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Stress Ulcer Prophylaxis

Evidence Based Medicine Guideline

Primary Author: Robert L. Ringersen III MD
Co-Authors: Nathan Smith MD
Editor: Michael L. Cheatham MD, Chadwick Smith MD
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SUMMARY

The incidence of clinically important gastrointestinal bleeding due to stress ulceration has declined with advances in the resuscitation and management of critically ill patients. Maintaining adequate systemic perfusion and initiating early enteral nutrition play a significant role in preventing stress ulceration. The efficacy of histamine-2 receptor antagonists (H_2RAs), antacids, and proton-pump inhibitors (PPI) in preventing stress ulceration remains controversial. Prophylaxis using these medications is associated with potential adverse effects and drug interactions as well as additional cost. Given the controversial efficacy of these agents, their use should be limited to patients with acute risk factors. In addition, these guidelines are not intended for patients that have an indication for treatment with acid suppressive therapy, such as duodenal ulcer disease, gastroesophageal disease, etc.

RECOMMENDATIONS

- **Level 1**
  - ➢ **None**
- **Level 2**
  - ➢ **Chemoprophylaxis for stress ulcer prevention is indicated in patients with acute risk factors.**
  - ➢ **Discontinue therapy when patients no longer have acute risk factors.**
  - ➢ **Consider discontinuing therapy when a patient is tolerating full enteral feeding.**
  - ➢ **Sucralfate is an acceptable alternative to a H_2RA and may decrease the incidence and severity of ventilator associated pneumonia.**
  - ➢ **A PPI is an alternative to a H_2RA or Sucralfate in situations where these agents cannot be used.**
- **Level 3**
  - ➢ **Stress ulcer prophylaxis should be continued in patients with any of the following risk factors for stress ulceration:**
    - ▪ **Mechanical ventilation (>48 hours) without enteral nutrition**
    - ▪ **Coagulopathy**
    - ▪ **Hypoperfusion (shock, or organ dysfunction)**
    - ▪ **High-dose corticosteroids (>250 mg/day hydrocortisone or equivalent)**
    - ▪ **Significant burn injury (total body surface area ≥ 20%)**
    - ▪ **Acute spinal cord injury**
    - ▪ **Severe traumatic brain injury**

INTRODUCTION

Stress ulceration is a form of hemorrhagic gastritis that may occur following trauma or critical illness (1). Although not completely understood, the pathophysiology is likely multifactorial. Inadequate systemic perfusion resulting in poor mucosal blood flow, and reperfusion injury play an important role in the development of stress ulceration (1,2). Decreased gastric pH, increased mucosal permeability, and alterations in normal protective mechanisms may also

LEVEL OF RECOMMENDATION DEFINITIONS

- **Level 1:** Convincingly justifiable based on available scientific information alone. Usually based on Class I data or strong Class II evidence if randomized testing is inappropriate. Conversely, low quality or contradictory Class I data may be insufficient to support a Level I recommendation.
- **Level 2:** Reasonably justifiable based on available scientific evidence and strongly supported by expert opinion. Usually supported by Class II data or a preponderance of Class III evidence.
- **Level 3:** Supported by available data, but scientific evidence is lacking. Generally supported by Class III data. Useful for educational purposes and in guiding future clinical research.

be contributing factors (2,3). There has been a decrease in the incidence of clinically important bleeding due to stress ulceration (1). This can likely be attributed to improved resuscitation, earlier initiation of enteral feeding, the cessation of high dose steroids for traumatic brain and spinal cord injury, and possibly the use of pharmacologic prophylaxis.

Medications used for stress ulcer prophylaxis act by inhibiting gastric acid secretion, neutralizing gastric acid, or protecting the gastric mucosa. The efficacy of H_2RAs and antacids has been extensively studied. Both placebo-controlled trials and meta-analyses, however, have yielded conflicting results (2). Similarly, PPIs for stress ulcer prophylaxis have been evaluated in a limited number of published trials. Although these agents effectively maintain gastric pH ≥ 4, this endpoint has not been proven to improve clinical outcome. Additionally, superiority over H_2RAs has not been demonstrated in a well-designed trial. Many investigators now question the value of pharmacologic prophylaxis, especially in the setting of improved resuscitation techniques and early enteral feeding. A randomized, controlled trial that compared a PPI, H_2RA, and sucralfate with placebo in 287 high-risk trauma/surgery patients demonstrated no difference in clinically significant upper GI bleeding with percentages of 1%, 3%, 4%, and 1%, respectively (4). Prophylactic medications are associated with potential adverse effects such as increased risk of Clostridium difficile infection and ventilator associated pneumonia, and drug interactions as well as additional cost.

LITERATURE REVIEW

Risk Factors for Stress Ulceration

In a multicenter study of 2,252 patients, Cook et al. identified respiratory failure (mechanical ventilation for at least 24 hours) and coagulopathy (platelet count <50,000 mm^3, INR >1.5, or aPTT > 2 times control) as independent risk factors for bleeding (5). Of the 33 patients (1.5%) with clinically important bleeding, 23 (70%) were receiving stress ulcer prophylaxis. However, the use of prophylaxis was not controlled, and various regimens were administered. Enteral nutrition was not addressed. Only a small number of trauma patients were represented (28 head injuries and 18 multiple traumas). (Class II)

A subsequent multivariate analysis by Cook et al. identified maximum serum creatinine as a risk factor (RR 1.16 [95% CI 1.02-1.32]) for clinically important upper gastrointestinal bleeding (3). All patients received either ranitidine or sucralfate. The use of enteral feeding was not randomized. Enteral nutrition (RR 0.3 [95%CI 0.13-0.67]) and ranitidine (RR 0.39 [95%CI 0.17-0.83]) were both protective against stress ulceration. The overall incidence of clinically important gastrointestinal bleeding was 2.8%. None of the 147 trauma patients had clinically important bleeding. (Class II)

Although other risk factors have been identified, they have not been well studied. These include sepsis, of intensive care unit (ICU) stay greater than one week, presence of occult bleeding for at least six days, and high dose corticosteroids (>250 mg/day hydrocortisone or equivalent) (2,6). There is evidence that the incidence of stress ulceration is higher when more than one risk factor is present (7).

Patients suffering burn or neurologic injury have frequently been excluded from studies due to their presumably high-risk for the development of stress ulcers. Additional populations frequently excluded from clinical trials include patients with a history of upper gastrointestinal hemorrhage, peptic ulcer disease, or non-steroidal anti-inflammatory drug (NSAID) use. Whether these conditions translate into an increased risk of acute, stress-induced bleeding is therefore unknown (5).

Stress Ulceration and Enteral Feeding

A meta-analysis published in 2010 included 17 randomized, controlled trials that enrolled a total of 1,836 patients (8). This meta-analysis distinguished between studies that used early, adequate enteral nutrition from those that did not to assess the efficacy of stress ulcer prophylaxis. Results of the analysis demonstrated a reduced risk of GI bleeding with use of a H_2RA only in the sub-group of patients that did not receive enteral nutrition. Stress ulcer prophylaxis did not decrease the risk for GI bleeding in the patients that were fed enterally. Although prophylaxis with H_2RAs had no effect on pneumonia and hospital mortality overall, there was an increase in the incidence of hospital-acquired pneumonia and hospital mortality in the subgroup of patients that received stress ulcer prophylaxis plus enteral feeds. (Class II)

In 2016, prospectively gathered data from 200 patients admitted to a single academic surgical/trauma ICU was analyzed for the risk of bleeding and the efficacy of their practice of discontinuing pharmacologic stress ulcer prophylaxis in patients tolerating full enteral nutrition (9). They found an overall incidence of 0.5% of clinically

significant GI bleeding, with the subset of traumatic brain injury patients at only 0.68%, drastically different than the previously reported rate of 1.5%. Combined with the findings of a small randomized controlled, double blind, exploratory study enrolling 102 critically ill, mechanically ventilated patients that revealed no benefit (or harm) to adding pantoprazole to enteral nutrition (10), full enteral nutrition is probably adequate prophylaxis for stress ulcer prophylaxis in most critically ill patients. (Class II)

Proton Pump Inhibitors (PPIs)

Phillips et al. performed a prospective, open-label trial evaluating the efficacy of omeprazole suspension for stress ulcer prophylaxis in 75 critically ill patients (11). Patients were considered for the study if they were admitted to the surgical or burn ICU with an intact stomach, a nasogastric tube, and an anticipated ICU length of stay > 48 hours. They also had to have a gastric pH < 4, be on mechanical ventilation, and have an additional risk factor for stress ulceration. Patients were excluded if they were receiving enteral feedings through the nasogastric tube. Omeprazole suspension was administered as 40 mg, followed by a second 40 mg dose 6 to 8 hours later, then 20 mg daily until there was no longer a need for stress ulcer prophylaxis. Ten patients received H_2RAs prior to omeprazole suspension. Of the 65 patients who received omeprazole suspension as their initial prophylaxis, none developed overt or clinically significant upper gastrointestinal bleeding. Omeprazole significantly increased the mean gastric pH within 4 hours of the start of therapy (3.5 to 7.1). (Class II)

In a similar study, the efficacy of omeprazole suspension was evaluated in 66 patients with severe trauma (12). In addition to mechanical ventilation, patients were required to have at least one other risk factor for stress ulceration. Patients were excluded if they were receiving gastric feedings. Omeprazole was administered as described in the previous study. None of the patients developed overt or clinically significant upper gastrointestinal bleeding. Gastric pH monitoring revealed a statistically significant increase following initiation of omeprazole therapy (3 patients required an increased dose to achieve adequate pH control). (Class II)

Levy et al. compared the efficacy of omeprazole versus ranitidine for prophylaxis against clinically important gastrointestinal hemorrhage in 67 patients admitted to an ICU who had at least one risk factor for stress ulceration (13). Patients were randomized to receive ranitidine (50 mg bolus followed by 150 mg daily by continuous infusion or intermittent administration) or omeprazole (40 mg daily orally or via nasogastric tube). Clinically important bleeding occurred in significantly more ranitidine patients compared to omeprazole patients (31% versus 6%; p=0.013). It should be noted that the ranitidine patients had significantly more risk factors for stress ulceration than the omeprazole patients did. The use of enteral nutrition was not addressed. (Class I)

A meta-analysis was performed pooling 936 patients from seven randomized, controlled trials to compare the efficacy and safety of H_2RAs to PPIs for stress ulcer prophylaxis (14). There was no statistically significant difference found in the incidence of upper gastrointestinal bleeding between PPIs and H_2RAs. In addition, no significant difference was found in the safety outcomes of pneumonia and ICU mortality. (Class II).

More recently, a randomized, double blind exploratory study out of Australia with the acronym “POP-UP” (Pantoprazole Or Placebo for stress Ulcer Prophylaxis: randomized double-blind exploratory study) in 2016 suggested that, in 214 mechanically ventilated patients, pantoprazole did not decrease bleeding events, nor did it increase the risk of ventilator associated pneumonias or Clostridium difficile infections (15). A similar study in 2017 of 91 patients randomized to pantoprazole or placebo from 10 ICUs in Canada and Australia found no statistically significant differences, but trends towards decreased ventilator associated pneumonias and Clostridium difficile infections in the placebo group (16). These two studies, and multiple pending pilot studies, suggest that with current critical care practices and modern incidences of stress ulcerative bleeding, the traditional decision to routinely give acid suppression therapy to ICU patients should be carefully studied and reconsidered.

In 2020, data from the Proton Pump Inhibitors vs. Histamine-2 Receptor Blockers for Ulcer Prophylaxis Treatment in the Intensive Care Unit (PEPTIC) cluster crossover randomized controlled trial was published in JAMA (17). The multi-country trial included 26,828 patients that were randomized into the proton pump inhibitor arm (13,436 patients) and histamine-2 receptor blocker arm (13,392 patients). 32.9% of the patients were admitted to the ICU after elective surgery and 18.4% after emergency surgery. The primary outcome of the trial was in-hospital mortality, which resulted in 18.3% mortality in the proton pump inhibitor arm and 17.5% in the histamine-2 receptor blocker arm. Overall, the PEPTIC trial did not show a statistically significant difference in all-cause mortality within 90 days during the index hospitalization for patients requiring mechanical ventilation within 24 hours of ICU admission when PPIs were used as the default stress ulcer prophylaxis medication compared to histamine-2 receptor blockers. In regards to upper gastrointestinal bleeding, 172 of 13,436 patients (1.3%) in the PPI group and 239 of 13,392 patients

(1.8%) in the histamine-2 receptor blocker group had clinically important bleeds (p=0.009), however it is believed this may have been due to the number of patients in the trial taking PPIs prior to ICU admission with resultant rebound acid secretion for those who were switched to histamine-2 receptor blockers. There was no statistically significant difference in *Clostridium difficile* infections or ICU and hospital length of stay.

Sucralfate

Sucralfate is a molecular complex of sucrose, sulfate, and aluminum that is thought to form a protective barrier on the mucosal surface of the stomach, decreasing acid's erosive effect. It has been historically used as an adjunct to PPI and H_2RA in refractory ulcerative GI bleeding or in patients intolerant to these medications.

In 2016, Gindlinger et al. performed a retrospective study after perceiving an association between ventilator acquired pneumonia and ventilator bundle compliance (18). Their bundle elements included stress ulcer prophylaxis, head of bed elevation to 30º, daily sedation vacation, and deep-venous thrombosis prophylaxis, similar to the 2005 study by Rezar that saw ventilator acquired pneumonias decrease by 45% (19). They retrospectively reviewed 504 patients and evaluated those receiving sucralfate as stress ulcer prophylaxis versus pantoprazole, omeprazole, or famotidine. In the PPI/H_2RA group, they found 10.2 ventilator associated pneumonias per 1,000 ventilator days versus 3.7 ventilator associated pneumonias per 1,000 ventilator days in the sucralfate group. Furthermore, the type of pneumonia contracted was significantly different, with the sucralfate group incurring oropharyngeal flora bacteria compared with gram negative rods, methicillin resistant Staphylococcus aureus and Pseudomonas in the PPI/H_2RA group. These initial data suggest a promising role for sucralfate as stress ulcer prophylaxis in at risk patients.

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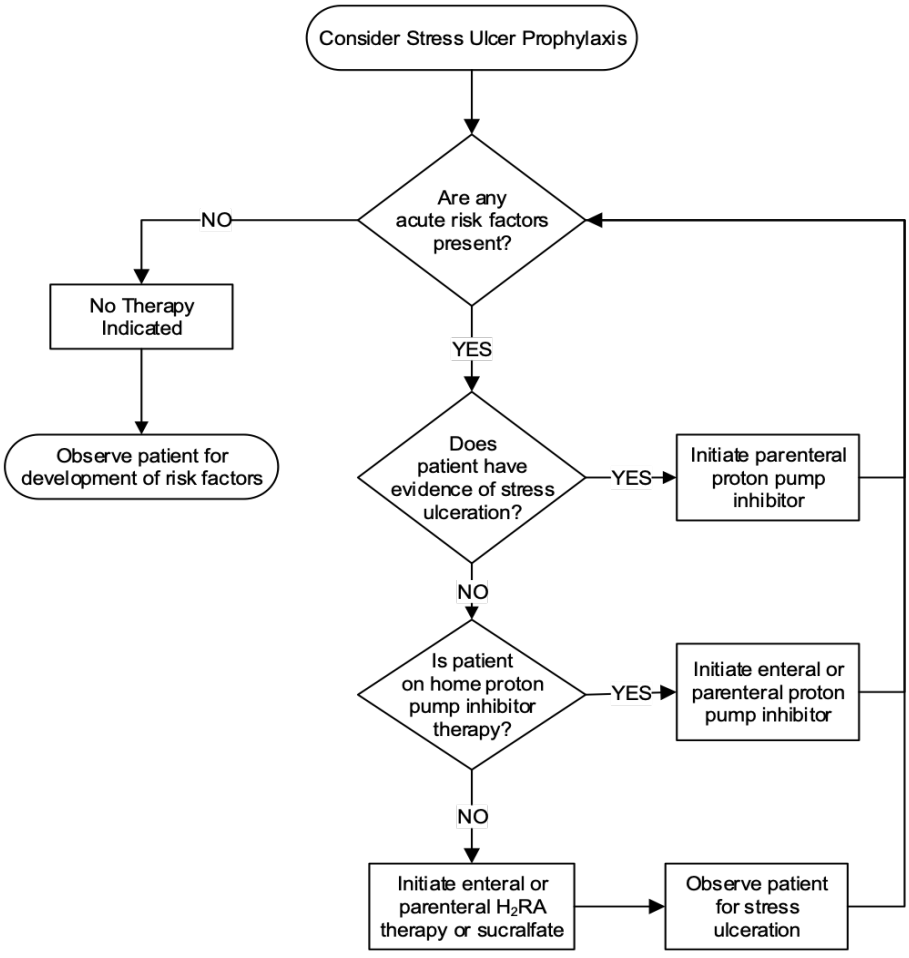
STRESS ULCER PROPHYLAXIS



Enteral therapy should be used whenever a functioning gastrointestinal tract is present and adequate absorption can be assumed.

Sucralfate is an acceptable substitute for H_2RA therapy if:
1) No drug interactions are present (i.e., use of quinolones or levothyroxine) AND
2) Gastric access is available