UMKC
School of Pharmacy
Drug Information Center

UMKC Drug Information Center
2464 Charlotte Street, Suite 1220
Kansas City, MO 64108

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Dr. ,

Thank you for your question regarding the use of stress ulcer prophylaxis (SUP) in intensive care unit (ICU) patients. Several guidelines provide information for the indication and use of SUP in this patient population.

- The 2014 Guidelines for Stress Ulcer Prophylaxis in the Intensive Care Unit recommend not using SUP routinely for adult ICU patients[1]
    - If SUP is indicated, proton pump inhibitors (PPIs) should be used over histamine 2 receptor antagonists (H2RAs)
- The 2020 Gastrointestinal Bleeding Prophylaxis for Critically Ill Patients: A Clinical Practice Guideline suggests using SUP in patients with higher risk of gastrointestinal (GI) bleeding (4% or higher)[2]
    - Mechanical ventilation or chronic liver disease (8-10% risk)
    - Coagulopathy or 2 or more risk factors from the 2-4% range (4-8% risk)
- The 2021 Surviving Sepsis Guidelines suggest using stress ulcer prophylaxis in adult patients with sepsis or septic shock with risk factors for GI bleeding.[3]
    - Downgraded recommendation from the previous version of this guideline, which was a strong recommendation[4]

Unfortunately, this treatment regimen has several guidelines with slightly different recommendations for treatment. Recent literature has provided mixed results on the efficacy of either PPIs or H2RAs in critically ill patients. These studies use inclusion criteria that generally mimic the guideline recommendations.

In 2018, Krag et al[5] published the results of the Stress Ulcer Prophylaxis in the Intensive Care Unit (SUP-ICU); this was a randomized, double-blind, placebo-controlled study in Europe. SUP-ICU aimed to evaluate if the use of pantoprazole in patients at high risk for GI bleeding in the ICU would reduce the risk of death 90 days after initiation.

- Eligible patients were adults admitted to the ICU with a least one risk factor for clinically important GI bleeding, defined as shock, use of anticoagulant agents, renal-replacement therapy, mechanical ventilation, history of liver disease, or history of ongoing coagulopathy.
- The use of daily intravenous pantoprazole (n=1664) was not associated with a reduction in death 90 days after initiation when compared to matching intravenous placebo (n=1647)
    - 510 deaths (31.1%) in pantoprazole group vs. 499 deaths (30.4%) in placebo group
    - RR 1.02, 95% CI [0.91 to 1.13]; p=0.76

Based on the results from SUP-ICU, Zhou et al[6] performed a meta-analysis of 11 studies, involving 4,521 patients, with reported data on clinically important GI bleeding.

- These trials had to include adult, ICU patients receiving either a H2RA or PPI versus placebo or no treatment.
- Primary endpoint: SUP was associated with a statistically significant decrease risk of clinically important GI bleeding
    - RR 0.58, 95% CI [0.42 to 0.81]; p=0.001; i^2=0%
        - PPIs (6 trials): RR 0.61, 95% CI [0.43 to 0.88]; p=0.008; i^2=0%
        - H2RAs (6 trials): RR 0.45, 95% CI [0.17 to 1.22]; p=0.116, i^2=42.6%
- Secondary endpoint: All-cause mortality did not show statistical significance between groups
    - RR 1.01, 95% CI [0.93 to 1.09]; p=0.842

The PEPTIC investigators[7] performed an open-label, multinational, cluster crossover trial comparing the use PPIs and H2Ras. The goal was to compare the risk of in-hospital all-cause mortality, up to 90 days after treatment initiation, between the two classes.

- Study participants had to be mechanically ventilated, adult ICU patients.
- 50 ICUs were randomized in a 1:1 fashion to use either a PPI or H2RA for 6-months before crossing over; however, patients could use either a PPI or H2RA regardless of ICU randomization at the discretion of the clinician.
- In total, 13,436 patients assigned to PPIs and 13,392 assigned to H2RAs by default were analyzed.
- The use of either agent was not associated with a statistically significant reduction in-hospital all-cause mortality.
    - 2459 deaths (18.3%) in PPI group vs. 2333 deaths (17.5%) in H2RA group
    - RR 1.05, 95% CI [1.00 to 1.10]; absolute risk difference 0.93, 95% CI [-0.01 to 1.88]; p=0.054

The use of SUP in ICU patients should be considered for each patient on an individual basis based on protocols in place at each health system. Overall, critical illness alone does not qualify a patient for SUP unless they have other risk factors present due to the risk of negative outcomes with unnecessary use.

Risk factors that indicate patients for SUP include:

- Most common[8]
    - Mechanical Ventilation for more than 48 hours
    - Coagulopathy (platelets <50,000 per m^3, INR >1.5, or PTT >2x normal value)
- Additional Factors[9–14]
    - Shock
    - Sepsis
    - Hepatic Failure
    - Renal failure and renal replacement therapy
    - History of peptic ulcer disease
    - History of upper GI bleeding
    - Three or more coexisting diseases
    - Extracorporeal life support
    - Multiple trauma, head trauma, spinal trauma
    - Burns over 35% of total BSA

    - Organ transplantation
    - Antiplatelet agents
    - NSAIDs
- Conflicting evidence
    - Glucocorticoid therapy[15]
    - *Helicobacter pylori*[16,17]
    - Enteral nutrition[18–22]

Please let us know if we can help you with anything else.

Sincerely,

Vance Howerton, PharmD Candidate 2022
UMKC Drug Information Center

References:

1. Madsen KR, Lorentzen K, Clausen N, et al. Guideline for Stress Ulcer Prophylaxis in the Intensive Care Unit. *Dan Med J*. 2014;61(3):C4811.
2. Ye Z, Reintam Blaser A, Lytvyn L, et al. Gastrointestinal bleeding prophylaxis for critically ill patients: a clinical practice guideline. *BMJ*. Published online January 6, 2020:l6722. doi:10.1136/bmj.l6722
3. Evans L, Rhodes A, Alhazzani W, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021. *Intensive Care Med*. 2021;47(11):1181-1247. doi:10.1007/s00134-021-06506-y
4. Rhodes A, Evans LE, Alhazzani W, et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. *Crit Care Med*. 2017;45(3):486-552. doi:10.1097/CCM.0000000000002255
5. Krag M, Marker S, Perner A, et al. Pantoprazole in Patients at Risk for Gastrointestinal Bleeding in the ICU. *N Engl J Med*. 2018;379(23):2199-2208. doi:10.1056/NEJMoa1714919
6. Zhou X, Fang H, Xu J, et al. Stress ulcer prophylaxis with proton pump inhibitors or histamine 2 receptor antagonists in critically ill adults - a meta-analysis of randomized controlled trials with trial sequential analysis. *BMC Gastroenterol*. 2019;19(1):193. doi:10.1186/s12876-019-1105-y
7. The PEPTIC Investigators for the Australian and New Zealand Intensive Care Society Clinical 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(7):616-626. doi:10.1001/jama.2019.22190
8. Cook DJ, Fuller HD, Guyatt GH, et al. Risk Factors for Gastrointestinal Bleeding in Critically Ill Patients. *N Engl J Med*. 1994;330(6):377-381. doi:10.1056/NEJM199402103300601
9. Shuman RB, Schuster DP, Zuckerman GR. Prophylactic Therapy for Stress Ulcer Bleeding: A Reappraisal. *Ann Intern Med*. 1987;106(4):562-567. doi:10.7326/0003-4819-106-4-562
10. 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(5):833-845. doi:10.1007/s00134-015-3725-1
11. Cook DJ. Stress Ulcer Prophylaxis: Gastrointestinal Bleeding and Nosocomial Pneumonia Best Evidence Synthesis. *Scand J Gastroenterol*. 1995;30(sup210):48-52. doi:10.3109/00365529509090271

12. Martin LF, Booth FV, Reines HD, et al. Stress ulcers and organ failure in intubated patients in surgical intensive care units. *Ann Surg*. 1992;215(4):332-337.
13. Hatton J, Lu WY, Rhoney DH, Tibbs PA, Dempsey RJ, Young B. A step-wise protocol for stress ulcer prophylaxis in the neurosurgical intensive care unit. *Surg Neurol*. 1996;46(5):493-499. doi:10.1016/s0090-3019(96)00245-5
14. McBride DQ, Rodts GE. Intensive care of patients with spinal trauma. *Neurosurg Clin N Am*. 1994;5(4):755-766.
15. Daley RJ, Rebuck JA, Welage LS, Rogers FB. Prevention of stress ulceration: current trends in critical care. *Crit Care Med*. 2004;32(10):2008-2013. doi:10.1097/01.ccm.0000142398.73762.20
16. Maury E, Tankovic J, Ebel A, Offenstadt G, Parisian Group of the Upper Gastrointestinal Bleeding Survey. An observational study of upper gastrointestinal bleeding in intensive care units: is Helicobacter pylori the culprit? *Crit Care Med*. 2005;33(7):1513-1518. doi:10.1097/01.ccm.0000168043.60624.3e
17. Robertson MS, Cade JF, Clancy RL. Helicobacter pylori infection in intensive care: increased prevalence and a new nosocomial infection. *Crit Care Med*. 1999;27(7):1276-1280. doi:10.1097/00003246-199907000-00010
18. Pingleton SK, Hadzima SK. Enteral alimentation and gastrointestinal bleeding in mechanically ventilated patients. *Crit Care Med*. 1983;11(1):13-16. doi:10.1097/00003246-198301000-00005
19. Raff T, Germann G, Hartmann B. The value of early enteral nutrition in the prophylaxis of stress ulceration in the severely burned patient. *Burns J Int Soc Burn Inj*. 1997;23(4):313-318. doi:10.1016/s0305-4179(97)89875-0
20. Cook D, Heyland D, Griffith L, Cook R, Marshall J, Pagliarello J. Risk factors for clinically important upper gastrointestinal bleeding in patients requiring mechanical ventilation. Canadian Critical Care Trials Group. *Crit Care Med*. 1999;27(12):2812-2817. doi:10.1097/00003246-199912000-00034
21. Marik PE, Vasu T, Hirani A, Pachinburavan M. Stress ulcer prophylaxis in the new millennium: a systematic review and meta-analysis. *Crit Care Med*. 2010;38(11):2222-2228. doi:10.1097/CCM.0b013e3181f17adf
22. Huang HB, Jiang W, Wang CY, Qin HY, Du B. Stress ulcer prophylaxis in intensive care unit patients receiving enteral nutrition: a systematic review and meta-analysis. *Crit Care Lond Engl*. 2018;22(1):20. doi:10.1186/s13054-017-1937-1