Society of Critical Care Medicine and American Society of Health-System Pharmacists Guideline for the Prevention of Stress-Related Gastrointestinal Bleeding in Critically Ill Adults

RATIONALE: Critically ill adults can develop stress-related mucosal damage from gastrointestinal hypoperfusion and reperfusion injury, predisposing them to clinically important stress-related upper gastrointestinal bleeding (UGIB).

OBJECTIVES: The objective of this guideline was to develop evidence-based recommendations for the prevention of UGIB in adults in the ICU.

DESIGN: A multiprofessional panel of 18 international experts from dietetics, critical care medicine, nursing, and pharmacy, and two methodologists developed evidence-based recommendations in alignment with the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) methodology. Conflict-of-interest policies were strictly followed during all phases of guideline development including task force selection and voting.

METHODS: The panel members identified and formulated 13 Population, Intervention, Comparison, and Outcome questions. We conducted a systematic review for each question to identify the best available evidence, statistically analyzed the evidence, and then assessed the certainty of the evidence using the GRADE approach. We used the evidence-to-decision framework to formulate the recommendations. Good practice statements were included to provide additional guidance.

RESULTS: The panel generated nine conditional recommendations and made four good practice statements. Factors that likely increase the risk for clinically important stress-related UGIB in critically ill adults include coagulopathy, shock, and chronic liver disease. There is no firm evidence for mechanical ventilation alone being a risk factor. Enteral nutrition probably reduces UGIB risk. All critically ill adults with factors that likely increase the risk for stress-related UGIB should receive either proton pump inhibitors or histamine-2 receptor antagonists, at low dosage regimens, to prevent UGIB. Prophylaxis should be discontinued when critical illness is no longer evident or the risk factor(s) is no longer present despite ongoing critical illness. Discontinuation of stress ulcer prophylaxis before transfer out of the ICU is necessary to prevent inappropriate prescribing.

CONCLUSIONS: The guideline panel achieved consensus regarding the recommendations for the prevention of stress-related UGIB. These recommendations are intended for consideration along with the patient's existing clinical status.

KEYWORDS: enteral nutrition; gastrointestinal bleeding; histamine 2 blockers; intensive care; proton pump inhibitors; stress ulcer prophylaxis

Robert MacLaren, PharmD, MPH[1]
Joanna C. Dionne, MD, PhD, MSc[2]
Anders Granholm, MD[3]
Waleed Alhazzani, MD, MSc[2,4]
Paul M. Szumita, PharmD[5]
Keith Olsen, PharmD[6]
Jeffrey F. Barletta, PharmD[7]
Morten Hylander Møller, MD, PhD[3]
Constantine J. Karvellas, MD, MSc[8]
Paul Wischmeyer, MD[9]
Ashley DePriest, MS, RDN, LD[10]
Victor Carlos[11]
Debora Argetsinger, DNP[12]
John J. Carothers, PharmD[13]
Rosemary Lee, DNP, APRN[14]
Lena Napolitano, MD[15]
Dan Perri, MD[2,16]
Douglas F. Naylor, MD[17]

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Critically ill adults can develop stress-related mucosal damage from gastrointestinal hypoperfusion and reperfusion injury, predisposing them to clinically important stress-related upper gastrointestinal bleeding

(UGIB). Since the introduction of stress ulcer prophylaxis (SUP) with histamine-2 receptor antagonists (H2RAs) and proton pump inhibitors (PPIs), the rate of stress-related UGIB has declined substantially, and these agents are now used ubiquitously in ICUs) (1–3). The scope of this guideline applies to all critically ill adults and includes: 1) identifying risk factors for stress-related UGIB, 2) determining the benefit of SUP in at risk patients, 3) delineating the preferred class of medications for SUP, 4) describing the optimal dosage regimen and route of administration, 5) identifying subgroups of critically ill patients who may or may not benefit from pharmacologic SUP, 6) describing the role of pharmacologic SUP in the setting of enteral nutrition (EN), and 7) providing guiding principles for discontinuing SUP. The target audiences of this guideline are healthcare clinicians, allied healthcare staff, and trainees working in ICUs or with critically ill adults and administrators with responsibility for ICU functions. The guideline also provides research priorities aimed at investigators and funding agencies.

METHODOLOGY

The Society of Critical Care Medicine (SCCM) commissioned a panel of experts in dietetics, critical care medicine, nursing, and pharmacy, and two methodologists from North America and Europe. Members of the panel were required to disclose conflicts of interest (COI) per the SCCMs COI policy. COI was assessed at each phase of the guideline process and at every panel meeting. Panel members with a COI were excluded from voting on recommendations when a COI was present.

The panel conducted a systematic review of the published scientific literature, focusing on patient-oriented, clinically relevant outcomes to answer Population, Intervention, Comparison, and Outcome (PICO) questions regarding clinically important and overt stress-related UGIB in the ICU. A summary of the PICO questions and final recommendations is presented in **Table 1**. The panel rated the relative importance of each outcome to determine which outcomes were critical vs. important for decision-making (4). A summary of searched outcomes used to address the PICO questions is presented in **Supplement Table 1** (http://links.lww.com/CCM/H544). The panel performed an extensive review of the scientific literature through April 2023 to retrieve articles that addressed the PICO questions. The search strategy was based upon a previous search strategy developed for a network meta-analysis of SUP in critically ill adults (5) and updated to encompass all the PICOs included in the guideline in conjunction with a medical librarian. The search was conducted using MEDLINE, Embase, Cochrane Central Register of Controlled Trials, ClinicalTrials.gov, and World Health Organization International Clinical Trials Registry Platform (search strategies and queries are provided in the **Supplemental Materials**, http://links.lww.com/CCM/H544). Search results were then uploaded to Covidence (Veritas Health Innovation Ltd, Melbourne, VIC, Australia) for screening and data extraction.

Data extraction and risk of bias assessment was performed independently and in duplicate by two panel members assigned to each PICO question using Covidence. To ensure that there were no errors in transcription of the data, consensus was performed on each variable by the methodologist (J.C.D.). The risk of bias was performed by the reviewers and consensus performed by the methodologist. The risk of bias for randomized controlled trials (RCTs) was assessed using the Cochrane Risk of Bias tool 1 for RCTs (6).

Meta-analyses and network meta-analyses were performed on the outcomes of interest, where possible, for each PICO question using RevMan, Version 5.4 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark)or R (R Core Team; R Foundation for Statistical Computing, Vienna, Austria), Version 4.1.0 using the gemtc (v. 1.0-1; JAGS v. 4.3.0; R Foundation for Statistical Computing, Vienna, Austria) and meta (v. 5.1-1; R Foundation for Statistical Computing) packages. PICO questions with insufficient studies to analyze the data were expressed narratively.

The clinical practice recommendations were then developed according to the Grading of Recommendations, Assessment, Development, and Evaluation process. The Evidence to Decision framework was completed by the panel using GradePro software (GRADEpro GDT: GRADEpro Guideline Development Tool software; McMaster University and Evidence Prime Inc., Hamilton, ON, Canada) for each PICO to develop a draft recommendation considering the balance of desirable and undesirable effects, certainty of the evidence, resource considerations, feasibility, acceptability, and

TABLE 1.
Population, Intervention, Comparison, and Outcome Questions and Recommendations

Patient, Intervention, Comparison, and Outcome Question		Recommendation
1)	Population: Critically ill adults in ICU with coagulopathy or shock or chronic liver disease Intervention: SUP Comparison: No SUP Outcome: Reduced occurrence of clinically important stress-related UGIB	We suggest critically ill adults with coagulopathy, shock, or chronic liver disease be considered at risk for clinically important UGIB (conditional recommendation, low to moderate certainty of evidence)
2)	Population: Critically ill at-risk adults in ICU Intervention: Enteral nutrition Comparison: No enteral nutrition Outcome: Reduced occurrence of clinically important stress-related UGIB	We suggest clinicians administer enteral nutrition to reduce clinically important stress-related UGIB in critically ill adults compared with no enteral nutrition (conditional recommendation, moderate certainty of evidence)
3)	Population: Critically ill adults in ICU with coagulopathy or shock or chronic liver disease Intervention: SUP Comparison: No SUP Outcome: Reduced occurrence of overt UGIB	We suggest critically ill adults with coagulopathy, shock, or chronic liver disease be considered at risk for overt UGIB (conditional recommendation, low to moderate certainty of evidence)
4)	Population: Critically ill adults in ICU with risk factors for developing stress-related UGIB Intervention: SUP Comparison: No SUP Outcome: Reduced occurrence of stress-related UGIB	We suggest clinicians provide SUP to prevent clinically important UGIB in critically ill adults with risk factors compared with no SUP (conditional recommendation, moderate certainty of evidence)
5)	Population: Neurocritically ill adults in ICU with risk factors for developing stress-related UGIB Intervention: SUP Comparison: No SUP Outcome: Reduced occurrence of clinically important stress-related UGIB	We suggest using SUP in neurocritical care adults to reduce clinically important stress-related UGIB compared with no SUP (conditional recommendation, very low certainty of evidence)
6)	Population: Critically ill adults with risk factors for developing stress-related UGIB who are enterally fed during ICU admission Intervention: SUP Comparison: No SUP Outcome: Reduced occurrence of clinically important stress-related UGIB	We suggest using SUP for critically ill adults who are enterally fed and possess one or more risk factor(s) for clinically important stress-related UGIB compared with no SUP (conditional recommendation, very low certainty of evidence)
7)	Population: Critically ill adults who are at low risk for developing stress-related UGIB and are enterally fed during ICU admission Intervention: SUP Comparison: No SUP Outcome: Reduced occurrence of clinically important stress-related UGIB	We suggest not using SUP for critically ill adults who are enterally fed and at low risk for clinically important stress-related UGIB (conditional recommendation, very low certainty of evidence)

(*Continued*)

TABLE 1. (*Continued*)

Population, Intervention, Comparison, and Outcome Questions and Recommendations

	Patient, Intervention, Comparison, and Outcome Question	Recommendation
8)	Population: Critically ill adults in the ICU with risk factors for developing stress-related UGIB Intervention: PPIs or H2RAs for SUP Comparison: No PPIs or H2RAs for SUP Outcome: Reduced occurrence of clinically important stress-related UGIB	We suggest using either PPIs or H2RAs as first-line agents for SUP in critically ill adults with risk factors for clinically important stress-related UGIB compared with no PPIs or H2RAs (conditional recommendation, moderate certainty of evidence)
9)	Population: Critically ill adults in the ICU with risk factors for developing stress-related UGIB Intervention: Enteral or IV routes for pharmacologic SUP Comparison: No enteral or IV routes for pharmacologic SUP Outcome: Reduced occurrence of clinically important stress-related UGIB	We suggest using either enteral or IV routes when administering SUP in critically ill adults with risk factors for clinically important stress-related UGIB compared with no enteral or IV routes (conditional recommendation, low certainty of evidence)
10)	Population: Critically ill adults in the ICU with risk factors for developing stress-related UGIB Intervention: Low-dose SUP Comparison: High-dose SUP Outcome: Reduced occurrence of clinically important stress-related UGIB	Low-dose SUP should be administered in critically ill adults with risk factors for clinically important stress-related UGIB compared with high-dose SUP (good practice statement). In critically ill adults with risk factors for developing clinically important stress-related UGIB, SUP should be discontinued when the risk factor(s) is no longer present and should be discontinued before transfer out of the ICU to prevent inappropriate prescribing (good practice statement)
11)	Population: Critically ill adults in the ICU with risk factors for developing stress-related UGIB that are no longer present Intervention: Discontinued use of SUP Comparison: Continued use of SUP Outcome: Reduced occurrence of clinically important stress-related UGIB	In critically ill adults with risk factors for developing clinically important stress-related UGIB, SUP should be discontinued when the risk factor(s) is no longer present. Discontinuation of SUP before transfer out of the ICU is necessary to prevent inappropriate prescribing (good practice statement)
12)	Population: Critically ill adults who do not have risk factors for developing stress-related UGIB but are on SUP before ICU admission Intervention: Discontinued use of SUP Comparison: Continued use of SUP Outcome: Reduced occurrence of clinically important stress-related UGIB	In critically ill adults who do not have risk factors for developing clinically important stress-related UGIB but are on a SUP agent before ICU admission, the indications for these medications should be reviewed and consideration made for discontinuing them (good practice statement)
13)	Population: Critically ill adults who have risk factors for developing stress-related UGIB but are on SUP before ICU admission Intervention: Continued use of SUP Comparison: Discontinued use of SUP Outcome: Reduced occurrence of clinically important stress-related UGIB	In critically ill adult patients with risk factors for developing clinically important stress-related UGIB and who are receiving a SUP agent before ICU, the consideration to change the medication to the most preferred agent for SUP must be weighed against the indication that required the SUP therapy before ICU admission (good practice statement)

H2RAs = histamine-2 receptor antagonists, PPI = proton pump inhibitor, SUP = stress ulcer prophylaxis, UGIB = upper gastrointestinal bleeding.

equity considerations (Supplemental Materials, http://links.lww.com/CCM/H544, for evidence to decision worksheets). Recommendations had to receive at least 80% of the vote of the panel to be approved.

RECOMMENDATIONS

The recommendations in this guideline define principles of practice that should meet the needs of most patients in most situations. Each recommendation statement was assigned a strength ("Strong" or "Conditional"). A "Strong" recommendation is one that clinicians should follow for almost all patients (i.e., something that might qualify as a quality measure). A "Conditional" recommendation reflects a lower degree of certainty in the appropriateness of the patient care strategy for all patients. It requires that the clinician use clinical knowledge and expertise and strongly considers the individual patient's values and preferences to determine the best course of action. Good practice statements are unGRADEd statements and reflect the general practice of panel experts. The ultimate judgment regarding any specific care must be made by the treating clinician and the patient, taking into consideration the individual circumstances of the patient, available treatment options, and resources. This clinical practice guideline reflects the state of knowledge at the time of publication.

The definitions of overt and clinically important UGIB may vary across individual studies. For consistency, the panel defined overt UGIB as any bleeding resulting in signs or symptoms of active bleeding including hematemesis, hematochezia, or melena and clinically important UGIB as any bleeding resulting in hemodynamic instability or the need for transfusion. EN was defined as any nutrition given via an enteral tube irrespective of tube location and quantity of nutrition. The definitions of shock, chronic liver disease, and coagulopathy were not consistent across studies and in some cases not defined at all. Therefore, it is not possible to provide accurate definitions of these terms.

Risk Factors for Clinically Important Bleeding and Overt Upper Gastrointestinal Bleeding

Recommendation 1. **We suggest critically ill adults with coagulopathy, shock, or chronic liver disease be considered at risk for clinically important UGIB (conditional recommendation, low to moderate certainty of evidence).**

After excluding studies with high risk of bias, a meta-analysis of two studies (7) performed by Granholm et al (8) demonstrated an increased absolute risk of stress-related UGIB of 4.8% (95% CI, 2.6–8.6%), 2.6% (95% CI, 1.2–5.4%), and 7.6% (95% CI, 3.3–17.6%) in patients with coagulopathy, shock, and chronic liver disease respectively (**Supplement Table 2**, http://links.lww.com/CCM/H544). Mechanical ventilation may be inherent in the definition of critical illness as many patients in the individual studies required invasive mechanical ventilation, but mechanical ventilation alone probably is not a risk factor and does not necessitate SUP. No evidence is available for noninvasive ventilatory strategies. Two additional studies published after Granholm et al (8) were reviewed by the panel but the additional outcomes were not considered in the recommendation because they require validation. A post hoc analysis of the SUP-ICU study found an association between clinically important UGIB and the need for circulatory support, renal replacement therapy, and severity of illness (9). A multivariable regression analysis of patients with aneurysmal subarachnoid hemorrhage found elevated intracranial pressure, cerebral vasospasm, coagulopathy, and renal impairment to be risk factors for clinically important UGIB (10). Therefore, risk factors that increase the likelihood of UGIB in critically ill adults are coagulopathy, shock, and chronic liver disease. Other factors likely do not infer risk. Studies applied to support other recommendations used many possible risk factors. Therefore, we have chosen to describe the risk for clinically important stress-related UGIB as "at risk" (critically ill and presence of coagulopathy, shock, or chronic liver disease) vs. "low-risk" (critically ill and absence of coagulopathy, shock, or chronic liver disease).

Recommendation 2. **We suggest clinicians administer EN to reduce clinically important stress-related UGIB in critically ill adults compared with no EN (conditional recommendation, moderate certainty of evidence).**

After excluding studies with high risk of bias, an analysis of one study (11) performed by Granholm et al (8) demonstrated a decreased absolute risk of stress-related UGIB of 0.3% (95% CI, 0.1–0.7%) in patients receiving EN (Supplement Table 2, http://links.lww.com/CCM/H544).

Recommendation 3. **We suggest critically ill adults with coagulopathy, shock, or chronic liver disease be considered at risk for overt UGIB (conditional recommendation, low to moderate certainty of evidence).**

After excluding studies with high risk of bias, a meta-analysis of 2 studies (7, 12) performed by Granholm et al (8) demonstrated an increased absolute risk of overt UGIB of 4.1% (95% CI, 2.7–6.9%), 2.6% (95% CI, 1.4–4.5%), and 4.5% (95% CI, 2.3–8.8%) in patients with coagulopathy, shock, and chronic liver disease, respectively (**Supplement Table 3**, http://links.lww.com/CCM/H544). EN was not assessed. There is no conclusive evidence for mechanical ventilation alone being a risk factor for overt UGIB.

Pharmacologic Stress Ulcer Prophylaxis

Recommendation 4. **We suggest clinicians provide SUP to prevent clinically important UGIB in critically ill adults with risk factors compared with no SUP (conditional recommendation, moderate certainty of evidence).**

The network meta-analysis conducted by the panel that compared SUP to control found PPIs reduced clinically important UGIB (relative risk [RR], 0.52; 95% CI, 0.30–0.81) (13–29) without any conclusive evidence of effects on pneumonia (RR, 1.14; 95% CI, 0.93–1.54) (20, 30–33), *Clostridioides difficile* infection (CDI) (RR, 0.73; 95% CI, 0.42–1.26) (30–32, 34), or mortality (RR, 1.02; 95% CI, 0.92–1.14) (15, 20, 30–34) (**Supplement Table 4**, http://links.lww.com/CCM/H544). Other systematic reviews and meta-analyses found similar results with PPIs (13, 33, 35, 36); however, H2RAs were also effective at preventing UGIB.

Stress Ulcer Prophylaxis in Neurocritical Care Patients

Recommendation 5. **We suggest using SUP in neurocritical care adults to reduce clinically important stress-related UGIB compared with no SUP (conditional recommendation, very low certainty of evidence).**

Neurocritical care patients may be at additional risk of UGIB due to physiologic changes resulting in hypersecretion of gastric acid. A recent meta-analysis of eight randomized controlled studies comparing PPIs or H2RAs to placebo or no prophylaxis across 829 neurocritical care patients found pharmacologic SUP was associated with reduced clinically important UGIB (RR, 0.31; 95% CI, 0.20–0.47), albeit still high overall rates of bleeding of 11–33% (37). All-cause mortality was also lower with SUP (RR, 0.70; 95% CI, 0.50–0.98), but the occurrence of nosocomial pneumonia was not statistically significantly different between groups (RR, 1.14; 95% CI, 0.67–1.94) (37). CDI was not assessed. No firm evidence was found for the outcomes of stress-related UGIB, all-cause mortality, or nosocomial pneumonia across prespecified subgroup analyses of studies with higher (high) vs. lower (low/unclear) risk of bias, pharmacologic classes (PPIs vs. H2RAs), comparator types (placebo vs. no prophylaxis), presence or absence of EN, diagnosis (traumatic brain injury vs. intracranial hemorrhage), and study location (Asia vs. non-Asian) (37).

Another meta-analysis of 14 randomized controlled studies found both PPIs and H2RAs were associated with reduced clinically important UGIB compared with no SUP (RR, 0.37; 95% CI, 0.23–0.59 and RR, 0.42; 95% CI, 0.3–0.58, respectively) but mortality and nosocomial pneumonia rates were not statistically significantly different (38). No significant difference was observed in clinically important UGIB comparing PPIs and H2RAs (RR, 0.53; 95% CI, 0.26–1.06) (38). The etiology of neurologic injury across all studies was largely attributed to traumatic brain injury and intracranial hemorrhage.

Stress Ulcer Prophylaxis and Enteral Nutrition

Recommendation 6. **We suggest using SUP for critically ill adults who are enterally fed and possess one or more risk factor(s) for clinically important stress-related UGIB compared with no SUP (conditional recommendation, very low certainty of evidence).**

Recommendation 7. **We suggest not using SUP for critically ill adults who are enterally fed and at low risk for clinically important stress-related UGIB (conditional recommendation, very low certainty of evidence).**

Remarks. Concurrent administration of SUP with EN may increase pneumonia risk.

Two systematic reviews (36, 39) were used to inform these recommendations. One showed a reduction in clinically important UGIB with SUP (RR, 0.57; 95% CI, 0.42–0.57) (36), whereas the other (39) did not

(RR, 0.8; 95% CI, 0.49–1.31) when compared with EN alone. There was no conclusive evidence of effects on the outcomes of mortality in either review (RR, 0.95; 95% CI, 0.87–1.05 and RR, 1.21; 95% CI, 0.94–1.56), CDI (RR, 1.28; 95% CI, 0.74–2.22 and RR, 0.89; 95% CI, 0.25–3.19), ICU length of stay (mean difference [MD], 0.04 d; 95% CI, −1.16 to 1.25 d and MD, 0.04 d; 95% CI, −0.79 to 0.87 d), or duration of mechanical ventilation (MD, −0.46 d; 95% CI, −0.97 to 1.89 d and MD, −0.38 d; 95% CI, −1.48 to 0.72 d) with SUP. There was an increase in healthcare-associated pneumonia with concurrent SUP and EN (RR, 1.55; 95% CI, 1.06–2.28 and RR, 1.53; 95% CI, 1.04–2.27)

Agents for Stress Ulcer Prophylaxis

Recommendation 8. **We suggest using either PPIs or H2RAs as first-line agents for SUP in critically ill adults with risk factors for clinically important stress-related UGIB compared with no PPIs or H2RAs (conditional recommendation, moderate certainty of evidence).**

Remarks. Despite reducing the occurrence of clinically important UGIB with PPIs compared with H2RAs, there is uncertainty regarding the influence of PPIs on mortality in patients with high severity of illness in the ICU. Although recent subgroup assessments of randomized trials suggest an association between PPIs and increased mortality (14, 32), our judgment is based on pooled analyses of all compiled aggregate data rather than pooled analyses of subgroup data.

The network meta-analysis conducted by the panel compared PPIs, H2RAs, and sucralfate for the outcomes of clinically important UGIB, overt UGIB, pneumonia, and mortality; however, the certainty of evidence varied (very low to high) considerably across analyses (Supplement Table 4, http://links.lww.com/CCM/H544). Compared with H2RAs, PPIs were associated with reduced clinically important UGIB (RR, 0.53; 95% CI, 0.34–0.83) but increased mortality (RR, 1.05; 95% CI, 1–1.10). These results are similar to other meta-analyses that found reduced UGIB with PPIs compared with H2RAs but possibly increased mortality (35, 40–43). Sucralfate was associated with less pneumonia compared with PPIs (RR, 0.49; 95% CI, 0.3–0.79) and H2RAs (RR, 0.83; 95% CI, 0.71–0.96) but many studies targeted gastric pH values greater than 3.5 which is not current practice and may predispose patients to pneumonia by altering bacterial flora. Network meta-analyses could not be conducted for the outcome of CDI since this outcome was absent or not prospectively defined in most randomized studies. No evidence supports the concurrent administration of sucralfate and acid suppressants for SUP.

Route of Administration in Stress Ulcer Prophylaxis

Recommendation 9. **We suggest using either enteral or IV routes when administering SUP in critically ill adults with risk factors for clinically important stress-related UGIB compared with no enteral or IV routes (conditional recommendation, low certainty of evidence).**

The data are limited by insufficient studies enrolling few subjects and none were designed to directly compare route of administration on clinically pertinent outcomes. Our network meta-analyses found no firm evidence for effects of route when all the routes of administration were combined and compared.

Dosing Regimen in Stress Ulcer Prophylaxis

Good Practice Statement 1. **Low-dose SUP should be administered in critically ill adults with risk factors for clinically important stress-related UGIB compared with high-dose SUP.**

Remarks. "Low-dose" PPI therapy is defined as a daily dose of less than or equal to 40 mg esomeprazole, omeprazole, or pantoprazole and less than or equal to 30 mg lansoprazole. "Low-dose" H2RA therapy is defined as a daily dose of less than or equal to 40 mg famotidine, less than or equal to 150 mg IV ranitidine, less than or equal to 300 mg enteral ranitidine, and less than or equal to 1200 mg cimetidine. "Low-dose" sucralfate is defined as a daily dose of less than or equal to 4 g.

The data are limited by insufficient studies enrolling few subjects and none were designed to directly compare dosage regimens on clinically pertinent outcomes.

Cessation of Prophylaxis

Good Practice Statement 2. **In critically ill adults with risk factors for developing clinically important stress-related UGIB, SUP should be discontinued when the risk factor(s) is no longer present. Discontinuation of SUP before transfer out of the ICU is necessary to prevent inappropriate prescribing.**

The evidence is limited to cohort studies comparing characteristics of patients in whom SUP was discontinued during the ICU stay or hospitalization to those in whom it was continued beyond the ICU stay or hospitalization. Factors contributing to the continuation of SUP after ICU discharge were admission diagnoses requiring mechanical ventilation, the presence of multiple traumas, hepatic failure, or head injury or spinal cord injury at admission, longer duration of mechanical ventilation, and longer stay in the ICU (44, 45). The use of PPIs for SUP may contribute to continued use of therapy after ICU discharge (46). Therefore, SUP should be discontinued when critical illness is no longer evident or the risk factor(s) is no longer present despite ongoing critical illness.

Good Practice Statement 3. **In critically ill adults who do not have risk factors for developing clinically important stress-related UGIB but are on a SUP agent before ICU admission, the indications for these medications should be reviewed and consideration made for discontinuing them.**

Remarks. Some critically ill patients without risk factors for stress ulcers may continue to require SUP therapy received before ICU admission. The most common situations likely require stronger acid suppression with PPIs and include but are not limited to recent UGIB, hypersecretory states, erosive esophagitis, and eradication therapy of *Helicobacter pylori* infections. Therapy or prevention of anaphylaxis, angioedema, or urticaria may necessitate continuation of maintenance therapy of H2RA. The benefit of continuing these agents for maintenance therapy of their pre-ICU condition must be weighed against possible adverse events, drug interactions, and availability of the route of administration.

Good Practice Statement 4. **In critically ill adult adults with risk factors for developing clinically important stress-related UGIB and who are receiving a SUP agent before ICU, the consideration to change the medication to the most preferred agent for SUP must be weighed against the indication that required the SUP therapy before ICU admission.**

Remarks. Patient-specific factors such as allergies to a specific class of agents or potential severe drug interactions may necessitate the choice of a specific class of agents for SUP.

The Proton Pump Inhibitors vs Histamine-2 Receptor Blockers for Ulcer Prophylaxis Treatment in the Intensive Care Unit (PEPTIC) study included patients receiving a SUP therapy before ICU admission and did not find evidence of effects that outcomes were influenced by prior use (14). Cohort studies also found no evidence of effects on outcomes based on usage before ICU admission (47–49).

RESEARCH AGENDA

Future research is needed on all topic areas covered by this guideline. A summary of research priorities for each topic is presented in **Supplement Table 5** (http://links.lww.com/CCM/H544).

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1 *Department of Clinical Pharmacy, University of Colorado Skaggs School of Pharmacy and Pharmaceutical Sciences, Aurora, CO.*

2 *Division of Gastroenterology and Critical Care Medicine, Department of Medicine, McMaster University, Hamilton, ON, Canada.*

3 *Department of Intensive Care, Righospitalet, University of Copenhagen, Copenhagen, Denmark.*

4 *Division of Critical Care, Department of Clinical Epidemiology and Biostatistics, McMaster University, Hamilton, ON, Canada.*

5 *Department of Pharmacy Services, Brigham and Women's Hospital, Boston, MA.*

6 *Department of Pharmacy Practice and Science, College of Pharmacy, University of Nebraska Medical Center, Omaha, NE.*

7 *Department of Pharmacy Practice, Midwestern University College of Pharmacy, Glendale, AZ.*

8 *Division of Gastroenterology (Liver Unit), Department of Critical Care Medicine, University of Alberta, Edmonton, AB, Canada.*

9 *Department of Anesthesiology and Surgery, Duke University Medical Center, Durham, NC.*

10 *Department of Food and Nutrition, Emory Healthcare, Atlanta, GA.*

11 *Patient representative, Denver, CO.*

12 *Neurology, University of Michigan Health-West, Wyoming, MI.*

13 *Department of Inpatient Pharmacy, United States Public Health Service, Alaska Native Medical Center, Anchorage, AK.*

14 *Critical Care and Progressive Care Units, Baptist Health South Florida, Miami, FL.*

15 *Acute Care Surgery, Surgical Critical Care, Department of Surgery, University of Michigan Health System, Ann Arbor, MI.*

16 *Divisions of Clinical Pharmacology & Toxicology and Critical Care Medicine, Department of Medicine, McMaster University, Hamiton, ON, Canada.*

17 *Department of Surgery-Trauma Surgery, Critical Care, and Acute Care Surgery, University Hospitals of Cleveland, Cleveland, OH.*

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For information regarding this article, E-mail: rob.maclaren@cuanschutz.edu

REFERENCES

1. Krag M, Perner A, Wetterslev J, et al: Stress ulcer prophylaxis versus placebo or no prophylaxis in critically ill patients. A systematic review of randomised clinical trials with meta-analysis and trial sequential analysis. *Intensive Care Med* 2014; 40:11–22
2. Preslaski CR, Mueller SW, Kiser TH, et al: A survey of prescriber perceptions about the prevention of stress-related mucosal bleeding in the intensive care unit. *J Clin Pharm Ther* 2014; 39:658–662
3. Barletta JF, Kanji S, MacLaren R, et al; American-Canadian consortium for Intensive care Drug utilization (ACID) Investigators: Pharmacoepidemiology of stress ulcer prophylaxis in the United States and Canada. *J Crit Care* 2014; 29:955–960
4. Guyatt GH, Oxman AD, Vist GE, et al; GRADE Working Group: GRADE: An emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008; 336:924–926
5. Alhazzani W, Alshamsi F, Belley-Cote E, et al: Efficacy and safety of stress ulcer prophylaxis in critically ill patients: A network meta-analysis of randomized trials. *Intensive Care Med* 2018; 44:1–11
6. Higgins JP, Thomas J, Chandler J, et al: *Cochrane Handbook for Systematic Reviews of Interventions*. Chichester, United Kingdom, John Wiley & Sons, 2019
7. Krag M, Perner A, Wetterslev J, et al; SUP-ICU co-authors: Prevalence and outcome of gastrointestinal bleeding and use of acid suppressants in acutely ill adult intensive care patients. *Intensive Care Med* 2015; 41:833–845
8. Granholm A, Zeng L, Dionne JC, et al; GUIDE Group: Predictors of gastrointestinal bleeding in adult ICU patients: A systematic review and meta-analysis. *Intensive Care Med* 2019; 45:1347–1359
9. Granholm A, Krag M, Marker S, et al: Predictors of gastrointestinal bleeding in adult ICU patients in the SUP-ICU trial. *Acta Anaesthesiol Scand* 2021; 65:792–800
10. Ali D, Barra ME, Blunck J, et al: Stress-related gastrointestinal bleeding in patients with aneurysmal subarachnoid hemorrhage: A multicenter retrospective observational study. *Neurocrit Care* 2021; 35:39–45
11. Cook D, Heyland D, Grifth L, et al: Risk factors for clinically important upper gastrointestinal bleeding in patients requiring mechanical ventilation. Canadian Critical Care Trials Group. *Crit Care Med* 1999; 27:2812–2817
12. Cook DJ, Fuller HD, Guyatt GH, et al: Risk factors for gastrointestinal bleeding in critically ill patients. *N Engl J Med* 1994; 330:377–381
13. Toews I, George AT, Peter JV, et al: Interventions for preventing upper gastrointestinal bleeding in people admitted to intensive care units. *Cochrane Database Syst Rev* 2018; 6:CD008687
14. Young PJ, Bagshaw SM, Forbes AB, et al; PEPTIC Investigators for the Australian and New Zealand Intensive Care Society Clinical Trials Group, Alberta Health Services Critical Care Strategic Clinical Network, and the Irish Critical Care Trials Group: Effect of stress ulcer prophylaxis with proton pump inhibitors vs histamine-2 receptor blockers on in-hospital mortality among ICU patients receiving invasive mechanical ventilation: The PEPTIC randomized clinical trial. *JAMA* 2020; 323:616–626
15. Powell H, Morgan M, Li S, et al: Inhibition of gastric acid secretion in the intensive care unit after coronary artery bypass graft. A pilot control study of intravenous omeprazole by bolus and infusion, ranitidine and placebo. *Theor Surg* 1993; 8:125–130
16. Conrad SA, Gabrielli A, Margolis B, et al: Randomized, double-blind comparison of immediate-release omeprazole oral suspension versus intravenous cimetidine for the prevention of upper gastrointestinal bleeding in critically ill patients. *Crit Care Med* 2005; 33:760–765
17. Fink M, Karlstadt RG, Maroko RT, et al: Intravenous pantoprazole (IVP) and continuous infusion cimetidine (C) prevent upper gastrointestinal bleeding (UGIB) regardless of APSII score (APACHE II) in high-risk intensive care unit (ICU) patients. *Gastroenterology* 2003; 124:A625–A626

18. Fogas J, Kiss K, Gyura F, et al: Effects of proton pump inhibitor versus H2-receptor antagonist stress ulcer prophylaxis on ventilator-associated pneumonia: A pilot study. *Crit Care* 2013; 17:P402
19. Hata M, Shiono M, Sekino H, et al: Prospective randomized trial for optimal prophylactic treatment of the upper gastrointestinal complications after open heart surgery. *Circ J* 2005; 69:331–334
20. Kantorova I, Svoboda P, Scheer P, et al: Stress ulcer prophylaxis in critically ill patients: A randomized controlled trial. *Hepatogastroenterology* 2004; 51:757–761
21. Kotlyanskaya A, Luka B, Mukherji R: A comparison of lansoprazole disintegrating tablet, lansoprazole suspension or ranitidine for stress ulcer prophylaxis in critically ill patients. *Crit Care Med* 2008; 7:A194
22. Lee T-H, Hung F-M, Yang L-H: Comparison of the efficacy of esomeprazole and famotidine against stress ulcers in a neurosurgical intensive care unit. *Adv Diges Med* 2014; 1:50–53
23. Levy MJ, Seelig CB, Robinson NJ, et al: Comparison of omeprazole and ranitidine for stress ulcer prophylaxis. *Dig Dis Sci* 1997; 42:1255–1259
24. Lou W, Xia Y, Xiang P, et al: Prevention of upper gastrointestinal bleeding in critically ill Chinese patients: A randomized, double-blind study evaluating esomeprazole and cimetidine. *Curr Med Res Opin* 2018; 34:1449–1455
25. Risaliti A, Terrosu A, Uzzau R, et al: Intravenous omeprazole vs ranitidine in the prophylaxis of stress ulcers. *Acta Chir Ital* 1993; 49:397–401
26. Solouki M, Marashian SM, Kouchak M, et al: Comparison between the preventive effects of ranitidine and omeprazole on upper gastrointestinal bleeding among ICU patients. *Tanaffos* 2009; 8:37–42
27. Somberg L, Morris J, Fantus R, et al: Intermittent intravenous pantoprazole and continuous cimetidine infusion: Effect on gastric pH control in critically ill patients at risk of developing stress-related mucosal disease. *J Trauma* 2008; 64:1202–1210
28. Wee B, Liu CH, Cohen H, et al: 731: IV famotidine vs. IV pantoprazole for stress ulcer prevention in the ICU: A prospective study. *Crit Care Med* 2013; 41:A181
29. Terzi CC, Dragosavac D, Coelho NJ, et al: Ranitidine is unable to maintain gastric pH levels above 4 in septic patients. *J Crit Care* 2009; 24:627.e7–627.13
30. Selvanderan S, Summers M, Finnis M, et al: Pantoprazole or Placebo for Stress Ulcer Prophylaxis (POP-UP): Randomized double-blind exploratory study. *Crit Care Med* 2016; 44:1842–1850
31. Alhazzani W, Guyatt G, Alshahrani M, et al; Canadian Critical Care Trials Group: Withholding pantoprazole for stress ulcer prophylaxis in critically ill patients: A pilot randomized clinical trial and meta-analysis. *Crit Care Med* 2017; 45:1121–1129
32. Krag M, Marker S, Perner A, et al; SUP-ICU trial group: Pantoprazole in patients at risk for gastrointestinal bleeding in the ICU. *N Engl J Med* 2018; 379:2199–2208
33. Lin C-C, Hsu Y-L, Chung C-S, et al: Stress ulcer prophylaxis in patients being weaned from the ventilator in a respiratory care center: A randomized control trial. *J Form Med Assoc* 2016; 115:19–24
34. El-Kersh K, Jalil B, McClave SA, et al: Enteral nutrition as stress ulcer prophylaxis in critically ill patients: A randomized controlled exploratory study. *J Crit Care* 2018; 43:108–113
35. Wang Y, Ge L, Ye Z, et al: Efficacy and safety of gastrointestinal bleeding prophylaxis in critically ill patients: An updated systematic review and network meta-analysis of randomized trials. *Intensive Care Med* 2020; 46:1987–2000
36. Reynolds PM, MacLaren R: Re-evaluating the utility of stress ulcer prophylaxis in the critically ill patient: A clinical scenario-based meta-analysis. *Pharmacotherapy* 2019; 39:408–420
37. Liu B, Liu S, Yin A, et al: Risks and benefits of stress ulcer prophylaxis in adult neurocritical care patients: A systematic review and meta-analysis of randomized controlled trials. *Crit Care* 2015; 19:409
38. Daou M, Dionne JC, Teng JF, et al: Prophylactic acid suppressants in patients with primary neurologic injury: A systematic review and meta-analysis of randomized studies. *J Crit Care* 2022; 71:154093
39. Huang HB, Jiang W, Wang CY, et al: Stress ulcer prophylaxis in intensive care unit patients receiving enteral nutrition: A systematic review and meta-analysis. *Crit Care* 2018; 22:20
40. He N, Yan Y, Su S, et al: Are proton pump inhibitors more effective than histamine-2-receptor antagonists for stress ulcer prophylaxis in critically ill patients? A systematic review and meta-analysis of cohort studies. *Ann Pharmacother* 2022; 56:988–997
41. Lee TC, Goodwin Wilson M, Lawandi A, et al: Proton pump inhibitors versus histamine-2 receptor antagonists likely increase mortality in critical care: An updated meta-analysis. *Am J Med* 2021; 134:e184–e188
42. Deliwala SS, Hamid K, Goyal H, et al: Proton pump inhibitors versus histamine-2-receptor antagonists for stress ulcer prophylaxis in critically ill patients: A meta-analysis and trial sequential analysis. *J Clin Gastroenterol* 2022; 56:204–217
43. Reynolds PM, Wells L, Powell M, et al: Associated mortality risk of proton pump inhibitor therapy for the prevention of stress ulceration in intensive care unit patients: A systematic review and meta-analysis. *J Clin Gastroenterol* 2022; 57:586–594
44. Farrell CP, Mercogliano G, Kuntz CL: Overuse of stress ulcer prophylaxis in the critical care setting and beyond. *J Crit Care* 2010; 25:214–220
45. Domond M, Struby C, Berson A, et al: The downward spiral of acid suppressive therapy in stress ulcer prophylaxis. *Am J Gastroenterol* 2017; 112:S621–S622
46. Boyd C, Hassig T, MacLaren R: A pragmatic assessment of proton pump inhibitors vs. histamine type 2 receptor antagonists on clinically important gastrointestinal bleeding and mortality when used for stress ulcer prophylaxis in the ICU. *Pharmacotherapy* 2021; 41:820–827
47. MacLaren R, Reynolds PM, Allen RR: Histamine-2 receptor antagonists vs proton pump inhibitors on gastrointestinal tract hemorrhage and infectious complications in the intensive care unit. *JAMA Intern Med* 2014; 174:564–574
48. Marker S, Perner A, Wetterslev J, et al; SUP-ICU investigators: Pantoprazole prophylaxis in ICU patients with high severity of disease: A post hoc analysis of the placebo-controlled SUP-ICU trial. *Intensive Care Med* 2019; 45:609–618
49. Murphy CE, Stevens AM, Ferrentino N, et al: Frequency of inappropriate continuation of acid suppressive therapy after discharge in patients who began therapy in the surgical intensive care unit. *Pharmacotherapy* 2008; 28:968–976