Pharmacological prevention of gastrointestinal bleeding in critically ill patients

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Purpose of review
Despite advances in critical care medicine, the incidence of clinically important upper gastrointestinal bleeding (UGIB) remains consistent. One therapy that reduces UGIB is the use of stress ulcer prophylaxis (SUP). In the past year, several key manuscripts have been published regarding SUP, providing updated recommendations for its prescription. In this review, we provide commentary on these recommendations and areas for future research.

Recent findings
Risk factors for UGIB include chronic liver disease, coagulopathy, severe neurologic illness or injury, and shock. The prescription of SUP is associated with a decreased occurrence of UGIB but no benefit in mortality. Although both histamine-2 receptor antagonists and proton pump inhibitors (PPIs) are recommended for SUP, it is possible that PPIs may be associated with increased mortality in critically ill patients. The short-term use of SUP is not expected to be associated with most adverse drug events, but inappropriate continuation of SUP increases this risk.

Summary
Patient-specific considerations based on recent data help with improving the prescription of SUP, although additional research is necessary. The use of artificial intelligence may be able to predict at risk patients with the potential to influence appropriate prescription of SUP and reduce the occurrence of UGIB.

Keywords
adverse drug event, critical illness, gastrointestinal agents, gastrointestinal hemorrhage, stress ulcer prophylaxis

INTRODUCTION

Critically ill patients are at risk for clinically important stress-related upper gastrointestinal bleeding (UGIB) caused by gastrointestinal hypoperfusion, reperfusion injury, and a breakdown of the network of defenses that protect the gastric epithelium [1▪▪]. Data from the 1990s indicate an incidence of UGIB of approximately 1.5–3.5%, which has not changed considerably despite advances in the management of critically ill patients such as aggressive resuscitation, initiation of enteral nutrition, and monitoring of global tissue perfusion [2,3▪▪]. Stress ulcer prophylaxis (SUP) therefore has been and remains a cornerstone of pharmacotherapy in the ICU in patients at risk for UGIB.

SUP is provided with gastric acid-lowering therapies [e.g., histamine-2 receptor antagonists (H2RAs), proton pump inhibitors (PPIs)] to counteract the unchecked acid that occurs with the degradation of the mucosal barrier and loss of GI integrity. SUP has been associated with reductions in UGIB rates but no differences in intensive care unit (ICU) length of stay or mortality. Recently, there has been concern with the widespread use of PPI's, particularly in the subgroup of ICU patients with severe critical illness, due to a possible signal for increased mortality. The purpose of this review is to provide commentary on recent published literature involving SUP and areas for future research.

EVIDENCE-BASED RECOMMENDATIONS

Guidelines for SUP in critically ill patients were first published in 1998 [2]. Subsequent guidelines in critical illness, focused on SUP and general ICU

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KEY POINTS

- Despite advances in the management of critically ill patients, the incidence of clinically important upper gastrointestinal bleed (UGIB) has remained stable.
- In patients at risk for UGIB, stress ulcer prophylaxis (SUP) is associated with a reduction in UGIB but no benefit in mortality
- Although either histamine-2 receptor antagonists or proton pump inhibitors (PPIs) are recommended for SUP, the use of PPIs may be associated with increased mortality in the most critically ill patients.
- Inappropriate continuation of SUP occurs in up to 70% of patients on ICU discharge and up to 40% of patients on hospital discharge.
- The risk of adverse drug events therapy is mostly associated with long-term use which should be avoided for the purpose of SUP.

patients, include those published by the Danish Society of Intensive Care Medicine in 2014 and BMJ Rapid Recommendations published in 2020 [4,5]. The most recent evidence-based guidelines are the 2024 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 [1▪▪]. The recommendations from these guidelines are summarized in Table 1, which shows how the management of SUP has progressed over the years. The most significant differences involve risk factors for UGIB and the recommended choice of agent. The most recent guidelines used GRADE methodology to provide updated recommendations on many aspects of SUP. Commentary on these recommendations as they relate to key SUP-related questions is described below, along with other important literature updates published after the guideline review [6▪].

Literature evaluating the use of adverse drug events

The 2024 guidelines suggest SUP be provided to critically ill patients who are at risk for clinically important UGIB. Clinically important bleeding is commonly defined as overt bleeding plus hemodynamic compromise leading to therapeutic interventions (e.g., decrease in mean arterial pressure, need for vasopressor support, a decrease in hemoglobin, and/or a requirement for blood transfusion). This recommendation was based on a network meta-analysis which reported a reduction in clinically important UGIB [relative risk (RR) 0.52, 95% confidence interval (CI) 0.3–0.81] but nonconclusive evidence on mortality, pneumonia, or Clostridium difficile infection. Following these guidelines were two pivotal publications evaluating the role of SUP versus no SUP.

The first was a large randomized controlled trial, known as REVISE, comparing intravenous pantoprazole to placebo in mechanically ventilated patients [6▪]. In this trial, they found a reduction in the adjudicated primary efficacy outcome of UGIB with pantoprazole compared to placebo (HR 0.3, 95% CI 0.19–0.47) but no overall difference in mortality (HR 0.94, 95% CI 0.85–1.04). REVISE also included a secondary outcome of 'patient-important UGIB'. This definition was created through interviews of ICU survivors and their families incorporating variables they considered important [7]. Similar to the primary outcome, the authors found that PPIs were deemed to be beneficial (HR 0.36, 95% CI 0.25–0.53) for this patient-important outcome. The second recent publication was a systematic review and meta-analysis of randomized trials comparing the efficacy and safety of PPIs for SUP. There were 12 trials, including REVISE, which evaluated a total of 9533 patients. PPI therapy was associated with a significant reduction in UGIB (RR 0.51, 95% CI 0.34–0.76) but no difference in mortality (RR 0.99, 95% CI 0.93–1.05) or infectious complications (pneumonia, *Clostridium difficile*) was noted. Collectively, these data reveal SUP can provide a benefit in reducing UGIB but have no benefit for mortality. Nevertheless, UGIB can be associated with significant morbidity and lead to deleterious effects that patients consider important. Clinicians should continue to provide SUP to critically ill patients considered at high risk for clinically important UGIB.

Risk factors for upper gastrointestinal bleeding

The 2024 guidelines provided four potential risk factors for UGIB with recommendations for SUP in adult patients with a noted removal of invasive mechanical ventilation as a risk factor [1▪▪]. This change was based on a meta-analysis, finding that shock, coagulopathy (unrelated to anticoagulation), and chronic liver disease were associated with increased relative risk of 2.6%, 4.8%, and 7.6% for UGIB, respectively. Neurocritical care patients, which may have alterations in physiology leading to hypersecretion of gastric acid were also identified at risk for UGIB. In a systematic review of 14 trials, both PPIs and H2RAs were associated with a lower incidence of UGIB compared to placebo (PPI: RR 0.37, 95% CI 0.23–0.59; H2RA: RR 0.42, 95% CI 0.3–

Table 1. Comparison of SUP Guideline Recommendations

Recommendations	ASHP 1998	DASAIM/DSIT 2014	BMJ rapid recommendations 2020	SCCM/ASHP 2024
Risk factors for UGIB	- Coagulopathy - Mechanical ventilation >48 hr - GI ulcer or bleeding within one year AND at least two of following o Sepsis o ICU stay >1 week o Occult bleed >6 days o Equivalent of HCT >250 mg/d - GCS ≤10 (or inability to follow simple commands) - Hepatic failure - Multiple trauma - Partial hepatectomy - Peri-op transplantation - Spinal cord injury - Thermal injury >35% of BSA	- Not assessed	• Highest risk o Mechanical ventilation without enteral nutrition o Chronic liver[a] disease • High risk o Coagulopathy[b] o Two or more risk factors from 'Moderate risk' group • Moderate risk o Acute kidney o injury o Mechanical ventilation with enteral nutrition o Sepsis Shock	- Chronic liver disease[a] - Coagulopathy[b] - Neurocritical care - Shock [all CR; L to M]
Enteral nutrition	- No specific recommendation	- Insufficient evidence to provide recommendation	- Not assessed	- Suggest initiation to reduce occurrence [CR; VL] - Suggest SUP even if enteral nutrition and at least one risk factor [CR; VL]
Choice of agent	- Choice of antacid, H2RA, or sucralfate dependent on institution practices - Based on available data and pharmacoeconomic evaluation, sucralfate recommended if enteral access available (over H_2RA) - Limited evidence for misoprostol or PPIs	- Suggest PPI [WR; Grade 2C]	- Suggest PPI [WR; L] - Sucralfate not recommended [SR]	- Suggest either H_2RA or PPI [CR; M] - Suggest low-dose therapy (over high-dose) [GPS]
Route of medication	Enteral preferred (if available)	- Not assessed	- Not assessed (statement: '… there is no evidence to suggest that the route of administration alters effectiveness.')	- Suggest enteral or IV route [CR; L]
Discontinuation	- Suggest discontinuation when risk factor is no longer present	- Not assessed	- No specific recommendation but stated that clinician should stop SUP when '… patient is no longer critically ill or the risk factor triggering prophylaxis is no longer present.'	- Suggest discontinuation when risk factor is no longer present [GPA]

[a]Defined as platelet count $<50\times10^9$/l, or international normalized ratio >1.5 or prothrombin time >20 s that is unrelated to anticoagulant therapy.
[b]Defined as any of: portal hypertension, cirrhosis diagnosed by biopsy, computed tomography scan or ultrasound, history of variceal bleeding or hepatic encephalopathy.
ADE, adverse drug events; BSA, body surface area; CR, conditional recommendation; DASAIM, Danish Society of Anesthesiology and Intensive Care Medicine; DSIT, Danish Society of Intensive Care Medicine; GCS, Glasgow Come Scale; GI, gastrointestinal; GPS, Good Practice Statement; H2RA, histamine-2 receptor antagonist; IV, intravenous; L, low quality of evidence; L to M, low to moderate quality of evidence; M, moderate quality of evidence; PPI, proton pump inhibitor; SR, strong recommendation; SUP, stress ulcer prophylaxis; UGIB, upper gastrointestinal bleed; VL, very low quality of evidence; WR, weak recommendation.

0.58) but a high degree of bias and uncertainty was present [8]. Furthermore, the populations included in these trials primarily consisted of patients with severe neurologic injury which must be considered when generalizing to other neurocritically ill patients.

The most notable change regarding risk factors was the lack of significance for respiratory failure (e.g., need for mechanical ventilation > 48 h) as an independent predictor of UGIB. Respiratory failure has long been regarded as a major risk factor for UGIB and the use of mechanical ventilation as an indication for SUP in prior trials is common. In fact, in the two largest randomized controlled trials conducted to date (SUP-ICU and REVISE), mechanical ventilation was required in 79% and 100% of patients, respectively [6▪,9]. These trials both demonstrated benefit with SUP on UGIB but it is difficult to determine the contribution of mechanical ventilation as a risk factor given shock was also widely present in these patient cohorts (approximately 70%). Nevertheless, mechanical ventilation was

not proposed as a surrogate for critical illness and not a risk factor in of itself. Future studies are needed to determine the role of respiratory failure as a risk factor for UGIB.

Choice of therapy for stress ulcer prophylaxis

The choice of therapy for SUP fluctuates currently between H2RAs and PPIs and the 2024 guidelines recommend as first-line therapy. PPIs are associated with lower rates of clinically important UGIB compared to H2RAs but there is considerable debate surrounding their possible association with mortality, specifically in patients with more severe critical illness.

In a subgroup analysis of the SUP-ICU trial, which evaluated the effects of pantoprazole compared to placebo on 90-day outcomes, there was significant heterogeneity of treatment effect based on severity of illness using a Simplified Acute Physiology Score (SAPS) II score threshold of 53 (RR 1.13, 95% CI 0.99–1.30) [9]. Similarly, the PEPTIC trial, which compared PPIs with H2RAs, found a significant interaction between PPI therapy and in-hospital mortality by APACHE II score quartile [10]. Subgroup analyses from the REVISE trial though found no difference in 90-day mortality between PPI therapy and placebo when evaluating the effect of severity of illness using the Acute Physiology and Chronic Health Evaluation (APACHE) II score threshold of $\geq$25 [6▪]. A subsequent meta-analysis of randomized controlled trials ($n = 12$) comparing PPIs to placebo for SUP found that PPI use may be associated with increased mortality in more severely ill patients (RR 1.08, 95% CI 0.96–1.2), while decreasing mortality in less severely ill patients (RR 0.89, 95% CI 0.8–0.98) [3▪▪,6▪,9]. Notably, this was based on the SUP-ICU and REVISE trials, which used different severity of illness scores, although the thresholds used are roughly comparable in terms of expected mortality. The cause for this increased mortality in more severely ill patients is unknown, one potential explanation is the impact of PPIs on the gut microbiome, which helps the body's fight critical illness such as sepsis [11,12].

Drug interactions pose another potential challenge, most often with PPIs compared to H2RAs. Due to their more profound impact on gastric pH than H2RAs, PPIs may interfere with absorption of certain medications (e.g., atazanavir, itraconazole, posaconazole, rilpivirine) dependent on the formulation used [13,14]. However, the clinical significance of these interactions is variable by patient population studied, although often does not include critically ill patients. Specific recommendations for management include spacing administration of PPIs from these medications, diluting in an acidic beverage, or the use of alternative medications as therapy, including for SUP. Drug interactions that may require a change from PPIs include high-dose methotrexate, which leads to delayed clearance of methotrexate and potential toxicity, and tyrosine kinase inhibitors (TKIs), where PPIs have been associated with increased mortality due to the decrease absorption of TKIs. There is also controversy on the clinical relevance of the drug–drug interaction between omeprazole and clopidogrel, with inconsistent effects on clinical outcomes [15].

Overall, the choice between H2RA and PPI for SUP should be dependent on patient-specific factors, including perceived risk for UGIB, severity of illness, institutional formulary, and clinically significant drug–drug interactions. Given the signal for increased mortality with the use of PPIs for SUP in the most critically ill patients, such as those with septic shock, the use of H2RAs may be preferred in this population, although there are limited data to support this association. Future studies should further evaluate this association, such as evaluating subgroups by presence of septic shock, where the intestinal microbiota is important for host defenses.

Cessation of pharmacologic prevention

SUP therapy should be discontinued when the patient no longer has risk factors for UGIB while critically ill. Therefore, the use of therapy for SUP is intended to be a short course while patients are in the ICU with risk factors for UGIB (e.g., median 5 days of therapy in REVISE trial) [6▪]. Appropriate discontinuation of therapy is recommended due to potential adverse drug events (ADEs) that SUP can cause, which are summarized in Table 2 and include data from ICU patients that were initiated on SUP, as well as chronic use in insurance claims databases. This table provides the potential mechanism for these ADEs, as well as potential time of ADE onset, although limited data were available on time to onset. Many of these ADEs are attributed to long-term use so deprescribing is important and confirmation of cessation during the medication reconciliation upon transfer/discharge.

Data suggest that SUP is often inappropriately continued (i.e., not home medication, no longer at risk for UGIB) upon ICU discharge, as well as at hospital discharge. Data suggest that the rate of inappropriate continuation upon ICU discharge occurs in up to 70% of patients, while inappropriate continuation on hospital discharge occurs in up to 44% of patients [16▪,17]. Interventions that have been successful at decreasing this incidence includes pharmacist-led or interprofessional efforts to

Table 2. Summary of reported adverse effects of H2RAs and PPIs used for SUP

Adverse effect	Established/potential mechanism(s)	Time frame to ADE	Supporting literature	Comments
H2RAs				
Delirium	Effect of H2RA on H2 receptors in brain leading to decrease neural cholinergic stimulation	ICU (unknown LOS)	Shiddapur A *et al.* Crit Care Explor 2021;3:e0507.	Higher RR of delirium with H2RA after controlling for age, ventilation status Age: RR 1.15 (95% CI 1.07–1.24) MV: RR 1.36 (95% CI 1.25–1.47)
Vitamin B12 deficiency	Decreased dietary absorption due to decreased gastric pH	2+ years of therapy (no association with increased duration)	Lam JR *et al.* JAMA 2013;310:2435–42.	OR 1.25 (95% CI 1.17–2.15)
PPIs				
Acute kidney injury	Unclear, proposed mechanisms include: - Calcium overload - Direct nephrotoxin - Hapten/IC - Hypomagnesemia - Induced cell necrosis - Oxidative stress and mitochondrial damage - Pyroptosis	No association found in posthospitalization risk of AKI	Zhang Y, *et al.* BMC Nephrol 2023;24:150.	RR 0.91 (95% CI 0.38–1.45)
		Not reported (meta-analysis)	Han CT *et al.* J Clin Med 2023;12:2467.	aRR 1.75 (95% CI 1.4–2.19)
		17.5 months (posthospital discharge)	Zhang *et al.* BMC Nephrology 2023;24:150.	RR (0.91, 95% CI 0.38–1.45)
		Not reported (within one year of hospital discharge)	Palmowski L *et al.* Crit Care Med 2024;52:190–9.	AIN: OR 1.21 (0.70–2.06)
Cardiovascular events (unclear definition)	- Impaired activity of dimethylarginine dimethylaminohydrolase → ↑ plasma asymmetric dimethylarginine levels → ↓ nitric oxide - Impaired function of proton pumps in endothelial cell lysosomes → disturbances of proteostasis → acceleration of endothelial aging - Reduced calcium, magnesium absorption	Not reported (within one year of hospital discharge)	Palmowski L *et al.* Crit Care Med 2024;52:190–9.	OR 1.17 (95% CI 1.08–1.26)
Clostridium difficile	Alterations in intestinal microbiota	ICU (median LOS 6 days)	Krag M *et al.* N Engl J Med 2018;379:2199–2208.	RR 0.76 (95% CI 0.42–1.39)
		Not reported (meta-analysis)	D'Silva KM *et al.* Clin Microbiol Infect 2021;27:697–703.	OR 1.69 (95% CI 1.46–1.96)
		Not reported (within one year of hospital discharge)	Palmowski L *et al.* Crit Care Med 2024;52:190–9.	OR 1.64 (95% CI 1.27–2.12)
		In-hospital (median LOS 20 days)	Cook D *et al.* N Engl J Med 2024;391:9–20.	In-hospital: HR 1.78 (95% CI 0.96–3.29)
		Not reported (meta-analysis)	Wang Y *et al.* NEJM Evid 2024;3.	RR 1.20 (95% CI 0.66–2.16)
Chronic kidney disease	- Progression of AKI to CKD - Renal interstitial fibrosis and renal tubular endothelial dysfunction	177 days (FAERS)	Wu B *et al.* Sci Rep 2021;11:3690.	ROR: 8.8 (95% CI 8.49–9.13); strongest signal with dexlansoprazole (compared to five other PPIs)
		Not reported (within one year of hospital discharge)	Palmowski L *et al.* Crit Care Med 2024;52:190–9.	OR 1.26 (95% CI 1.12–1.41)
Hypomagnesemia	Decreased dietary absorption due to decreased gastric pH	Not reported (within one year of hospital discharge)	Palmowski L *et al.* Crit Care Med 2024;52:190–9.	OR 1.55 (95% CI 1.22–1.96)

Table 2 (*Continued*)

Adverse effect	Established/potential mechanism(s)	Time frame to ADE	Supporting literature	Comments
Mortality (all-cause)	- Effect of PPIs on intestinal microbiota - Effect of adverse effects associated with PPIs	90-day mortality	Krag M *et al.* N Engl J Med 2018;379:2199–208.	RR 1.02 (95% CI 0.91–1.13) SAPS >53: RR 1.13 (95% CI 0.99–1.30)
		90-day in-hospital mortality	PEPTIC Investigators. JAMA 2020;323:616–26.	RR 1.05 (95% CI 1.00–1.10) APACHE II 18–23: RR 1.15 (95% CI 1.05–1.25) APACHE II 24–61: RR 1.05 (95% CI 1.00–1.11)
		Not reported (within one year of hospital discharge)	Palmowski L *et al.* Crit Care Med 2024;52 : 190–9.	HR 1.17 (95% CI 1.08–1.27)
		90-day mortality	Cook D *et al.* N Engl J Med 2024;391:9–20.	HR 0.94 (95% CI 0.85–1.04) APACHE II ≥25: HR 1.04 (95% CI 0.89–1.20)
			Wang Y *et al.* NEJM Evid 2024;3.	RR 0.99 (95% CI 0.93–1.05) More severely ill: RR 1.08 (95% CI 0.96–1.20)
Pneumonia	Alterations in intestinal microbiota	ICU (median LOS 6 days)	Krag M *et al.* N Engl J Med 2018;379:2199–208.	HR 1.00 (95% CI 0.84–1.19)
		Not reported (within one year of hospital discharge)	Palmowski L *et al.* Crit Care Med 2024;52:190–9.	OR 1.27 (95% CI 1.15–1.39)
		VAP in ICU (median LOS 10 days)	Cook D *et al.* N Engl J Med 2024;391:9–20.	HR 1.00 (95% CI 0.89–1.12)
		Not reported (meta-analysis)	Wang Y *et al.* NEJM Evid 2024;3.	RR 1.00 (95% CI 0.92–1.09)
Vitamin B12 deficiency	Decreased dietary absorption due to decreased gastric pH	2+ years of therapy (associated with longer duration of therapy)	Lam JR *et al.* JAMA 2013;310:2435–42.	OR 1.65 (95% CI 1.58–1.73)
		Not reported (within one year of hospital discharge)	Palmowski L *et al.* Crit Care Med 2024;52:190–9.	OR 1.3 (95% CI 1.13–1.49)

AIN, acute interstitial nephritis; AKI, acute kidney injury; FAERS, Food and Drug Administration Adverse Event Reporting System; H2RA, histamine-2 receptor antagonist; ICU, intensive care unit; LOS, length of stay; MV, mechanical ventilation; OR, odds ratio; PPI, proton pump inhibitor; ROR, reporting odds ratio; RR, risk ratio; VAP, ventilator-associated pneumonia.

develop guidelines or medication reconciliation, which can have significant pharmacoeconomic implications [18,19]. Development of clinical decision support (e.g., indication for H2RA or PPI in medication order) and/or the use of checklists to ensure that continued prescription of SUP is necessary can be ways to appropriately prescribe these medications while reducing the likelihood that they are inappropriately continued, which will increase the risk of ADEs.

It is important to note, that ICU stay alone is not necessarily a marker for critical illness. Some patients may require ICU care for increased monitoring (e.g., mild head injury, alcohol withdrawal) or advanced nursing care but not possess risk factors for clinically significant bleeding. Furthermore, challenges with disposition such as placement or bed availability could prolong ICU length of stay in absence of critical illness. Patients should be assessed daily for both the initiation and cessation of SUP based on their level of risk. Conversely, some patients on the general ward may be critically ill (albeit a smaller cohort) and have risk factors for UGIB but given that they are not in an ICU, would not be recommended for SUP. Further research is required in this area.

FUTURE STEPS FOR STRESS ULCER PROPHYLAXIS RESEARCH

Although the use of SUP has been evaluated for decades, there are still research gaps that need to be addressed. A better elucidation of risk factors for SUP and their potential synergistic effect would be beneficial in determining appropriate prescription. Additionally, the impact of acid suppressive agents on mortality and other deleterious outcomes such as infection, delirium, and cardiovascular adverse effects requires further study. Despite the strengths of randomized trials and their focus with the 2024 guidelines in their network meta-analyses, as well as in the most recently published meta-analysis,

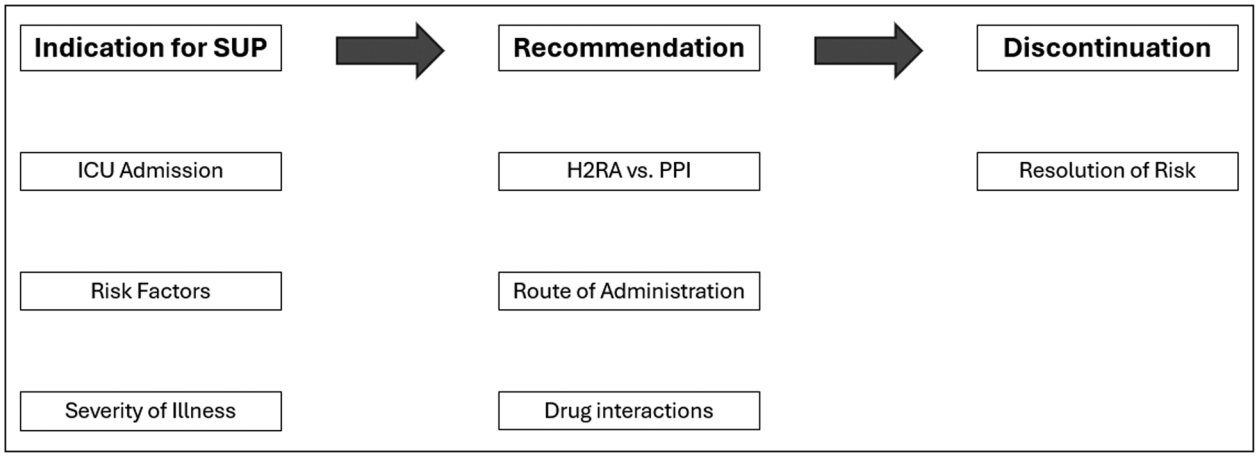

FIGURE 1. Example of artificial intelligence powered clinical decision support for improving use of SUP. An example of how AI could be used to provide patient-specific recommendations for the use of SUP in critically ill patients. The model integrated into the electronic health record would be based on identified cases of UGIB in critically ill patients, determining potential additional risk factors not identified by current literature. The AI model would provide a patient-specific recommendation via clinical decision support to the clinician on the utility of SUP, including the type of therapy and dose. Finally, when the patient is no longer at risk for UGIB, it would provide clinical decision support to recommend the discontinuation of therapy at ICU as well as hospital discharge. Importantly, the AI model should continue to develop, including identifying cases of UGIB in patients administered SUP, to identify areas of improvement.

inclusion of observational studies may highlight more pragmatic use of SUP.

Role of artificial intelligence

Given the rarity of UGIB despite the use of SUP, the use of artificial intelligence (AI) has high potential to identify at risk patients to optimize therapy in critically ill patients. The AI model would need to be trained with an adequate sample of patients with and without UGIB in the ICU to be able to learn, adapt and generate an appropriate patient-specific recommendation. This model should be optimally designed with input from front-line clinicians and continually refined with front-line clinician feedback to continue to optimize its performance. An example of how AI could optimize clinical decision support for the use of SUP is shown in Fig. 1, including patient-specific risk for UGIB, most appropriate SUP therapy, risk for ADEs associated with SUP, appropriate discontinuation of therapy.

CONCLUSION

Despite advances in the management of critically ill patients, the incidence of UGIB has largely remained stable. The administration of SUP in patients with high risk for UGIB is associated with a decrease in its occurrence but no effect on mortality. Appropriate discontinuation of SUP is needed to prevent the occurrence of ADEs, especially with PPI therapy. Ongoing research to evaluate the appropriateness of SUP in critically ill patients to address research gaps, including the potential role of AI in decreasing the occurrence of UGIB and increasing appropriateness of SUP therapy.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

1. ■■ MacLaren R, Dionne JC, 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; 52:e421.

This is the most updated guideline regarding the use of SUP in critically ill patients, which was authored by an interdisciplinary group. These guidelines provide recommendations including risk factors for SUP, the impact of enteral nutrition on the use of SUP, and which therapy to use for SUP.

2. ASHP Therapeutic Guidelines on Stress Ulcer Prophylaxis. Am J Health Syst Pharm 1999; 56:347–349.
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This is the most recent systematic review and meta-analysis on the role of PPIs for SUP, which includes the REVISE clinical trial, but was not included in the most recent guidelines. This analysis provides support for the use of PPIs, although may be associated with increased mortality in the most critically ill patients.

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