Don’t Stress Over Prophylaxis- A Stress Ulcer Prophylaxis Review

A presentation for HealthTrust members
June 10, 2026

Rebecca Hilton, PharmD, BCCCP
Critical Care Pharmacy Specialist
Mercy Hospital Southeast

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Your life is our life’s work.

Disclosures

I have no conflicts of interest related to this presentation.

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Learning Objectives

Recall the known risk factors for gastrointestinal bleeding to determine the need for stress ulcer prophylaxis.

Recognize disease states of neurocritical care patients and their respective need for stress ulcer prophylaxis.

Identify the role of enteral nutrition in the risk of gastrointestinal bleeding and need for stress ulcer prophylaxis.

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Abbreviations

AKI- acute kidney injury

Cdiff- Clostridium difficile infection

CIB- clinically important bleeding

EN- enteral nutrition

GI bleed- gastrointestinal bleeding

H2RAs- histamine 2 receptor antagonist

HAP- hospital acquired pneumonia

ICU- intensive care unit

PPI- proton pump inhibitor

RE- relative effect

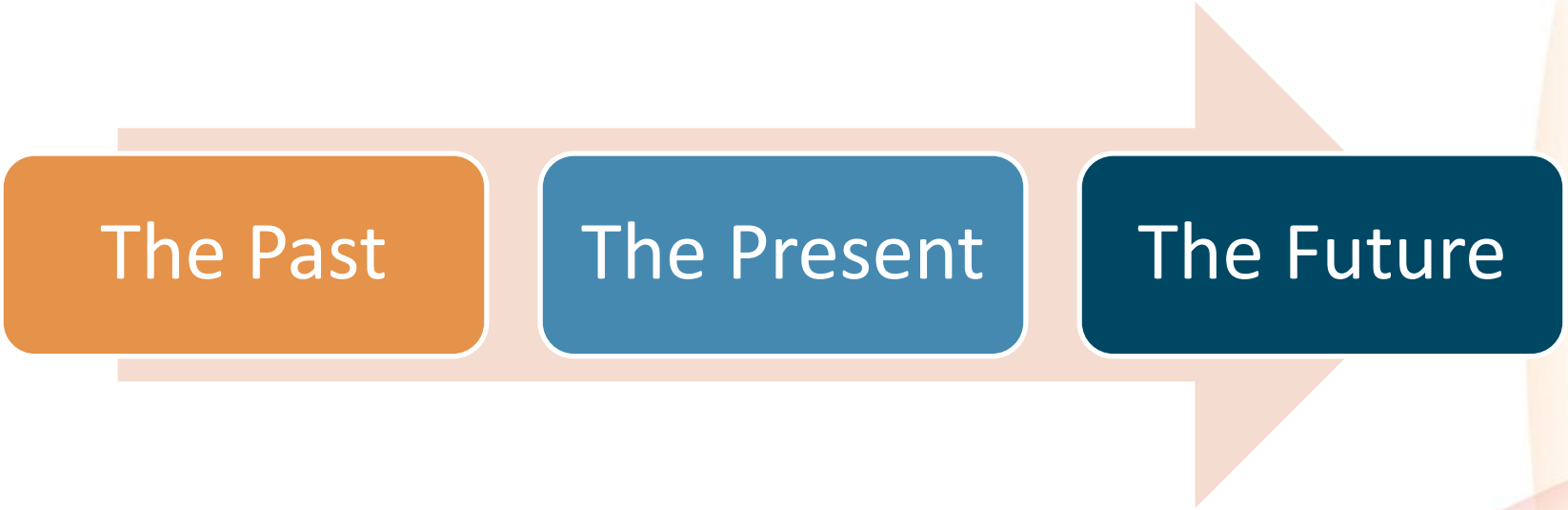
RR- relative risk

SUP- stress ulcer prophylaxis

UGIB- upper gastrointestinal bleeding

VAP- ventilator associated pneumonia

Outline



“An ounce of prevention is worth a pound of cure.”

Brown, S. Uncertain Answers- Proton-Pump Inhibition in the ICU. *NEJM.* 2024;391(1):78-79.

The Past…

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Who was at risk before?

Table. Risk factors associated with stress-related mucosal disease*

Type	Risk factor
Independent	1. Coagulopathy (including medication-induced coagulopathy): platelet count <50,000 mm^3, INR >1.5, or PTT >2× control value 2. Respiratory failure: mechanical ventilation ≥48 hours
Other	1. Spinal cord injuries 2. Multiple trauma†: trauma sustained to more than one body region 3. Hepatic failure†: total bilirubin level >5 mg/dL, AST >150 U/L (3× ULN), or ALT >150 U/L (3× ULN). 4. Thermal injuries >35% of body surface area 5. Partial hepatectomy 6. Head injury with Glasgow coma score of ≤10 or inability to obey simple commands 7. Hepatic or renal transplantation 8. History of gastric ulceration or bleeding during year before admission 9. Sepsis/septic shock†: vasopressor support and/or positive microbiologic cultures/suspected infection 10. Intensive care unit stay >1 week 11. Occult or overt bleeding >6 days 12. Corticosteroid therapy

*From American Society of Health-System Pharmacists guidelines (5).

†Modified from ASHP guidelines.

ALT indicates alanine aminotransferase; AST, aspartate aminotransferase; INR, international normalized ratio; PTT, partial thromboplastin time; ULN, upper limit of normal.

Mohebbi L, Hesch K. Stress Ulcer Prophylaxis in the Intensive Care Unit. *Pharmacology Notes- Baylor University Medical Center Proceedings*. 2009;22(4):373-376.

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The New Guidelines…

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Stress Ulcer Prophylaxis Guidelines

Published in August 2024

Collaboration between the Society of Critical Care Medicine and the American Society of Health-System Pharmacists

Applies to all critically ill adults

MacLaren R, Dionne J, Granholm A, et al. 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. *Crit Care Med*. 2024. doi:10.1097/CCM.0000000000006330.

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Goals of the Guideline

- Identify risk factors for upper gastrointestinal bleeding (UGIB) caused by stress.
- Determine the benefit of stress ulcer prophylaxis for patients at risk.
- Delineate the preferred class of medications for stress ulcer prophylaxis (SUP).
- Describe the optimal regimen including dose and route.
- Identify subgroups of critically ill patients who may or may not benefit from SUP.
- Describe the role of pharmacologic SUP alongside enteral nutrition (EN).
- Provide guidance for discontinuing SUP.

MacLaren R, Dionne J, Granholm A, et al. 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. *Crit Care Med*. 2024. doi:10.1097/CCM.0000000000006330.

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Defining the Strength of Recommendations

Strong: clinicians should follow for almost all patients

Conditional: reflects a lower degree of certainty in the appropriateness as a treatment strategy for all patients

MacLaren R, Dionne J, Granholm A, et al. 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. *Crit Care Med*. 2024. doi:10.1097/CCM.0000000000006330.

Definitions within the Guidelines

Overt UGIB- any bleeding resulting in signs or symptoms of an active bleed. Examples include:

- Hematemesis
- Hematochezia
- Melena

Clinically important UGIB- any bleeding accompanied by hemodynamic instability or requiring a transfusion.

EN- any nutrition given per enteral tube irrespective of tube location or quantity of nutrition.

No standard definition from this guideline for shock, chronic liver disease or coagulopathy.

MacLaren R, Dionne J, Granholm A, et al. 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. *Crit Care Med*. 2024. doi:10.1097/CCM.0000000000006330.

Risk Factors for Clinically Important UGIB

“We suggest critically ill patients with coagulopathy, shock or chronic liver disease be considered at risk for clinically important UGIB”

- Considered a conditional recommendation with low to moderate certainty of evidence

MacLaren R, Dionne J, Granholm A, et al. 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. *Crit Care Med*. 2024. doi:10.1097/CCM.0000000000006330.

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Risk Factors for Clinically Important UGIB, *cont.*

Guidelines discuss how mechanical ventilation may be inherent in the definition of critical illness. However, mechanical ventilation alone is probably not a risk factor and does not necessitate SUP.

No evidence regarding noninvasive ventilation

MacLaren R, Dionne J, Granholm A, et al. 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. *Crit Care Med*. 2024. doi:10.1097/CCM.0000000000006330.

Risk Factors for Overt UGIB

"We suggest critically ill patients with coagulopathy, shock or chronic liver disease be considered at risk for overt UGIB"

- Considered a conditional recommendation with low to moderate certainty of evidence
- Did not assess EN
- No conclusive evidence for mechanical ventilation alone being a risk factor

MacLaren R, Dionne J, Granholm A, et al. 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. *Crit Care Med*. 2024. doi:10.1097/CCM.0000000000006330.

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Risk Factors Supporting Literature

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Prevalence & Outcome of GI Bleeding & Use of Acid Suppressants in Acutely Ill Adult ICU Patients

Design: international 7-day inception cohort study with prospective data collection

Inclusion criteria: adults

Exclusion criteria: patients with GI bleed upon admission or previous admitted to ICU within the same admission

Krag M, Perner A, Wetterslev J, et al. Prevalence and Outcome of Gastrointestinal Bleeding and Use of Acid Suppressants in Acutely Ill Adult Intensive Care Patients. *Intensive Care Med.* 2015;41:883-845. doi:10.1007/s00134-015-3725-1.

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Prevalence & Outcome of GI Bleeding & Use of Acid Suppressants in Acutely Ill Adult ICU Patients, *cont.*

Definitions:

- Overt GI bleeding- required at least one: **hematemesis,** coffee ground emesis, **melena, hematochezia**, or bloody NG aspirate.
- Clinically important GI bleeding- overt bleeding and at least one within 24 hours: decrease in BP of 20 mmHg or more, start of/increase of vasopressors of 20% or more, decrease in Hgb of at least 2 g/dL, transfusion of 2 or more units of red blood cells

Krag M, Perner A, Wetterslev J, et al. Prevalence and Outcome of Gastrointestinal Bleeding and Use of Acid Suppressants in Acutely Ill Adult Intensive Care Patients. *Intensive Care Med.* 2015;41:883-845. doi:10.1007/s00134-015-3725-1.

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Table 1 Baseline characteristics of patients

Characteristic	All (n = 1,034)	No clinically important bleeding (n = 1,007)	Clinically important bleeding (n = 27)	P[a]	Patients with missing values, n (%)[†]
Age, years, median (IQR)	63 (48–74)	64 (48–75)	58 (51–70)	0.324	0 (0.0)
Male, gender, n (%)	576 (55.7)	562 (55.8)	14 (51.9)	0.683	0 (0.0)
SOFA score, median (IQR)	6 (4–8)	6 (4–8)	10 (7–14)	<0.001	245 (23.4)
SAPS II, median (IQR)	42 (31–54)	41 (31–53)	52 (45–66)	<0.001	180 (17.4)
Chronic obstructive pulmonary disease, asthma or other chronic lung disease, n (%)	205 (19.8)	201 (20.0)	4 (14.8)	0.508	0 (0.0)
Previous myocardial infarction, n (%)	101 (9.8)	99 (9.8)	4 (14.8)	0.394	0 (0.0)
Severe chronic heart failure (NYHA 3–4), n (%)	56 (5.4)	54 (5.4)	2 (7.4)	0.643	0 (0.0)
Chronic renal failure, n (%)	74 (7.2)	72 (7.1)	2 (7.4)	0.959	0 (0.0)
Liver cirrhosis or increased bilirubin (>33 µmol/l), n (%)	124 (12.0)	110 (10.9)	14 (51.9)	<0.001	38 (3.7)
Metastatic cancer, n (%)	46 (4.4)	44 (4.4)	2 (7.4)	0.459	0 (0.0)
Active haematologic cancer, n (%)	36 (3.5)	34 (3.4)	2 (7.4)	0.260	0 (0.0)
AIDS, n (%)	3 (0.3)	3 (0.3)	0 (0)	0.776	0 (0.0)
Immunosuppression[b], n (%)	50 (4.8)	49 (4.9)	1 (3.7)	0.781	0 (0.0)
Coagulopathy on ICU admission[c], n (%)	128 (12.4)	118 (11.7)	10 (37.0)	<0.001	0 (0.0)
Comorbidities, n (%)					
0	501 (48.5)	496 (49.3)	5 (18.5)	0.002	0 (0.0)
1	318 (30.8)	308 (30.6)	10 (37.0)	0.474	0 (0.0)
2	153 (14.8)	147 (14.6)	6 (22.2)	0.271	0 (0.0)
3	46 (4.4)	41 (4.1)	5 (18.5)	0.005	0 (0.0)
>3	16 (1.5)	15 (1.5)	1 (3.7)	0.347	0 (0.0)
Mechanical ventilation on ICU admission, n (%)	544 (52.6)	527 (52.3)	17 (63.0)	0.275	0 (0.0)
Circulatory support on ICU admission, n (%)	469 (45.4)	450 (44.7)	19 (70.3)	0.009	7 (0.7)
Renal replacement therapy on ICU admission, n (%)	70 (6.8)	61 (6.1)	9 (33.3)	<0.001	0 (0.0)
Treatment with NSAID or acetylsalicylic acid prior to hospital admission, n (%)	210 (20.3)	206 (20.5)	4 (14.8)	0.472	0 (0.0)
Treatment with NSAID or acetylsalicylic acid initiated during present hospital admission prior to ICU admission, n (%)	70 (6.8)	68 (6.8)	2 (7.4)	0.894	0 (0.0)
Treatment with anticoagulant drugs prior to hospital admission, n (%)	134 (13.0)	130 (12.9)	4 (14.8)	0.771	0 (0.0)
Treatment with anticoagulant drugs initiated during present hospital admission prior to ICU admission, n (%)	81 (7.8)	77 (7.6)	4 (14.8)	0.171	0 (0.0)
Use of acid suppressants on ICU admission, n (%)	387 (37.4)	374 (37.1)	13 (48.1)	0.243	0 (0.0)

Krag M, Perner A, Wetterslev J, et al. Prevalence and Outcome of Gastrointestinal Bleeding and Use of Acid Suppressants in Acutely Ill Adult Intensive Care Patients. *Intensive Care Med.* 2015;41:883-845. doi:10.1007/s00134-015-3725-1.

Prevalence & Outcome of GI Bleeding & Use of Acid Suppressants in Acutely Ill Adult ICU Patients , *cont.*

Primary outcome- clinically important GI bleeding during ICU stay

- 27/1034 patients (incidence of 2.6%, 95% ci 1.6-3.6) developed clinically important bleeding

Secondary outcomes

- 90 day mortality rate
  - 25.4% without clinically important bleeding compared to 55.6% with clinically important bleeding
- Overt GI bleeding and mortality 90 days after inclusion association
  - Not statistically significant

Krag M, Perner A, Wetterslev J, et al. Prevalence and Outcome of Gastrointestinal Bleeding and Use of Acid Suppressants in Acutely Ill Adult Intensive Care Patients. *Intensive Care Med.* 2015;41:883-845. doi:10.1007/s00134-015-3725-1.

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Prevalence & Outcome of GI Bleeding and Use of Acid Suppressants in Acutely Ill Adult ICU Patients, *cont.*

Conclusion:

- Clinically important GI bleeding was not associated with increased adjusted 90-day mortality. Mortality can largely be explained through severity of comorbidity, other organ failures, and age.
- Unsure on overall benefit or harm with SUP?

Krag M, Perner A, Wetterslev J, et al. Prevalence and Outcome of Gastrointestinal Bleeding and Use of Acid Suppressants in Acutely Ill Adult Intensive Care Patients. *Intensive Care Med.* 2015;41:883-845. doi:10.1007/s00134-015-3725-1.

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Predictors of GI Bleeding in Adult ICU Patients

Design: systematic review and meta-analysis of retrospective and prospective cohorts

Primary outcome: Clinically important bleeding during ICU stay

- Effects of mechanical ventilation were unclear (3 studies, 484 events/73,379 patients, RE 1.93, 95% CI 0.57-6.5)
- Coagulopathy (2 studies, 60 events/3286 patients, RE 4.76, 95% CI 2.62-8.63)
- Shock (2 studies, 60 events/3286 patients, RE 2.6, 95% CI 1.25-5.42)
- Chronic liver disease (1 study, 27 events/1034 patients, RE 7.64, 95% CI 3.32-17.58)

Granholm A, Zeng L, Dionne J, et al. Predictors of Gastrointestinal Bleeding in Adult ICU Patients: a Systematic Review and Meta-Analysis. *Intensive Care Med.* 2091;45:1347-1359. doi.org/10.1007/s00134-019-05751-6.

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Predictors of GI Bleeding in Adult ICU Patients, *cont.*

Secondary outcome: overt GI bleeding during the stay

- Effects of mechanical ventilation were unclear (5 studies, 764 events/79324 patients, RE 1.11, 95% CI 0.64-1.91)
- Coagulopathy (2 studies, 82 events/3286 patients, RE 4.14, 95% CI 2.69-2.9)
- Shock (2 studies, 82 events/3286 patients, RE 2.56, 95% CI 1.44-4.54)
- Chronic liver disease (1 study, 49 events/1034 patients, RE 4.51, 95% CI 2.3-8.85)

Granholm A, Zeng L, Dionne J, et al. Predictors of Gastrointestinal Bleeding in Adult ICU Patients: a Systematic Review and Meta-Analysis. *Intensive Care Med.* 2091;45:1347-1359. doi.org/10.1007/s00134-019-05751-6.

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Back to the Guidelines!

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Role of Enteral Nutrition

“We suggest clinicians administer EN to reduce the clinically important stress-related UGIB in critically ill patients compared with no EN”

- Considered a conditional recommendation with moderate certainty of evidence

MacLaren R, Dionne J, Granholm A, et al. 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. *Crit Care Med*. 2024. doi:10.1097/CCM.0000000000006330.

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Role of Enteral Nutrition, *cont.*

"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."

- Considered a conditional recommendation with very low certainty of evidence

MacLaren R, Dionne J, Granholm A, et al. 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. *Crit Care Med*. 2024. doi:10.1097/CCM.0000000000006330.

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Role of Enteral Nutrition, *cont.*

"We suggest not using SUP for critically ill adults who are enterally fed and at low risk for clinically important stress related UGIB."

- Considered a conditional recommendation with very low certainty of evidence
- Potential concern that concurrent administration of SUP and EN may increase pneumonia risk

MacLaren R, Dionne J, Granholm A, et al. 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. *Crit Care Med*. 2024. doi:10.1097/CCM.0000000000006330.

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Enteral Nutrition Supporting Literature

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Predictors of GI Bleeding in Adult ICU Patients

One study in this meta-analysis demonstrated a decreased absolute risk of stress-related UGIB of 0.3% (95% CI 0.1-0.7%).

Granholm A, Zeng L, Dionne J, et al. Predictors of Gastrointestinal Bleeding in Adult ICU Patients: a Systematic Review and Meta-Analysis. *Intensive Care Med.* 2091;45:1347-1359. doi.org/10.1007/s00134-019-05751-6.

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Re-Evaluating the Utility of Stress Ulcer Prophylaxis in the Critically Ill Patient

Design: Meta-analysis of randomized controlled trials to assess PPIs or H2RAs compared to placebo with or without EN

Reynolds P, MacLaren, R. Re-Evaluating the Utility of Stress Ulcer Prophylaxis in the Critically Ill Patient: A Clinical Scenario-Based Meta-Analysis. *Pharmacotherapy*. 2019;39(3)408-420. doi:10.1002/phar.2172.

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Re-Evaluating the Utility of Stress Ulcer Prophylaxis in the Critically Ill Patient, *cont.*

CIB was defined as overt GI bleeding with at least one of the following:

- Reduction in MAP, SBP or DBP by 20 mmHg or greater within 24 hours absent of another cause
- Reduction in Hgb level of greater than or equal to 2 g/dL within 24 hours requiring at least 2 units in packed red blood cells
- Need for endoscopy or surgery to achieve hemostasis
- Failure of Hgb level to increase after transfusion
- Orthostatic increase in pulse rate of greater than or equal to 20 beats/min
- Decrease in SBP of greater than or equal to 10 mmHg
- Death attributed to GI bleeding

Reynolds P, MacLaren, R. Re-Evaluating the Utility of Stress Ulcer Prophylaxis in the Critically Ill Patient: A Clinical Scenario-Based Meta-Analysis. *Pharmacotherapy*. 2019;39(3)408-420. doi:10.1002/phar.2172.

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Re-Evaluating the Utility of Stress Ulcer Prophylaxis in the Critically Ill Patient, *cont.*

Primary outcome: evaluation of the effects of SUP on CIB

- SUP was associated with a significant reduction in relative risk of CIB (RR 0.53, 95% CI 0.37-0.76, p<0.001)
- Risk was reduced from 8.2% to 3.6%

Reynolds P, MacLaren, R. Re-Evaluating the Utility of Stress Ulcer Prophylaxis in the Critically Ill Patient: A Clinical Scenario-Based Meta-Analysis. *Pharmacotherapy*. 2019;39(3)408-420. doi:10.1002/phar.2172.

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Re-Evaluating the Utility of Stress Ulcer Prophylaxis in the Critically Ill Patient, *cont.*

Primary outcome: SUP on development of overt GI bleeding

- Overt GI bleeding was defined as one of the following:
  - Hematemesis
  - Bloody gastric aspirate
  - Melena
  - Hematochezia
- SUP significantly reduced relative risk of overt GI bleeding (RR 0.55, 95% CI 0.39-0.76, p=0.001)
- Risk reduced with SUP from 15.9% to 9.2%

Reynolds P, MacLaren, R. Re-Evaluating the Utility of Stress Ulcer Prophylaxis in the Critically Ill Patient: A Clinical Scenario-Based Meta-Analysis. *Pharmacotherapy*. 2019;39(3)408-420. doi:10.1002/phar.2172.

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Re-Evaluating the Utility of Stress Ulcer Prophylaxis in the Critically Ill Patient, *cont.*

Primary outcome: SUP on development for any GI bleeding

- Defined as overt GI bleeding plus CIB
- SUP significantly reduced relative risk of any GI bleeding (RR 0.54, 95% CI 0.41-0.71, p<0.001)
- Absolute risk reduced from 20% to 11%

Reynolds P, MacLaren, R. Re-Evaluating the Utility of Stress Ulcer Prophylaxis in the Critically Ill Patient: A Clinical Scenario-Based Meta-Analysis. *Pharmacotherapy*. 2019;39(3)408-420. doi:10.1002/phar.2172.

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Re-Evaluating the Utility of Stress Ulcer Prophylaxis in the Critically Ill Patient, *cont.*

Secondary outcomes

- SUP did not significantly increase risk of Clostridium difficile infection (Cdiff) or pneumonia.
- SUP did not significantly affect mortality.
- SUP significantly reduced CIB regardless of enteral nutrition (RR 0.57 with nutrition vs. 0.39 without, p=0.05).

Reynolds P, MacLaren, R. Re-Evaluating the Utility of Stress Ulcer Prophylaxis in the Critically Ill Patient: A Clinical Scenario-Based Meta-Analysis. *Pharmacotherapy*. 2019;39(3)408-420. doi:10.1002/phar.2172.

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SUP in the ICU Patients Receiving EN

Design: systematic review and meta-analysis

Inclusion criteria: RCTs of adult ICU patients receiving EN with SUP

Primary outcome: bleeding rate

- Bleeding rate was defined as overt GI bleedings or CIB
- SUP did not reduce the risk of GI bleeding in patients receiving EN (RR 0.8, 95% CI 0.49-1.31, p=0.96)

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. *Critical Care*. 2018;22(20). Doi:10.1186/s13054-017-1937-1.

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SUP in the ICU Patients Receiving EN, *cont.*

Secondary outcomes:

- No difference in overall mortality (RR 1.21, 95% CI 0.94-1.56, p=0.14)
- No difference in Cdiff infection (RR 0.89, 95% CI 0.29-3.19, p=0.86)
- No difference in ICU length of stay (mean difference 0.04 days, 95% CI -0.79-0.87, p=0.92)
- No difference in duration of mechanical ventilation (mean difference -0.38 days, 95% CI -1.48-0.72, p=0.5)

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. *Critical Care*. 2018;22(20). Doi:10.1186/s13054-017-1937-1.

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SUP in the ICU Patients Receiving EN, *cont.*

Secondary outcomes:

- Incidence of HAP was higher with SUP (RR 1.53, 95% CI 1.04-2.27, p=0.03)
- No difference in VAP (RR 1.24, 95% CI 0.72-2.15, p=0.44)

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. *Critical Care*. 2018;22(20). Doi:10.1186/s13054-017-1937-1.

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Quiz Time!

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Assessment Question #1

RH is a 45 yr old female admitted to ICU for diabetic ketoacidosis (DKA) and septic shock. RH was started on norepinephrine 0.5 mcg/kg/min and vasopressin 0.03 units/min along with broad spectrum antibiotics. Unfortunately, RH required intubation after resolution of DKA for agitation from alcohol withdrawal. Tube feeds were started after intubation. The intensivist asks if the patient qualifies for stress ulcer prophylaxis. Which of the following is correct?

A. Yes- SUP is required due to the patient requiring vasopressors and is in shock.
B. Yes- SUP is required due to the patient being in DKA.
C. No- SUP is not required as the patient is on tube feeds, which is sufficient even if the patient has risk factors for stress ulcers.
D. No- SUP is not required regardless of tube feeds as the patient does not have risk factors.

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Assessment Question #1 – Correct Answer

RH is a 45 yr old female admitted to ICU for diabetic ketoacidosis (DKA) and septic shock. RH was started on norepinephrine 0.5 mcg/kg/min and vasopressin 0.03 units/min along with broad spectrum antibiotics. Unfortunately, RH required intubation after resolution of DKA for agitation from alcohol withdrawal. Tube feeds were started after intubation. The intensivist asks if the patient qualifies for stress ulcer prophylaxis. Which of the following is correct?

A. Yes- SUP is required due to the patient requiring vasopressors and is in shock.

B. Yes- SUP is required due to the patient being in DKA.

C. No- SUP is not required as the patient is on tube feeds, which is sufficient even if the patient has risk factors for stress ulcers.

D. No- SUP is not required regardless of tube feeds as the patient does not have risk factors.

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Back to the Guidelines!

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Combating the Risk Factors

"We suggest clinicians provide SUP to prevent clinically important UGIB in critically ill adults with risk factors compared with no SUP."

- Considered a conditional recommendation with moderate certainty of evidence

MacLaren R, Dionne J, Granholm A, et al. 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. *Crit Care Med*. 2024. doi:10.1097/CCM.0000000000006330.

Combating the Risk Factors Supporting Literature

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Panel's Meta-Analysis

Compared SUP to control

Found PPIs reduced clinically important UGIB (RR 0.52, 95% CI 0.3-0.81)

No conclusive effects on following complications:

- Pneumonia (RR 1.14, 95% CI 0.93-1.54)
- Clostridioides difficile infection (RR 0.73, 95% CI 0.42-1.26)
- Mortality (RR 1.02, 95% CI 0.92-1.14)

H2RAs are also effective at preventing UGIB

MacLaren R, Dionne J, Granholm A, et al. 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. *Crit Care Med*. 2024. doi:10.1097/CCM.0000000000006330.

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Back to the Guidelines!

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Neurocritical Care Patients

"We suggest using SUP in neurocritical care adults to reduce clinically important stress-related UGIB compared with no SUP"

- Considered a conditional recommendation with very low certainty of evidence
- Reasoning: Physiological changes cause hypersecretion of gastric acid, which is an additional risk of UGIB.

MacLaren R, Dionne J, Granholm A, et al. 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. *Crit Care Med*. 2024. doi:10.1097/CCM.0000000000006330.

Neurocritical Care Patient Literature

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Risk & Benefits of SUP in Adult Neurocritical Care Patients

Design: systematic review of randomized controlled trials

Inclusion criteria: adult patients who received critical care for one of the following:

- **Traumatic brain injury**
- Subarachnoid hemorrhage
- **Intracranial hemorrhage**
- Ischemic stroke
- Anoxic brain injury
- Spinal cord injury
- Central nervous system infections
- Other acute neurological injuries

Liu B, Li S, Yin A, Siddiqi J. 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). Doi: 10.1186/s13054-015-1107-2.

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Risk & Benefits of SUP in Adult Neurocritical Care Patients, *cont.*

Primary outcome: UGIB

- SUP in neurocritical care patients resulted in lower incidence of UGIB compared to placebo (11% vs. 33%, random effects [RR] 0.31, 95% CI 0.2-0.47, p<0.00001)

Secondary outcomes:

- All-cause mortality
  - Statistically significant decrease for patients receiving SUP compared to placebo (23% vs. 30%, RR 0.7, 95% CI 0.5-0.98, p=0.04)

Liu B, Li S, Yin A, Siddiqi J. 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). Doi: 10.1186/s13054-015-1107-2.

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Risk & Benefits of SUP in Adult Neurocritical Care Patients, *cont.*

Secondary outcomes:

- Nosocomial pneumonia
  - Incidence was not greater between patients with SUP compared to placebo (20% vs. 17%, RR 1.14, 95% CI 0.67-1.94, p=0.16)

Conclusions:

- SUP may significantly lower right of UGIB and all-cause mortality in neurocritical care patients
- SUP in neurocritical care patients does not increase rate of nosocomial pneumonia

Liu B, Li S, Yin A, Siddiqi J. 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). Doi: 10.1186/s13054-015-1107-2.

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Prophylactic Acid Suppressants in Patients with Primary Neurologic Injury

Design: systematic review and meta-analysis of randomized controlled trials

Inclusion criteria: adult patients admitted to ICU for a primary neurological condition including:

- **Traumatic brain injury**
- Subarachnoid hemorrhage
- **Intracranial hemorrhage**
- Ischemic stroke
- Anoxic brain injury
- Spinal cord injury
- Central nervous system tumor
- Other acute neurological injuries

Daou M, Dionne J, Teng J, et al. Prophylactic Acid Suppressants in Patients with Primary Neurologic Injury: a Systematic Review and Meta-Analysis of Randomized Controlled Trials. *J. Crit. Care*. 2022. doi.org/10.1016/j.jcrc2022.154093.

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Prophylactic Acid Suppressants in Patients with Primary Neurologic Injury, *cont.*

Primary outcome- UGIB defined as **hematemesis**, coffee ground nasogastric aspirate, **melena**

- H2RAs resulted in lower incidence of UGIB (RR 0.42, 95% CI 0.3-0.58, p<0.001)
- PPIs also were associated with a lower incidence of UGIB (RR 0.37, 95% CI 0.23-0.59, p<0.001)
- No significant difference between PPIs and H2RAs in clinically important UGIB

Daou M, Dionne J, Teng J, et al. Prophylactic Acid Suppressants in Patients with Primary Neurologic Injury: a Systematic Review and Meta-Analysis of Randomized Controlled Trials. *J. Crit. Care*. 2022. doi.org/10.1016/j.jcrc2022.154093.

Prophylactic Acid Suppressants in Patients with Primary Neurologic Injury, *cont.*

Secondary outcomes:

- All-cause 30 day mortality
  - No statistically significant difference in all-cause mortality in patients receiving H2RAs compared to placebo (RR 0.77, 95% CI 0.55-1.07, p=0.12).
- Nosocomial pneumonia
  - Incidence was not statistically significant between patients receiving H2RAs compared to placebo (RR 1.12, 95% CI 0.66-1.91, p=0.68).
  - No difference between PPIs compared to H2RAs (17% vs. 15%, RR 1.08, 95% CI 0.56-2.08, p=0.82).
  - Too few trials to look at PPIs vs. placebo.

Daou M, Dionne J, Teng J, et al. Prophylactic Acid Suppressants in Patients with Primary Neurologic Injury: a Systematic Review and Meta-Analysis of Randomized Controlled Trials. *J. Crit. Care*. 2022. doi.org/10.1016/j.jcrc2022.154093.

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Quiz Time!

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Assessment Question #2

AK is a 80 yr male presenting to the ICU with a motor vehicle accident. The patient is found to have a traumatic brain injury. The patient is on mechanical ventilation but is not requiring vasopressor support. His past medical history includes diabetes, hyperlipidemia, hypertension, and seizures. How should the stress ulcer prophylaxis guidelines be applied to this patient?

A. Stress ulcer prophylaxis is recommended based on the patient requiring mechanical ventilation.

B. Stress ulcer prophylaxis is not recommended since the patient is not in shock.

C. The patient is considered neurocritical care, which is a risk factor. Stress ulcer prophylaxis would be recommended in this patient.

D. More information is needed to decide.

Assessment Question #2: Correct Response

AK is a 80 yr male presenting to the ICU with a motor vehicle accident. The patient is found to have a traumatic brain injury. The patient is on mechanical ventilation but is not requiring vasopressor support. His past medical history includes diabetes, hyperlipidemia, hypertension, and seizures. How should the stress ulcer prophylaxis guidelines be applied to this patient?

A. Stress ulcer prophylaxis is recommended based on the patient requiring mechanical ventilation.

B. Stress ulcer prophylaxis is not recommended since the patient is not in shock.

C. The patient is considered neurocritical care, which is a risk factor. Stress ulcer prophylaxis would be recommended in this patient.

D. More information is needed to decide.

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Back to the Guidelines!

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First Line Agents

"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."

- Considered a conditional recommendation with a moderate certainty of evidence.
- There is uncertainty regarding the influence of PPIs on mortality in patients with high severity of illness.

MacLaren R, Dionne J, Granholm A, et al. 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. *Crit Care Med*. 2024. doi:10.1097/CCM.0000000000006330.

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First Line Agent Literature

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Effects of SUP with PPIs vs. H2RAs on In-Hospital Mortality Among ICU Patients Receiving Mechanical Ventilation

Also known as the PEPTIC RCT

Design: International, open label, cluster crossover, registry embedded RCT comparing PPI vs. H2RA

Inclusion criteria: adult ICU patients requiring mechanical ventilation within 24 hours of ICU admission

Exclusion criteria: patients diagnosed with UGIB

Young P, Bagshaw S, Forbes A, et al. 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. *JAMA*. 2020;323(7)616-626. doi: 10.1001/jama.2019.22190.

Table 2. Primary, Secondary, and Tertiary Outcomes.

	Proton Pump Inhibitors	Histamine-2 Receptor Blockers	Estimate (95% CI)	Absolute Risk Difference (95% CI)	*P* Value
Primary Outcome					
Died at the hospital by 90 d, No./total No. (%)	2459/13 415 (18.3)	2333/13 356 (17.5)	RR, 1.05 (1.00 to 1.10)	0.93 (−0.01 to 1.88) percentage points	.054
Secondary Outcomes					
Types of complications, No./total No. (%)					
Clinically important upper gastrointestinal bleeding[a]	172/13 436 (1.3)	239/13 392 (1.8)	RR, 0.73 (0.57 to 0.92)	−0.51 (−0.90 to −0.12) percentage points	.009
Clostridioides difficile infection[b]	40/13 436 (0.30)	57/13 392 (0.43)	RR, 0.74 (0.51 to	−0.11 (−0.25 to 0.03) percentage	.13

Young P, Bagshaw S, Forbes A, et al. 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. *JAMA*. 2020;323(7)616-626. doi: 10.1001/jama.2019.22190.

	Proton Pump Inhibitors	Histamine-2 Receptor Blockers	Estimate (95% CI)	Absolute Risk Difference (95% CI)	*P* Value
Length of stay variables and duration of ventilation					
Days until discharged alive from the ICU					
No. of patients	13 425	13 384			
Median (interquartile range)[c]	3.6 (1.6 to 10.4)	3.3 (1.5 to 10.0)	ROM, 1.00 (0.97 to 1.03)[d]		.85
Days until discharged alive from the hospital					
No. of patients	13 418	13 370			
Median (interquartile range)[c]	12.2 (6.0 to 40.0)	12.0 (6.0 to 39.3)	ROM, 1.01 (0.98 to		.66

Young P, Bagshaw S, Forbes A, et al. 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. *JAMA*. 2020;323(7)616-626. doi: 10.1001/jama.2019.22190.

	Proton Pump Inhibitors	Histamine-2 Receptor Blockers	Estimate (95% CI)	Absolute Risk Difference (95% CI)	*P* Value
			1.03)[d]		
Tertiary Outcomes					
Hours until removed alive from mechanical ventilation					
No. of patients	6047	5438			
Median (interquartile range)	48.0 (12.1 to 271)	48.0 (14.3 to 265)	ROM, 0.98 (0.92 to 1.04)[d]		.43
Ventilator-associated conditions, No./total No. (%)[e]	143/2217 (6.5)	124/2148 (5.8)	RR, 1.18 (0.87 to 1.59)	1.11 (−0.89 to 3.11) percentage points	.28

Young P, Bagshaw S, Forbes A, et al. 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. *JAMA*. 2020;323(7)616-626. doi: 10.1001/jama.2019.22190.

Pantoprazole in Patients at Risk for GI Bleeding in the ICU

Also known as the SUP-ICU trial

Design: multicenter, stratified, parallel group, placebo controlled, blinded clinical trial

Inclusion criteria: adults admitted to ICU for acute condition with at least 1 risk factor for CIB

- Shock
- Use of anticoagulant agents
- Renal replacement therapy
- Mechanical ventilation (expected for 24 hours)
- Any history of liver disease
- Any history of or ongoing coagulopathy

Krag M, Marker S, Perner A, et al. Pantoprazole in Patients at Risk for Gastrointestinal Bleeding in the ICU. *NEJM*. 2018;379(23):2199-2208.

Pantoprazole in Patients at Risk for GI Bleeding in the ICU, *cont.*

Primary outcome: death by 90 days after randomization

- No difference between groups (RR 1.02, 95% CI 0.91-1.13, p=0.76)

Secondary outcomes:

- Clinically important events- including CIB, new onset pneumonia, Cdiff, acute myocardial ischemia
  - No significant difference (RR 0.96, 95% CI 0.83-1.11)

Krag M, Marker S, Perner A, et al. Pantoprazole in Patients at Risk for Gastrointestinal Bleeding in the ICU. *NEJM*. 2018;379(23):2199-2208.

Pantoprazole in Patients at Risk for GI Bleeding in the ICU, *cont.*

Secondary outcome

- CIB-defined as overt GI bleeding with at least one of the following within 24 hours of GI bleeding
  - Spontaneous decrease in SBP, MAP or DBP of 20 mmHg or more
  - Initiation of treatment with a vasopressor or 20% increase in vasopressor dose
  - Decrease in Hgb of at least 2 g/dL
  - Transfusion of 2 or more units of packed red cells
- 2.5% with PPI vs. 4.2% with placebo
- Adverse events- No difference (RR 0.99, 95% 0.84-1.16)
- Severe adverse reaction- Both groups reported 0
- Median percentage of days alive without use of life support- No difference

Krag M, Marker S, Perner A, et al. Pantoprazole in Patients at Risk for Gastrointestinal Bleeding in the ICU. *NEJM*. 2018;379(23):2199-2208.

Panel's Meta-Analysis

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 1-1.1).

There was a reduced incidence of UGIB with PPIs compared with H2RAs but possibly increased mortality.

MacLaren R, Dionne J, Granholm A, et al. 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. *Crit Care Med*. 2024. doi:10.1097/CCM.0000000000006330.

Back to the Guidelines!

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Route of Administration

"We suggest using either enteral or IV routes when administering SUP in critically ill adult patients with risk factors for clinically important stress-related UGIB compared with no enteral or IV routes."

- Considered a conditional recommendation with low certainty of evidence.

MacLaren R, Dionne J, Granholm A, et al. 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. *Crit Care Med*. 2024. doi:10.1097/CCM.0000000000006330.

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Good Practice Statements

"Low-dose SUP should be administered in critically ill adults with risk factors for clinically important stress-related UGIB compared with high dose SUP."

"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."

MacLaren R, Dionne J, Granholm A, et al. 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. *Crit Care Med*. 2024. doi:10.1097/CCM.0000000000006330.

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Good Practice Statements, *cont.*

"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."

"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."

MacLaren R, Dionne J, Granholm A, et al. 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. *Crit Care Med*. 2024. doi:10.1097/CCM.0000000000006330.

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Moving Forward…

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SUP During Invasive Mechanical Ventilation- 2024

Also known as the REVISE trial

Design: investigator-initiated, randomized blinded trial to compare PPI vs. placebo for 90 days or when mechanical ventilation stopped

Inclusion criteria: adults on invasive mechanical ventilation in the ICU

Exclusion criteria:

- Patients on mechanical ventilation 72 hours or more prior to randomization
- Received more than 1 daily dose equivalent of acid suppression in the ICU
- An indication or contraindication for acid suppression

Cook D, Deane A, Lauzier F, et al. Stress Ulcer Prophylaxis During Invasive Mechanical Ventilation. *NEJM*. 2024;391(1). Doi:10.1056/NEJMoa240245.

Table 2. Primary Efficacy and Safety Outcomes.

Outcome	Pantoprazole (N=2417)	Placebo (N=2404)	Absolute Difference (95% CI)	Hazard Ratio (95% CI)*	P Value
	no./total no. (%)		*percentage points*		
Primary efficacy outcome: clinically important upper gastrointestinal bleeding	25/2385 (1.0)	84/2377 (3.5)	2.5 (1.6 to 3.3)	0.30 (0.19 to 0.47)	<0.001
Primary safety outcome: 90-day mortality	696/2390 (29.1)	734/2379 (30.9)	1.7 (–0.9 to 4.3)	0.94 (0.85 to 1.04)	0.25

* Hazard ratios were adjusted for prehospital use of histamine 2–receptor antagonists or proton-pump inhibitors. Mortality analyses were also adjusted for the baseline APACHE II score.

Cook D, Deane A, Lauzier F, et al. Stress Ulcer Prophylaxis During Invasive Mechanical Ventilation. *NEJM*. 2024;391(1). Doi:10.1056/NEJMoa240245.

SUP During Invasive Mechanical Ventilation- 2024, *cont.*

Secondary outcomes

- VAP- 23.4% in PPI group vs. 23.8% in placebo group
- Cdiff- 1.2% in PPI group vs. 0.7% in placebo group
- Patient important GIB occurred less with PPI (1.5% vs. 4.2%, HR 0.36, 95% CI 0.25-0.53, p<0.001)
- No difference in mortality in ICU (20.3% with PPIs vs. 21.5%,HR 0.98, 95% CI 0.87-1.1, p=0.94)
- No difference in hospital mortality (26.3% with PPIs vs. 28.4%, HR 0.96, 95% CI 0.86-1.07, p=0.91)

Cook D, Deane A, Lauzier F, et al. Stress Ulcer Prophylaxis During Invasive Mechanical Ventilation. *NEJM*. 2024;391(1). Doi:10.1056/NEJMoa240245.

PPIs are Not Associated with an Increased Risk of Cdiff- 2025

Design: systematic review and meta-analysis of RCTs

Inclusion criteria: adult patients treated with PPI

Outcomes:

- No difference in risk of developing Cdiff (RR 1.19, 95% CI 0.75-1.89)
- No difference in developing Cdiff between PPI vs. H2RA (RR 0.72, 95% CI 0.49-1.07).

Floria DE, Obeidat M, Vancsa S, et al. Proton Pump Inhibitors are not Associated with an Increased Risk of *Clostridioides difficile* Infection: a Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Gut Microbes*. 2025;15(1). Doi.org/10.1080/19490976.2025.2562341.

Prophylactic PPI Use & All-Cause Mortality in Adult Sepsis Patients- 2025

Design: retrospective study using MIMIC database

Inclusion criteria: fulfillment of diagnostic criteria for sepsis 3.0 with either a suspected of confirmed infection alongside a sequential organ failure assessment (SOFA) score of 2 points or higher

Exclusion criteria:

- ICU stay of less than 24 hours
- Instances of non first time data from multiple ICU admissions
- Prior use of PPI before ICU admission
- Therapeutic use of PPIs post admission for other conditions

Ma C, Zhang L, Wang M, et al. Prophylactic Proton Pump Inhibitor Use and All-Cause Mortality in Adult Sepsis Patients: a Retrospective Analysis Based on the MIMIC-IV Database. *Front. Pharmacol*. 2025. doi:10.3389/fphar.2025.1545533.

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Prophylactic PPI Use & All-Cause Mortality in Adult Sepsis Patients- 2025, *cont.*

Results:

- Patients utilizing PPIs exhibited higher prevalence of complications including pneumonia, COPD, CHF, MI, renal disease, hepatic disease, diabetes and cancer.
- Patients receiving PPIs had a significantly greater proportion of mechanical ventilation, renal replacement therapy and ECMO ($p<0.001$).
- Increase risk of complexity and severity of patient conditions was seen among PPI users.
- Significant association between PPIs and all cause mortality within 90 days of admission to ICU (HR 0.74, 95% CI 0.64-0.82, $p<0.001$).
- Significant association was NOT seen between PPI and all cause mortality within 28 days of ICU admission ($P=0.910$).
- Mortality at 28 days was 18% vs. 25% at 90 days.

Ma C, Zhang L, Wang M, et al. Prophylactic Proton Pump Inhibitor Use and All-Cause Mortality in Adult Sepsis Patients: a Retrospective Analysis Based on the MIMIC-IV Database. *Front. Pharmacol*. 2025. doi:10.3389/fphar.2025.1545533.

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Prophylactic PPI Use & All-Cause Mortality in Adult Sepsis Patients- 2025, *cont.*

Subgroup analysis

- Significant interaction between disease severity (SOFA score) and PPI use in 28 day mortality
- Mechanical ventilation showed stronger interaction- concern that mechanical ventilation may increase short term risk of PPI.
- Mechanical ventilation risk continued at 90 days alongside lactic acid.
- Lactic acid metabolism disorders may be associated with the long term poor prognosis with PPIs.

Ma C, Zhang L, Wang M, et al. Prophylactic Proton Pump Inhibitor Use and All-Cause Mortality in Adult Sepsis Patients: a Retrospective Analysis Based on the MIMIC-IV Database. *Front. Pharmacol*. 2025. doi:10.3389/fphar.2025.1545533.

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Where Do We Go From Here?

REVISE trial made some clinicians resurrect the idea of mechanical ventilation still being a risk factor.

Important to consider patient population of REVISE compared to other trials

- REVISE patient population:
  - 100% on invasive mechanical ventilation
  - 70% receiving inotrope/vasopressor infusion
  - 6% on renal replacement therapy.
- SUP ICU patient population
  - 77% on invasive mechanical ventilation
  - 67% receiving inotrope/vasopressor infusion
  - 6-7% on renal replacement therapy

Brown, S. Uncertain Answers- Proton-Pump Inhibition in the ICU. *NEJM.* 2024;391(1):78-79.

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Where Do We Go From Here?, *cont.*

2024 Editorial- Uncertain Answer: PPI in the ICU

- SUP-ICU and PEPTIC suggest effects of PPIs on mortality may depend on severity of the patient's condition.
- Meta-analysis of REVISE and SUP-ICU confirmed a possible effect on mortality.
  - Suggest a decreased mortality among less severely ill patients?
- Author's conclusion was to consider mechanical ventilation a risk factor based on severity of illness (APACHE II score of less than 25).

Brown, S. Uncertain Answers- Proton-Pump Inhibition in the ICU. *NEJM.* 2024;391(1):78-79.

Where Do We Go From Here?, *cont.*

Consensus on definition of shock, chronic liver disease, neurocritical care and coagulopathy

Consensus on bleeding definition

Consensus of duration of SUP for the identified risk factors, especially chronic liver disease and neurocritical care

Future research needs to look severity of illness.

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Conclusions

Established risk factors from the guidelines requiring SUP include patients in shock, neurocritical care disease states, with chronic liver disease, or coagulopathy.

Clinicians should use the supporting literature for these recommendations to define these risk factors until formal definitions are created.

SUP is not one size fits all. Beyond the risk factors, clinicians should consider severity of illness.

PPIs may or may not influence on patient's mortality, but other commonly considered risks of pneumonia and Cdiff no longer are a concern.

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Quiz Time!

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Assessment Question #3

Three months later, AK is readmitted with diabetic ketoacidosis precipitated by a urinary tract infection. When admitted to the ICU, he has seizure-like activity. The intensivist intubated AK and started propofol. Based on the REVISE trial and the stress ulcer prophylaxis guidelines, should stress ulcer prophylaxis be started?

A. While the guidelines suggest mechanical ventilation alone is not a risk factor, the REVISE trial suggests that the severity of patient illness should be considered alongside mechanical ventilation.

B. The guidelines state mechanical ventilation is not a risk factor. The REVISE trial should not be considered until the guidelines are updated.

C. Based on the REVISE trial being published after the guidelines, all mechanically ventilated patients should have stress ulcer prophylaxis.

Assessment Question #3: Correct Response

Three months later, AK is readmitted with diabetic ketoacidosis precipitated by a urinary tract infection. When admitted to the ICU, he has seizure-like activity. The intensivist intubated AK and started propofol. Based on the REVISE trial and the stress ulcer prophylaxis guidelines, should stress ulcer prophylaxis be started?

A. **While the guidelines suggest mechanical ventilation alone is not a risk factor, the REVISE trial suggests that the severity of patient illness should be considered alongside mechanical ventilation.**

B. The guidelines state mechanical ventilation is not a risk factor. The REVISE trial should not be considered until the guidelines are updated.

C. Based on the REVISE trial being published after the guidelines, all mechanically ventilated patients should have stress ulcer prophylaxis.

References

Brown, S. Uncertain Answers- Proton-Pump Inhibition in the ICU. *NEJM.* 2024;391(1):78-79.

Cook D, Deane A, Lauzier F, et al. Stress Ulcer Prophylaxis During Invasive Mechanical Ventilation. *NEJM*. 2024;391(1). Doi:10.1056/NEJMoa240245.

Daou M, Dionne J, Teng J, et al. Prophylactic Acid Suppressants in Patients with Primary Neurologic Injury: a Systematic Review and Meta-Analysis of Randomized Controlled Trials. *J. Crit. Care*. 2022. doi.org/10.1016/j.jcrc2022.154093.

Floria DE, Obeidat M, Vancsa S, et al. Proton Pump Inhibitors are not Associated with an Increased Risk of *Clostridioides difficile* Infection: a Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Gut Microbes*. 2025;15(1). Doi.org/10.1080/19490976.2025.2562341.

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Krag M, Perner A, Wetterslev J, et al. Prevalence and Outcome of Gastrointestinal Bleeding and Use of Acid Suppressants in Acutely Ill Adult Intensive Care Patients. *Intensive Care Med.* 2015;41:883-845. doi:10.1007/s00134-015-3725-1.

Liu B, Li S, Yin A, Siddiqi J. 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). Doi: 10.1186/s13054-015-1107-2.

Ma C, Zhang L, Wang M, et al. Prophylactic Proton Pump Inhibitor Use and All-Cause Mortality in Adult Sepsis Patients: a Retrospective Analysis Based on the MIMIC-IV Database. *Front. Pharmacol*. 2025. doi:10.3389/fphar.2025.1545533.

MacLaren R, Dionne J, Granholm A, et al. 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. *Crit Care Med*. 2024. doi:10.1097/CCM.0000000000006330.

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Young P, Bagshaw S, Forbes A, et al. 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. *JAMA*. 2020;323(7)616-626. doi: 10.1001/jama.2019.22190.

Thank you!!

Rebecca Hilton, PharmD, BCCCP
Critical Care Pharmacy Specialist
Mercy Hospital Southeast

Rebecca.Hilton@mercy.net

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Your life is our life's work.