,70].

Low-risk patients — Among critically ill patients who are not considered high risk for GI bleeding (eg, patients ventilated for less than 48 hours, few morbidities, no coagulopathy or history of GI bleeding), we believe that SUP should be administered on a case-by-case basis. The rationale for this approach is that the benefit is likely to be marginal given the low baseline rate of bleeding in this population (likely <1 percent). Factors that influence the decision include whether the patient is receiving enteral nutrition, the severity of the patient's illness, the number of comorbidities, and other risk factors that may increase the risk of bleeding. Factors that influence agent choice and duration of SUP are similar to high-risk patients. (See 'Choosing an agent' above and 'Duration' above.)

Pharmacologic agents

- **H2 blockers** – H2 blockers antagonize the H2 receptors on the parietal cell, resulting in diminished gastric acid secretion. They can be given orally, via nasogastric tube, or intravenously [71]. The dose depends on which H2 blocker is used (cimetidine, ranitidine, famotidine, nizatidine). While continuous intravenous infusions are more effective than bolus dosing at controlling gastric pH [72,73], most clinicians use bolus dosing since there are no data indicating that infusions are more effective at preventing clinically significant

GI bleeding. H2 blockers are generally well tolerated, but a number of uncommon side effects have been reported (ranitidine was been taken of the market in April 2020 due to product contamination [74]). (See "Antiulcer medications: Mechanism of action, pharmacology, and side effects", section on 'Histamine-2 receptor antagonists'.)

- **Proton pump inhibitors** – PPIs block acid secretion by irreversibly binding to and inhibiting the hydrogen-potassium ATPase pump that resides on the luminal surface of the parietal cell membrane. They can be given orally, via nasogastric tube, or intravenously [75]. The dose depends on which PPI is used (omeprazole, lansoprazole, rabeprazole, pantoprazole, esomeprazole). PPIs are an extremely safe class of drugs, although some risks have been described. (See "Antiulcer medications: Mechanism of action, pharmacology, and side effects", section on 'Proton pump inhibitors' and "Proton pump inhibitors: Overview of use and adverse effects in the treatment of acid related disorders", section on 'Adverse effects'.)

- Sucralfate – Sucralfate is a sulfated polysaccharide complexed with aluminum hydroxide. It exerts its effects by coating and protecting the gastric mucosa, without altering gastric acid secretion or significantly buffering acid [76,77]. Sucralfate is administered orally or via nasogastric tube at a dose of 1 gram four times per day. There is no intravenous formulation. It is generally well tolerated, except for infrequent cases of aluminum toxicity, particularly in those with renal impairment [78].

- **Antacids** – Antacids are rarely used in critically ill patients. Antacids neutralize gastric acid and protect the gastric mucosa. Antacids are generally administered every one to two hours at a dose of 30 to 60 mL either orally or via nasogastric tube. Nasogastric tube obstruction can be problematic. Side effects of antacids include hypermagnesemia, hypercalcemia, hypophosphatemia, constipation, and diarrhea. (See "Hypermagnesemia: Causes, symptoms, and treatment", section on 'Oral ingestion' and "Hypophosphatemia: Causes of hypophosphatemia", section on 'Medications' and "Antiulcer medications: Mechanism of action, pharmacology, and side effects", section on 'Antacids' and "Etiology of hypercalcemia", section on 'Increased calcium intake'.)

- **Prostanoids** – Prostanoids (ie, prostaglandin analogs), such as misoprostol, inhibit gastric acid secretion by selectively reducing the ability of the parietal cell to generate cyclic adenosine monophosphate (AMP) in response to histamine. They also exert a cytoprotective effect by enhancing mucosal defense mechanisms [79,80]. Prostanoids are not commonly used for SUP in ICU patients because there are a paucity of data regarding their impact on clinically important outcomes and they have a propensity to cause

diarrhea [9,22]. (See "Antiulcer medications: Mechanism of action, pharmacology, and side effects", section on 'Misoprostol'.)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Gastrointestinal stress ulcer prophylaxis".)

SUMMARY AND RECOMMENDATIONS

- **Epidemiology** – Stress ulceration is defined as ulceration of the upper gastrointestinal (GI) tract (esophagus, stomach, duodenum) that occurs due to hospitalization. Stress ulceration is common in critically ill patients. Bleeding can be occult (eg, 15 to 50 percent), overt (eg, 1.5 to 8.5 percent), or clinically significant (eg, 1 to 3 percent) and is associated with increased mortality. (See 'Definition' above and 'Incidence' above.)

- **Pathophysiology** – In critically ill patients, stress ulcerations usually occur in the fundus and body of the stomach but sometimes develop in the antrum, duodenum, or distal esophagus. They tend to be shallow and cause oozing of blood from superficial capillary beds. Deeper lesions may also occur, which can erode into the submucosa and cause significant hemorrhage and/or perforation. (See 'Pathophysiology' above.)

- **Diagnostic evaluation and management** – Stress ulcers should be suspected in critically ill patients with evidence of hematemesis, melena, anemia, and/or hypotension and shock. (See 'Diagnostic evaluation and management' above.)

  - **Occult bleeding** – In cases with occult bleeding, the diagnosis is an assumptive one, and most experts do not perform diagnostic endoscopy.

  - **Overt or clinically significant bleeding** – For those with overt and/or clinically significant bleeding, endoscopy is typically indicated, particularly when the results are likely to affect decision-making and/or a potentially treatable lesion is suspected.

  - **Diagnosis** – The diagnosis is typically confirmed by the visualization of superficial erosions in the gastric mucosa on endoscopic evaluation.

  - **Treatment** – Most experts treat occult bleeding using a strategy of increased surveillance and optimization of prophylactic agents, while those with overt bleeding

are treated using similar principles to patients who are not critically ill. (See "Approach to acute upper gastrointestinal bleeding in adults".)

- **Prophylaxis for high-risk patients** – For critically ill patients who are assessed as high risk for GI bleeding, we suggest stress ulcer prophylaxis (SUP) rather than no prophylaxis (**Grade 2B**). (See 'High-risk patients' above and 'Risk factors' above.)

  - **High-risk patients** – We consider patients at high risk to include any of the following (table 1):

    - Mechanical ventilation for more than 48 hours
    - Bleeding diathesis (thrombocytopenia [platelet count <50,000 per m^3]
    - Elevated international normalized ratio >1.5 or a partial thromboplastin time >2 times the control value
    - GI ulceration or bleeding within the past year
    - Traumatic brain or spinal cord injury
    - Severe burns >35 percent of the body surface area
    - Two or more minor risk factors (eg, sepsis, intensive care unit stay >1 week, occult GI bleeding ≥6 days, glucocorticoid therapy)
    - Nonsteroidal antiinflammatories or antiplatelet agents

    The impact *of Helicobacter pylori* infection and enteral nutrition is unclear.

  - **Agent selection and mode of administration** – For critically ill patients at high risk of GI bleeding, we suggest a proton pump inhibitor (PPI) rather than an alternative prophylactic agent (eg, histamine-2 receptor antagonist [H2 blocker], sucralfate, or antacids) (**Grade 2C**). We prefer oral rather than intravenous (IV) agents. Our preference for a PPI is based upon randomized trials and meta-analyses, which report that PPIs are more effective at reducing the risk of GI bleeding than other agents, especially in those at highest risk. (See 'Efficacy' above and 'Choosing an agent' above and 'Pharmacologic agents' above.)

    For patients in whom an oral PPI is not tolerated, an oral H2 blocker is an appropriate alternative.

    In rare cases where PPIs or H2 blockers cannot be administered, sucralfate is a suitable oral alternative.

    Antacids or prostanoids are rarely, if ever, used.

- For critically ill patients who cannot receive enteral medications, we prefer an IV PPI, although an IV H2 blocker is often chosen based upon cost and a perceived benefit of PPIs that is believed to be uncertain when compared with H2 blockers.

- While older data suggest that prophylactic agents that increase gastric pH (PPI, H2 blockers, antacids) may increase the frequency of nosocomial pneumonia and *Clostridioides difficile* infection, these studies did not adequately account for confounding variables. We believe that the risk of infection is not sufficiently high enough to justify withholding SUP from patients at high risk of GI bleeding.

- **Prophylaxis for low-risk patients** – For critically ill patients who are at low risk of GI bleeding (eg, patients ventilated for less than 48 hours, few morbidities, no bleeding diathesis, or history of GI bleeding), we suggest that SUP be administered on a case-by-case basis. Factors that influence the decision include whether the patient is receiving enteral nutrition, the severity of the patient's illness, the number of comorbidities, and other risk factors that may increase the risk of bleeding. (See 'Low-risk patients' above.)

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Topic 1611 Version 53.0

GRAPHICS

Risk factors for bleeding from stress ulceration

Major risk factors
▪ Mechanical ventilation for more than 48 hours (includes extracorporeal life support)
▪ Coagulopathy (eg, a platelet count <50,000 per m^3, an INR >1.5, partial thromboplastin time >2 times the control value
Other risk factors
Acute illnesses
▪ Sepsis
▪ Shock
▪ Hepatic failure
▪ Renal replacement therapy
▪ Trauma – multiple, brain, or spinal injury
▪ Burns over 35% of total body surface area
▪ Organ transplantation
Chronic illnesses
▪ History of peptic ulcer disease
▪ History of upper GI bleeding (within 1 year)
▪ Three or more coexisting diseases
Drugs
▪ Antiplatelet agents
▪ Nonsteroidal anti-inflammatories
Other
▪ ICU stay >1 week
▪ Occult bleeding for 6 or more days
Factors with unclear risk
▪ Glucocorticoids (eg, 250 mg hydrocortisone or the equivalent)
▪ *Helicobacter pylori*

INR: international normalized ratio; GI: gastrointestinal; ICU: intensive care unit.

Graphic 121491 Version 1.0

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