Stress Ulcer Prophylaxis in the Intensive Care Unit – Adult/Pediatric/Neonatal – Inpatient Clinical Practice Guideline

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Executive Summary

Guideline Overview
The purpose of this guideline is to provide a framework for appropriate use and prescribing of acid-suppressive agents for adult, pediatric and neonatal patients in intensive care units for stress ulcer prophylaxis.

Key Revisions (2016 Periodic Review)
1. Change scope of focus to the intensive care unit (ICU)
2. Removal of multitrauma as an indicator of stress ulcer prophylaxis in adults
3. Removal of GCS ≤ 10, inability to obey commands, dual antiplatelet therapy and therapeutic anticoagulation as reasonable indications for stress ulcer prophylaxis in adults
4. Removal of acute renal failure, hepatic/renal transplantation, hepatic failure or 2 of the following risk factors (sepsis, ICU stay > 1 week, occult bleeding ≥ 6 days, use of high dose corticosteroids) as indications where stress ulcer prophylaxis may be considered in adults
5. Histamine receptor blockers are now recommended as the preferred agent for stress ulcer prophylaxis in adults over proton pump inhibitors
6. Change qualification of thermal injury percentage (≥ 20%) required for stress ulcer prophylaxis in both adults and pediatrics
7. Recommendations for stress ulcer prophylaxis inclusion criteria for pediatric patients with non-invasive positive pressure ventilation was added
8. Histamine receptor blockers are now recommended as the preferred agent for stress ulcer prophylaxis in pediatric thermal injuries over proton pump inhibitors
9. Recommendation for the use of stress ulcer prophylaxis in neonates was removed
10. Recommendations were added to consider discontinuation of stress ulcer prophylaxis when patients tolerate enteral nutrition, even if other complicating factors are present
11. Recommendations were added to consider discontinuation of stress ulcer prophylaxis in traumatic brain injury patients 2 weeks after injury if other complicating factors are absent

Key Practice Recommendations

Recommendations – Adult ICU Patients
1. Appropriate indications for the use of pharmacologic stress ulcer prophylaxis in adults
2. Inappropriate indications for the use of pharmacologic stress ulcer prophylaxis in adults
3. PPIs and H2RAs are considered appropriate for stress ulcer prophylaxis in adults, and sucralfate is an alternative agent for adults unable to tolerate H2RAs or PPIs

Recommendations – Pediatric ICU Patients
4. Appropriate indications for the use of pharmacologic stress ulcer prophylaxis in pediatric patients
5. Inappropriate indications for the use of pharmacologic stress ulcer prophylaxis in pediatric patients
6. PPIs and H2RAs are considered appropriate for stress ulcer prophylaxis in pediatrics
7. Sucralfate is not recommended for pediatric patients

Recommendations – Neonatal ICU Patients
8. The use of stress ulcer prophylaxis in neonates is not recommended
9. The use of proton pump inhibitor is not approved for use in infants < 1 year of age and sucralfate in neonates is not recommended and may be harmful
10. Inappropriate indications for the use of pharmacologic stress ulcer prophylaxis in neonates

Recommendations – Adult, Pediatric, and Neonatal ICU Patients
11. Recommended duration of stress ulcer prophylaxis for all patients
Companion Documents
1. Prevention of Ventilator Associated Events (VAE) – Adult – Inpatient Clinical Practice Guideline
2. Clostridium difficile Infection: Prevention, Diagnosis and Treatment – Adult/Pediatric – Inpatient/Ambulatory/Emergency Department Clinical Practice Guideline
3. Renal Function-Based Dose Adjustments - Adult -Inpatient/Ambulatory Clinical Practice Guideline

Scope

Disease/Condition(s):
Stress ulcer prophylaxis in the intensive care unit.

This guideline does not address the following conditions and patient populations due to either direct indication for acid suppression therapy or ulcer formation due to non-stress related mechanisms:
- active treatment of gastric ulcers, GI bleeding, or hypersecretory disorders
- acid suppression treatment following total gastrectomy or other bariatric procedures
- prevention of gastrointestinal bleeding in patients with high risk medications (e.g. nonsteroidal antiinflammatory drugs, anticoagulants, antiplatelet agents, or steroids) when no other risk factors for stress ulcers are present
- Solid organ transplant recipients
- Stress ulcer prophylaxis outside of the ICU

Clinical Speciality:
Critical Care – adult, pediatric and neonatal

Intended Users:
Critical Care Physicians, Advanced Practice Providers, Clinical Pharmacists and Registered Nurses

Objective(s):
To provide an evidenced based guideline to assist clinicians in identifying critically ill patients requiring stress ulcer prophylaxis, in selecting appropriate pharmacologic agents for stress ulcer prophylaxis and to minimize inappropriate use of stress ulcer prophylaxis

Target Population:
Adult, pediatric, and neonatal intensive care patients at risk for stress ulcers

Interventions and Practices Considered:
- Pharmacologic prophylaxis of stress ulcers

Major Outcomes Considered:
- Preventing stress ulcers
- Reducing inappropriate prescribing
- Reducing adverse event related to inappropriate stress ulcer prophylaxis

Methodology

Methods Used to Collect/Select the Evidence:
The UW Health Guidelines for Stress Ulcer Prophylaxis in Adults and Pediatrics was updated with a literature search using MEDLINE and Cochrane databases, and an evaluation of referenced literature. Searches were extended to reviews and studies conducted in humans and published in English. Reference lists of relevant studies were also reviewed.

Methods Used to Formulate the Recommendations:
The workgroup members agreed to adopt recommendations developed by external organizations and/or arrived at a consensus through discussion of the literature and expert experience. All recommendations endorsed or developed by the guideline workgroup were reviewed and approved by other stakeholders or committees (as appropriate).
Methods Used to Assess the Quality of the Evidence/Strength of the Recommendations:
Recommendations developed by external organizations maintained the evidence grade assigned within the original source document and were adopted for use at UW Health.

Internally developed recommendations, or those adopted from external sources without an assigned evidence grade, were evaluated by the guideline workgroup using an algorithm adapted from the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology (see Figure 1 in Appendix A).

Rating Scheme for the Strength of the Evidence/Recommendations:
See Appendix A for the rating scheme(s) used within this document.

Recognition of Potential Health Care Disparities:
None noted

Definitions
Stress ulcers: erosions that may develop in acid and pepsin secreting mucosa of the stomach within hours to days in critically ill patients, and commonly occur in multiple sites.¹

Clinically important bleeding: for the purpose of these guidelines, was defined as gastroduodenal bleeding associated with hemodynamic compromise, need for blood transfusion, or requirement for surgery.²

Neonates: patients from birth to 28 days of age³

Pediatrics: patients from 29 days of age to 18 years of age³

Adults: patients 19 years of age or older³

Introduction
Background
Theories for causes of stress ulcer formation include gastric hypoperfusion, acid over secretion, underproduction of gastric mucus, and Helicobacter pylori infection.² The incidence of stress ulceration is estimated to be 5-25% in ICU patients.²,⁴,⁵ However, clinically significant GI bleeding has been shown to occur in only 1-6% of these patients at most, although the definitions of clinically significant bleeding varied widely between studies (many of which were published 15-20 years ago or more).²,⁴,⁵ In patients who develop clinically significant GI bleeding, approximately half of these patients develop bleeding within the first 48 hours of their ICU stay.⁶ Mortality in critically ill patients who experience clinically significant bleeding has been estimated at 48.5% compared to 9.1% for those without significant bleeding in a study from 1994.⁷ Furthermore, clinically significant bleeding is associated with an estimated excess ICU length of stay of 4-8 days in a 2001 study.⁸ Despite these early estimates, there have been many changes to the care of critically ill patients over the past several decades, and therefore it is likely that the incidence of GI bleeding as well as the outcomes in patients who bleed may have also changed significantly.⁹

Stress ulcer prophylaxis (SUP) using pharmacologic agents has since become standard therapy to prevent stress ulcer formation and bleeding in intensive care units. It is recommended by international guidelines for critically ill patients at risk of stress ulcers, and has also become increasingly common in general medicine patients, although not recommended in this population.²,⁹,¹⁰

Indications for SUP
SUP is not necessary for all ICU patients, and is often prescribed inappropriately.⁹ In a study of 2,252 adults (651 receiving SUP, 1,568 not receiving SUP), 33 (1.5%) had clinically significant bleeding (10 having received SUP, 23 not receiving SUP).¹ In the independent risk factors for bleeding in this study were respiratory failure requiring mechanical ventilation for more than 48 hours (odds ratio 15.6, p<0.001), and...
coagulopathy in patients not receiving exogenous anticoagulation (odds ratio 4.3, p<0.001). The risk of clinically significant bleeding in the population of patients without these risk factors was 0.1% (2 out of 1405 patients). Smaller studies have suggested several additional risk factors for stress ulcers in the critically ill, including burns, organ transplantation, spinal cord injuries, hepatic failure, multiple trauma, history of GI bleed, sepsis, extended ICU stays, occult bleeding, and corticosteroid use, although the clinical relevance of these risk factors has not been thoroughly defined in the literature.\textsuperscript{2,11-13} With respect to corticosteroid use, a 2013 systematic review of 3 meta-analyses indicated that peptic ulceration in the setting of concomitant corticosteroid therapy was rare, with a reported incidence of 0.4-1.8%.\textsuperscript{14}

While the use of SUP is associated with approximately a 2-fold decrease in the risk of clinically important bleeding compared to no prophylaxis,\textsuperscript{15} no study or analysis to date has shown a benefit to mortality or reduction in ICU length of stay associated with SUP therapy. It should also be noted that prophylaxis only reduces and does not eliminate the risk of bleeding.

The impact enteral nutrition has on the need for SUP is not clearly defined. A systematic review and meta-analysis of 17 randomized controlled studies conducted from 1980 to 2004 (1836 patients) was conducted to evaluate the benefit and risks of SUP to prevent clinically significant GI bleeding in ICU patients receiving histamine 2 receptor antagonists (H2RAs) compared to placebo when patients received enteral nutrition.\textsuperscript{16} No publication bias was seen on funnel plots. Only 3 of the included trials provided enteral nutrition to patients studied (262 patients). In the overall population, SUP was associated with a reduction in clinically significant GI bleeding (OR 0.47; 95% CI 0.29-0.76; p<0.002; I\textsuperscript{2}=44%), but not an increased risk of hospital acquired pneumonia (OR 1.53; 95% CI 0.89-2.61; p=0.12; I\textsuperscript{2}=41%). In the subgroup of patients receiving enteral nutrition, SUP did not affect the incidence of clinically significant GI bleeding (OR 1.26; 95% CI 0.43-3.7) but was associated with increased risk of hospital acquired pneumonia (OR 2.81; 95% CI 1.2-6.56; p=0.02; I\textsuperscript{2}=0%). No difference in mortality was shown between H2RA and placebo in the overall population, but was higher in the subgroup that received SUP and enteral nutrition (OR 1.89; 95% CI 1.04-3.44; p=0.04).

In pediatric populations, the rate of clinically significant bleeding was 1.6% in a cohort of 1006 patients in a pediatric intensive care unit, and was associated with several risk factors including respiratory failure, coagulopathy, and mortality score.\textsuperscript{17} However, studies regarding morbidity and mortality related to clinically significant gastrointestinal bleeding has not been well studied in children, and specific indications for SUP in pediatrics and neonates are poorly defined.\textsuperscript{18}

A systematic review of 8 randomized controlled trials was conducted to evaluate the efficacy of stress ulcer prophylaxis treatments for the prevention of gastrointestinal bleeding in critically ill children.\textsuperscript{19} Two studies had high risk of bias, and the remaining six studies had unclear risk of bias. A meta-analysis of two trials (300 patients) revealed that stress ulcer prophylaxis (omeprazole, ranitidine, sucralfate, and almagate) was associated with a reduced incidence of gastrointestinal bleeding compared with no prophylaxis (RR 0.41; 95% CI 0.19-0.91; I\textsuperscript{2}=12%), but significance was lost when a third trial comparing prophylaxis to placebo was included in the analysis (N=340 patients total; RR 0.69; 95% CI 0.41-1.17; I\textsuperscript{2}=63%). There were no significant differences in rates of nosocomial pneumonia (2 trials) or mortality (1 trial) between groups. Additionally, no differences in incidences of bleeding, mortality, or nosocomial pneumonia were found between omeprazole, ranitidine, famotidine, sucralfate, or almagate in the studies. Publication bias was not assessed as outcomes were pooled for no greater than three studies; however the methodological quality of the studies was noted to be poor.

A prospective, single-center, randomized controlled trial in a pediatric intensive care unit of 165 patients with risk factors for gastrointestinal hemorrhage was conducted to investigate the impact of almagate, ranitidine, and sucralfate prophylaxis on the incidence of gastrointestinal hemorrhage.\textsuperscript{19} Patients admitted to the pediatric intensive care unit with shock, acute cardiac, respiratory, hepatic, or renal failure, sepsis, coagulopathy, neurologic dysfunction, multi-trauma, severe acidosis, or major surgery were included in the study, but excluded if they experienced nasal or pharyngeal bleeding. Patients were randomized into 4 groups (N=35 patients each) to receive almagate, ranitidine, sucralfate, or no prophylaxis (control), respectively. For the outcome of important gastrointestinal bleeding, any prophylaxis (5.7%; 6/105 patients) was superior to no prophylaxis (20%; 7/35 patients; p<0.05), however...
there were no significant differences between individual treatment groups (almagate group: 5.7%; 2/35 patients, ranitidine group: 8.5%; 3/35 patients, sucralfate group: 2.8%; 1/35 patients). There was a trend toward significantly higher mean gastric pH in the almagate group (pH 6.1) and the ranitidine group (pH 4.8) compared to the sucralfate group (pH 3.5), but all were significantly increased compared to control (pH 2.4; p=0.001). No difference in mortality between groups was observed, and no nosocomial pneumonia was identified over the course of the study. This trial was limited by the unblinded nature of the study and by the small number of patients included.

Another prospective, single-center, randomized controlled trial of 160 patients requiring mechanical ventilation upon admission to the pediatric intensive care unit to investigate the incidence of ventilator-associated pneumonia in patients receiving stress ulcer prophylaxis.20 Patients were randomized to receive sucralfate (N=38), ranitidine (N=42), omeprazole (N=38), or no prophylaxis (N=42). For the primary outcome of ventilator-associated pneumonia, there were no significant differences between sucralfate (42%; 17/38 patients), ranitidine (48%; 20/42 patients), omeprazole (45%; 17/38 patients), or control groups (41%; 17/42 patients; p=0.963). There were no significant differences in the outcomes of mortality or gastrointestinal bleeding between groups. This trial was limited by the unblinded nature of the study and by the small number of patients included.

Choice of Agent for SUP

The specific agent for SUP has also not been clearly identified. A systematic review and meta-analysis of 14 prospective randomized controlled trials (1720 patients) was conducted to compare H2RAs to PPIs for the prevention of gastrointestinal bleeding in critically ill patients.5 PPI therapy was associated with less clinically significant bleeding (1.2%; 12/1019 patients) compared to H2RA therapy (6.4%; 38/595 patients; RR 0.36; 95% CI 0.19-0.68; p=0.002; I²=0%). There were no differences in rates of nosocomial pneumonia, ICU length of stay, or ICU mortality between groups. The definition of clinically significant bleeding differed between authors, likely publication bias was noted on funnel plot. Risk of bias varied among the trials in the analysis, with only 3 trials at an overall low risk of bias. Significance between treatment groups for prevention of gastrointestinal bleeding was lost when trials with high or unclear risk of bias were excluded from the analysis.

A meta-analysis of 8 randomized controlled trials and 5 abstracts (1587 patients combined) was also conducted to compare the efficacy of H2RAs to PPIs for the prevention of stress-related gastrointestinal bleeding in critically ill patients.21 PPI therapy was associated with less clinically significant bleeding (1.3%; 13/967 patients) compared to H2RA therapy (6.6%; 41/620 patients; OR 0.30; 95% CI 0.17-0.54), and no heterogeneity was detected (p=0.93; I²=0%). There were no significant differences in rates of nosocomial pneumonia or mortality between groups. No publication bias was detected on funnel plot, but the definition of clinically significant bleeding differed between authors, which limits the robustness of the results. Furthermore, the authors noted that many of the studies included in the analysis were of poor methodological quality, and significant heterogeneity (p=0.03; I²=46%) was noted in a sensitivity analysis using risk difference rather than odds ratio for the primary outcome. However, the overall conclusion in the sensitivity analysis remained significant in favor of PPIs over H2RAs for the prevention of gastrointestinal bleeding (risk difference -0.026; 95% CI -0.049 to -0.003).

A meta-analysis of 7 randomized controlled trials (936 patients) published prior to June 2008 was conducted to compare H2RAs to PPIs for the prevention of gastrointestinal bleeding in critically ill patients.22 The difference in the risk of gastrointestinal bleeding for PPI therapy compared to H2RAs was -0.04 (95% CI -0.09 to 0.01; p=0.08), however significant heterogeneity was noted across the studies included in the analysis (p=0.08; I²=66%). When a single trial from 1997(67 patients) that showed a significant benefit of PPI therapy over H2RA therapy for the reduction of bleeding events (risk difference -0.25; 95% CI -0.43 to -0.08) was removed from the analysis, the difference in risk among the remaining trials was -0.02 (95% CI -0.05 to 0.01; p=0.19), and the heterogeneity was reduced (I²=26%). There were no significant differences in rates of nosocomial pneumonia or mortality between groups. Likely publication bias was also revealed on a funnel plot, indicating possible flawed estimates due to poor study quality and methodology or minimal publication of studies with opposing results.
In contrast to the previously discussed meta-analyses of prospective trials, a recently published pharmacoepidemiologic cohort study of 35,312 patients receiving mechanical ventilation for 24 hours or longer across 71 hospitals was conducted to compare H2RAs to PPIs for the prevention of gastrointestinal bleeding as well as the risk of nosocomial pneumonia and *Clostridium difficile* infections.\(^2\)\(^3\) PPI therapy, compared to H2RA therapy, was associated with increased rates of clinically significant bleeding (5.9%; 1287/21873 patients vs. 2.1%; 276/13439 patients, respectively; p<0.001), nosocomial pneumonia (38.6%; 8435/21873 patients vs. 27%; 3630/13439 patients, respectively; p<0.001), and *Clostridium difficile* infection (3.8%; 835/21873 patients vs. 2.2%; 294/13439 patients, respectively; p<0.001). Data presented in this study is from a database collected prior to January 2009, and baseline patient characteristics varied between groups.

A multicenter, blinded, placebo-controlled randomized controlled trial of 1200 patients compared sucralfate with ranitidine for the prevention of gastrointestinal bleeding in patients requiring mechanical ventilation.\(^2\)\(^4\) Ranitidine was associated with a lower rate of clinically significant bleeding (1.7%; 10/596 patients) compared to sucralfate (3.8%; 23/604 patients; RR 0.44; 95% CI 0.21-0.92; p=0.02). There were no significant differences in the rates of nosocomial pneumonia or mortality. No studies have been published demonstrating outcome superiority of PPIs over sucralfate for stress ulcer prophylaxis.\(^2\)\(^5\)

**Risks of SUP**

The use of acid suppressive therapies for SUP is not benign, and increases gastric pH allowing for bacterial overgrowth in the GI tract which may lead to infection.\(^2\)\(^3\) In fact, SUP has been associated with both an increased risk of developing hospital-acquired pneumonia and *Clostridium difficile*-associated diarrhea.\(^2\)\(^6\)-\(^2\)\(^8\) In a prospective, single-center cohort study in non-intensive care unit inpatients revealed an increased risk of hospital-acquired pneumonia in the patients exposed to either PPI or H2RA therapy with an adjusted OR of 1.3 (95% CI 1.1-1.4) compared to no acid-suppressive therapy.\(^2\)\(^7\) This risk remained significant only in the group exposed to PPIs (OR 1.3; 95% CI 1.1-1.4) and was not significant in the group exposed to H2RAs (OR 1.2; 95% CI 0.98-1.4).\(^2\)\(^7\) Furthermore, pantoprazole was shown to have an increased risk of nosocomial pneumonia when compared directly with ranitidine in a retrospective analysis of a cardiothoracic surgery database, with pantoprazole being identified as an independent risk factor for nosocomial pneumonia (OR 2.7; 95% CI 1.1-6.7; p=0.0034).\(^2\)\(^6\) A retrospective case-control study also revealed an association between PPI therapy and *Clostridium difficile* associated diarrhea (OR 3.6; 95% CI 1.7-8.3; p<0.001), whereas H2RA therapy did not show a significant association.\(^2\)\(^8\) Finally, the risk of nosocomial *Clostridium difficile* infection has been shown to increase with increasing level of acid suppression in a cohort study of hospitalized patients, where the level of acid suppression was defined as no acid suppression, H2RA therapy, PPI daily, and PPI more frequently than daily (listed from lowest level to highest level of acid suppression).\(^2\)\(^9\) Thus, acid suppressive therapies should only be used in patients at risk of developing gastric stress ulcers.

**Recommendations – Adult ICU Patients**

1. Appropriate indications for the use of pharmacologic stress ulcer prophylaxis in adults
   1.1. SUP is recommended in the following situations:
      1.1.1. Mechanical ventilation for more than 48 hours\(^2\)\(^,\)\(^3\)\(^,\)\(^3\)\(^0\) (UW Health Strong Recommendation, High Quality of Evidence)
      1.1.2. Coagulopathy (platelet count < 50,000/µL, INR > 1.5, or PTT > 2 times the control value while not on exogenous anticoagulation)\(^2\)\(^,\)\(^7\)\(^,\)\(^3\)\(^0\) (UW Health Strong Recommendation, High Quality of Evidence)
      1.1.3. Acute traumatic brain injury (with Glasgow coma score ≤10 or inability to obey simple commands)\(^2\)\(^,\)\(^3\)\(^0\) (UW Health Strong Recommendation, Moderate Quality of Evidence)
      1.1.4. Acute spinal cord injury \(^2\)\(^,\)\(^3\)\(^1\) (UW Health Strong Recommendation, Low Quality of Evidence)
      1.1.5. Major thermal injury (≥20% of total body surface area)\(^2\)\(^,\)\(^3\)\(^0\),\(^3\)\(^2\) (UW Health Strong Recommendation, Moderate Quality of Evidence)
1.2. SUP may be considered in the following situations:
   1.2.1. History of GI ulceration or bleeding within 12 months before admission to the ICU\(^2\) (UW Health Weak/Conditional Recommendation, Very Low Quality of Evidence)
   1.2.2. Partial hepatectomy in the ICU\(^{31,32}\) (UW Health Weak/Conditional Recommendation, Low Quality of Evidence)

1.3. Discontinuation of SUP may be considered in patients tolerating enteral nutrition despite the persistent presence of indications for SUP prophylaxis\(^6,16\) (UW Health Weak/Conditional Recommendation, Low Quality of Evidence)

<table>
<thead>
<tr>
<th>Table 1. Adult indications for stress ulcer prophylaxis in the ICU</th>
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<tbody>
<tr>
<td><strong>Recommended prophylaxis</strong></td>
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<tr>
<td>• Mechanical ventilation for more than 48 hours</td>
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<tr>
<td>• Coagulopathy while not on exogenous anticoagulation</td>
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<tr>
<td>o platelets &lt; 50,000/µL</td>
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<tr>
<td>o INR &gt; 1.5</td>
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<tr>
<td>o PTT &gt; 2 times the control value</td>
</tr>
<tr>
<td>• Acute traumatic brain injury with Glasgow coma score ≤10 or inability to obey simple commands</td>
</tr>
<tr>
<td>• Acute spinal cord injury</td>
</tr>
<tr>
<td>• Major thermal injury (≥20% of total body surface area)</td>
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</table>

2. Inappropriate indications for the use of pharmacologic stress ulcer prophylaxis in adults
   2.1. Continuation of SUP beyond when indications no longer exist\(^2,9\) (UW Health Strong Recommendation, Low Quality of Evidence)
   2.2. Therapeutic anticoagulant therapy without additional risk factors\(^9\) (UW Health Strong Recommendation, Moderate Quality of Evidence)
   2.3. Short-term high dose corticosteroid therapy without additional risk factors\(^33\) (UW Health Strong Recommendation, Moderate Quality of Evidence)
   2.4. During the temporary period when patients are NPO after surgery or procedures with no additional risk factors (UW Health Strong Recommendation, Low Quality of Evidence)

3. Selection of agent for SUP
   3.1. Both proton pump inhibitors (PPIs) and histamine 2 receptor antagonists (H2RAs) are considered appropriate for stress ulcer prophylaxis in adults. There is conflicting evidence in the literature with regards to which agent is superior.\(^5,10,21-23\) Limited data exists about the incidence of hospital acquired infections associated with these agents.\(^22,23,26-29\) (UW Health Weak/Conditional Recommendation, Moderate Quality of Evidence)
   3.1.1. Stress ulcer prophylaxis with an H2RA may be considered as preferred over prophylaxis with a PPI due to the concern for hospital acquired infections. (UW Health Weak/Conditional Recommendation, Very Low Quality of Evidence)
   3.1.2. See Table 2 for dosing recommendations. (UW Health Strong Recommendation, Low Quality of Evidence)
   3.2. Sucralfate is an alternative agent for adults unable to tolerate H2RAs (UW Health Strong Recommendation, High Quality of Evidence) or PPIs\(^24,25\) (UW Health Strong Recommendation, Low Quality of Evidence)
   3.3. Sucralfate may bind several drugs (e.g., digoxin, warfarin, phenytoin, quinolones, etc.) if administered concomitantly. Sucralfate should be administered one hour before or two hours after such interacting medications. Sucralfate must be administered into the stomach to be effective as a protective agent. Administration through a post-pyloric or jejunal feeding tube is of no benefit.
3.4. An enteral route is preferred for both PPIs and H2RAs when feasible. (UW Health Strong Recommendation, Low Quality of Evidence)

Recommendations – Pediatric ICU Patients

4. Appropriate indications for the use of pharmacologic stress ulcer prophylaxis in pediatric patients
4.1. SUP is recommended in patients with at least two of the following risk factors (UW Health Strong Recommendation, Moderate Quality of Evidence):
   4.1.1. Mechanical ventilation > 48 hours
   4.1.2. Organ failure
      4.1.2.1. Respiratory failure (peak inspiratory pressure > 25 cm H₂O).
      4.1.2.1.1. There is no data for or against use of SUP in non-invasive positive pressure ventilation (NIPPV); however, it would be reasonable to use the same guideline regarding peak inspiratory pressures in intubated patients (UW Health Strong Recommendation, Low Quality of Evidence)
   4.1.2.2. Renal failure (serum creatinine ≥2 times the upper limit of normal for age, or two-fold increase in baseline serum creatinine)
   4.1.2.3. Neurologic failure (Glasgow coma score ≤11, or acute mental status change with a decrease in Glasgow coma score ≥3 from baseline)
   4.1.2.4. Hepatic failure (total bilirubin ≥4 mg/dL or serum alanine transaminase ≥2 times the upper limit of normal for age)
   4.1.3. Coagulopathy (platelet count <100,000/µL or PT, aPTT, or thrombin time >20% of control value)
   4.1.4. Pediatric Risk of Mortality Score ≥10 (UW Health Strong Recommendation, Low Quality of Evidence)
   4.1.5. Shock (hypotensive for age and poor peripheral perfusion or acidosis)
   4.1.6. Surgery time ≥3 hours
   4.1.7. Multi-trauma (trauma to at least two systems)
   4.1.8. Pneumonia
   4.1.9. SUP is recommended in patients with thermal injury (≥20% total body surface area) (UW Health Weak/Conditional Recommendation, Very Low Quality of Evidence)

5. Inappropriate indications for the use of pharmacologic stress ulcer prophylaxis in pediatric patients
5.1. Continuation of SUP in patients when risk factors are no longer present (UW Health Strong Recommendation, Low Quality of Evidence)
5.2. There is no evidence of benefit for the use of SUP for pediatric patients on short-term high dose corticosteroid therapy for acute respiratory illness without additional risk factors (UW Health Strong Recommendation, Low Quality of Evidence).

6. PPIs and H2RAs are considered appropriate for stress ulcer prophylaxis in children. See Table 2 for dosing recommendations. (UW Health Weak/Conditional Recommendation, Moderate Quality of Evidence)
6.1. H2RAs may be considered as preferred over PPIs for stress ulcer prophylaxis in children with thermal injuries (UW Health Weak/Conditional Recommendation, Very Low Quality of Evidence)

7. Sucralfate is not recommended for pediatric patients. (UW Health Strong Recommendation, Moderate Quality of Evidence)

Recommendations – Neonatal ICU Patients

8. Appropriate indications for the use of pharmacologic stress ulcer prophylaxis in neonates
8.1. Very little evidence is available for stress ulcer prophylaxis in neonates. One small, randomized controlled trial found mechanical ventilation as a significant risk factor for upper gastrointestinal bleeding. This study also noted abnormal mode of delivery or hypotension may increase risk of stress induced lesions. However, the study noted the majority of lesions noted were not clinically significant.
8.2. There is a lack of evidence to support use of SUP in neonates (UW Health Strong Recommendation, Low Quality of Evidence)

9. Inappropriate indications for the use of pharmacologic stress ulcer prophylaxis
9.1. Continuation of SUP beyond when high-risk situations no longer exist\(^2\) (UW Health Strong Recommendation, Low Quality of Evidence)
9.2. When the risk of SUP outweighs the benefit based on clinical judgment (UW Health Strong Recommendation, Low Quality of Evidence)
9.2.1. Potential risks of SUP in neonates:\(^4\)
   9.2.1.1. Hypergastrinemia
   9.2.1.2. Enterochromaffin-like cell hyperplasia
   9.2.1.3. Carcinoid formation
   9.2.1.4. Vitamin B12 deficiency
   9.2.1.5. Hypomagnesemia
   9.2.1.6. Necrotizing enterocolitis
   9.2.1.7. Osteoporosis
   9.2.1.8. Atrophic gastritis
   9.2.1.9. Infection

10. If SUP is chosen, H2RAs may be considered as PPIs have not been approved for use in infants younger than 1 year of age.\(^3,42\) (UW Health Weak/Conditional Recommendation, Low Quality of Evidence)

11. The use of sucralfate in neonates is not recommended and may be harmful due to the risk of bezoar formation, particularly in neonates with gastrointestinal motility disorders, and aluminum toxicity in neonates with renal impairment.\(^2\) (UW Health Strong Recommendation, Low Quality of Evidence)

Table 2: Dosing recommendations for stress ulcer prophylaxis\(^2\)
(UW Health Strong Recommendation, Low Quality of Evidence)

<table>
<thead>
<tr>
<th>Adult Dosing</th>
<th>Medication</th>
<th>Pantoprazole(^4) *Famotidine(^4) *</th>
<th>Sucralfate(^4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parenteral Dose</td>
<td>40 mg IV once daily</td>
<td>20 mg IV every 12 hours</td>
<td>N/A</td>
</tr>
<tr>
<td>Enteral Dose</td>
<td>40 mg PO/NG once daily</td>
<td>20 mg PO/NG twice daily</td>
<td>1 g PO/NG four times daily</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pediatric Dosing</th>
<th>Medication</th>
<th>Pantoprazole(^4) *Famotidine(^4,3) *</th>
<th>Sucralfate(^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parenteral Dose</td>
<td>1 mg/kg IV once daily</td>
<td>0.25 mg/kg/dose IV every 12 hours</td>
<td>N/A</td>
</tr>
<tr>
<td>Do not exceed adult doses listed above</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enteral Dose</td>
<td>1 mg/kg PO/NG once daily</td>
<td>0.5 mg/kg/dose PO/NG twice daily</td>
<td>Avoid use</td>
</tr>
<tr>
<td>Do not exceed adult doses listed above</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Neonatal Dosing</th>
<th>Medication</th>
<th>Pantoprazole(^4) *Famotidine(^4,3) *</th>
<th>Sucralfate(^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parenteral Dose</td>
<td>0.5-1 mg/kg IV once daily</td>
<td>0.5 mg/kg/dose IV per day</td>
<td>N/A</td>
</tr>
<tr>
<td>Do not exceed adult doses listed above</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enteral Dose</td>
<td>0.5-1 mg/kg PO/NG</td>
<td>0.5 mg/kg/dose PO/NG</td>
<td>Avoid use</td>
</tr>
</tbody>
</table>
Do not exceed adult doses listed above once daily per day

*Refer to the UWHC Renal Dosing Guideline for famotidine dose recommendations in renal impairment

**Recommendations – Adult, Pediatric, and Neonatal ICU Patients**

12. Duration of Prophylaxis

12.1. Patients should be evaluated for the need of SUP: $^{2,9,30}$ (UW Health Strong Recommendation, Low Quality of Evidence)

12.1.1. On a daily basis

12.1.2. Upon transfer to a different level of care

12.1.3. Upon discharge from the hospital

12.1.4. When tolerating enteral feeding $^6,^16$

12.2. Stress ulcer prophylaxis may be discontinued once the original stressors are removed. $^{2,9,30}$ Continuation of therapy after stress factors are eliminated exposes the patient to unnecessary risks and increases the cost of therapy. (UW Health Strong Recommendation, Low Quality of Evidence)

12.2.1. In adult patients with acute traumatic brain injury, discontinuation of SUP may be considered at 2 weeks following the injury. A longer course of SUP therapy may be indicated based on individual patient factors such as the presence of sympathetic storming or neurological compromise. (UW Health Weak/Conditional Recommendation, Very Low Quality of Evidence)
UW Health Implementation

Potential Benefits:
Implementation of recommendations within this guideline provides a consistent approach to minimizing the incidence of stress ulcer bleeding while avoiding adverse drug events from inappropriate use.

Potential Harms:
Patients receiving a medication for stress ulcer prophylaxis may be at higher risk of adverse drug events such as pneumonia and Clostridium difficile infection. See section 9.2.1 for additional risks in neonatal populations.

Qualifying Statements
There is currently a paucity of literature on many of the clinical indications for stress ulcer prophylaxis, particularly in pediatric and neonatal populations, and several of the indications have been specifically excluded from trials due to a presumed high risk of stress ulcer bleeding.

There are several studies and meta-analyses on the individual medications used for stress ulcer prophylaxis, however the data from this literature is conflicting regarding the superiority of one agent over another. Studies of the individual medications in pediatric and neonatal populations are particularly limited.

As new data becomes available, recommendations may change.

Implementation Plan/Tools
1. Guideline will be housed on U-Connect in a dedicated folder for CPGs.
2. Release of the guideline will be advertised in the Physician/APP briefing newsletter.
3. Content and hyperlinks within clinical tools, documents, or Health Link related to the guideline recommendation will be reviewed for consistency and modified as appropriate.

Disclaimer
CPGs are described to assist clinicians by providing a framework for the evaluation and treatment of patients. This Clinical Practice Guideline outlines the preferred approach for most patients. It is not intended to replace a clinician's judgment or to establish a protocol for all patients. It is understood that some patients will not fit the clinical condition contemplated by a guideline and that a guideline will rarely establish the only appropriate approach to a problem.
Appendix A. Evidence Grading Scheme(s)

Figure 1. GRADE Methodology adapted by UW Health

GRADE Ranking of Evidence

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>We are confident that the effect in the study reflects the actual effect.</td>
</tr>
<tr>
<td>Moderate</td>
<td>We are quite confident that the effect in the study is close to the true effect, but it is also possible it is substantially different.</td>
</tr>
<tr>
<td>Low</td>
<td>The true effect may differ significantly from the estimate.</td>
</tr>
<tr>
<td>Very Low</td>
<td>The true effect is likely to be substantially different from the estimated effect.</td>
</tr>
</tbody>
</table>

GRADE Ratings for Recommendations for or Against Practice

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong</td>
<td>The net benefit of the treatment is clear, patient values and circumstances are unlikely to affect the decision.</td>
</tr>
<tr>
<td>Weak/conditional</td>
<td>Recommendation may be conditional upon patient values and preferences, the resources available, or the setting in which the intervention will be implemented.</td>
</tr>
</tbody>
</table>
References


42. Lexicomp Online®, Lexi-Drugs®, Hudson, Ohio: Lexi-Comp, Inc.; October 24, 2014.