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

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

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The occurence rate of stress-related upper gastrointestinal bleeding (UGIB) in the ICU has declined substantially over the past 25 years as clinical practice has evolved to include early initiation of enteral nutrition (EN), use of lung protective ventilation, aggressive resuscitation, and restrictive transfusion policies (1, 2). The use of stress ulcer prophylaxis (SUP), however, remains ubiquitous and may pose risks that outweigh the benefit of preventing UGIB. A multi-professional, international panel was formed to develop an evidence-based guideline for the use of SUP in the modern era of critical care medicine and to identify knowledge gaps in the current body of research. The panel has summarized the existing evidence and provides evidence-based recommendations and good practice statements on the use of SUP in critically ill adults (see full online guideline in [3]). The Population, Intervention, Comparison, and Outcome (PICO) questions included in this executive summary are presented in **Table 1**.

RECOMMENDATIONS

The panel issued a total of nine conditional evidence-based recommendations and four good practice statements for this clinical practice guideline (see full article in [3]). A subset of these recommendations deemed most important for the prevention of UGIB are summarized below including a rationale for each. The strength of each recommendation was informed by the certainty of the evidence and other components of the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) evidence-to-decision framework. Conditional recommendations reflect 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 consider the individual patient's values and preferences to determine the best course of action. 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. For this guideline, overt UGIB was considered as any bleeding resulting in signs or symptoms of

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TABLE 1.
Population, Intervention, Comparison, and Outcome (PICO) Questions and Summary of Recommendations

PICO Question	Recommendation
Population: critically ill adults in ICU with coagulopathy or shock or chronic liver disease Intervention: stress ulcer prophylaxis Comparison: no stress ulcer prophylaxis 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)
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)
Population: critically ill adults in ICU with risk factors for developing stress-related UGIB Intervention: stress ulcer prophylaxis Comparison: no stress ulcer prophylaxis 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)
Population: critically ill adults with risk factors for developing stress-related UGIB who are enterally fed during ICU admission Intervention: stress ulcer prophylaxis Comparison: no stress ulcer prophylaxis 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)
Population: critically ill adults who are at low-risk for developing stress-related UGIB and are enterally fed during ICU admission Intervention: stress ulcer prophylaxis Comparison: no stress ulcer prophylaxis 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)
Population: critically ill adults in the ICU with risk factors for developing stress-related UGIB Intervention: PPIs or H2RAs for stress ulcer prophylaxis Comparison: no PPIs or H2RAs for stress ulcer prophylaxis 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)

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

active bleeding including hematemesis, hematochezia, or melena. Clinically important UGIB was considered as any bleeding resulting in hemodynamic instability or the need for transfusion (4). EN was considered as any nutrition given via an enteral tube irrespective of tube location and quantity of nutrition.

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 (5, 6) performed by Granholm et al (7) 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. There is no conclusive evidence for mechanical ventilation being an independent risk factor for UGIB. Mechanical ventilation alone does not necessitate SUP. 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 confer risk.

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 (8) performed by Granholm et al (7) demonstrated a decreased absolute risk of stress-related UGIB of 0.3% (95% CI, 0.1–0.7) in patients receiving EN.

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 found only proton pump inhibitors (PPIs) reduced clinically important UGIB (relative risk [RR] 0.52; 95% CI, 0.30–0.81) (8–24) without any conclusive evidence of effects on pneumonia (RR 1.14; 95% CI, 0.93–1.54) (15, 25–28), *Clostridioides difficile* infection (CDI) (RR 0.73; 95% CI, 0.42–1.26) (25–27, 29) and mortality (RR 1.02; 95% CI, 0.92–1.14) (10, 15, 25–29). Other systematic reviews and meta-analyses found similar results with PPIs (8, 28, 30, 31); however, H2RAs were also effective at preventing UGIB when compared with control.

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).

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 (31, 32) 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) (31) whereas the other (32) 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 and MD 0.04 d; 95% CI, –0.79 to 0.87), or duration of mechanical ventilation (MD –0.46 d; 95% CI, –0.97 to 1.89 and MD –0.38 d; 95% CI, –1.48 to 0.72) 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).

We suggest using either PPIs or histamine-2 receptor antagonists (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 (9, 33), our judgement 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. Compared with H2RAs, PPIs were associated with reduced clinically important UGIB (RR 0.53; 95% CI, 0.34–0.83). These results are similar to other meta-analyses that found reduced UGIB with PPIs compared with H2RAs but possibly increased mortality (30, 32, 34–36). 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). 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.

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