Stress Ulcer Prophylaxis

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Objectives: Stress ulcer prophylaxis is commonly administered to critically ill patients for the prevention of clinically important stress-related mucosal bleeding from the upper gastrointestinal tract. Despite widespread incorporation of stress ulcer prophylaxis into practice around the world, questions are emerging about its indications and impact. This clinically focused article will review current controversies related to stress ulcer prophylaxis for critically ill adult patients, including bleeding frequency, risk factors, comparative efficacy, adverse effect profile, and overall cost-effectiveness of the available stress ulcer prophylaxis regimens.

Data Sources: A MEDLINE search was conducted from inception through August 2015.

Study Selection: Selected publications describing stress ulcer prophylaxis in adult patients were retrieved (original research, systematic reviews, and practice guidelines); their bibliographies were also reviewed to identify additional pertinent publications.

Data Extraction: Data from relevant publications were abstracted and summarized.

Data Synthesis: The existing evidence is organized to describe the patients most likely to benefit from stress ulcer prophylaxis, review the comparative efficacy of proton pump inhibitors and histamine 2 receptor antagonists, the adverse effects of stress ulcer prophylaxis, and overall cost-effectiveness.

Conclusions: Many stress ulcer prophylaxis recommendations are based on older studies at risk of bias, which may not be applicable to modern practice. Stress ulcer prophylaxis should be limited to patients considered to be at high risk for clinically important bleeding. When evaluating only the trials at low risk for bias, the evidence does not clearly support lower bleeding rates with proton pump inhibitors over histamine 2 receptor antagonists; however, proton pump inhibitors appear to be the dominant drug class used worldwide today. The current rate of upper gastrointestinal bleeding and the relative adverse effects of acid suppression on infectious risk may drive not only the effectiveness, but also the cost-effectiveness of stress ulcer prophylaxis today. Research is currently underway to better address these issues. (*Crit Care Med* 2016; 44:1395–1405)

Key Words: critically ill; hemorrhage; histamine-2-receptor antagonist; intensive care; proton pump inhibitor; stress ulcer prophylaxis

Stress ulcer prophylaxis (SUP) is commonly administered to critically ill patients for the prevention of clinically important stress-related mucosal upper gastrointestinal bleeding (CIB). Despite the supporting randomized trial evidence for this practice, and endorsement in various practice guidelines, there are a number of unanswered questions pertaining to SUP at present. Most data supporting routine SUP originate from studies conducted in the 1980s and 1990s, which may be of limited application to modern day management of the critically ill patient. The clinical perception of lower CIB rates today, questions about current risk factors, and the adverse effects of SUP have led to debate about the utility or disutility of SUP in the ICU.

Building on a symposium held at the 43rd Society of Critical Care Medicine Congress in 2014, this review will address some current controversies associated with SUP. We used MEDLINE to search for publications through to August 2015, selected original research, systematic reviews, and practice guidelines on critically ill adults, and extracted and summarized relevant data. Herein, we summarize information on bleeding prevalence, risk factors for CIB, comparative efficacy, adverse effects, and overall cost-effectiveness of the available regimens.

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PREVALENCE OF CLINICALLY IMPORTANT BLEEDING

The frequency of mucosal injury (via endoscopic studies) in critically ill patients ranges from 75% to 100% with occult bleeding occurring in roughly 5–25% (1). However, the prevalence of CIB due to stress ulceration is markedly lower. A large study published in 1994 found the overall prevalence of CIB was 1.5% (2). Significant risk factors associated with CIB were respiratory failure and coagulopathy. The frequency of CIB was 0.1%, 0.5%, 2%, and 8.4% in patients with no risk factors, coagulopathy, respiratory failure, or both risk factors, respectively. Two decades later, an international study published in 2015 reported the frequency of CIB as 2.6% (3). In this study, 48% of patients who developed a CIB did so within 48 hours of ICU admission, emphasizing the importance of early identification of patients who are at high risk for CIB. Despite some differences in study definitions, ICU admission diagnoses, and use of SUP medications, these data raise questions about whether the CIB prevalence has actually decreased over the last 20 years, given the perception of less stress ulceration due to advances in resuscitation and nutrition. When interpreting bleeding rates over time and across settings, it is important to note that although early stress ulceration may develop in some patients in the ICU, others may be admitted to the ICU with a different gastrointestinal pathology that predates the critical illness, but is unmasked by critical illness, then manifest as serious bleeding in the ICU setting. Such bleeding may not be modifiable by SUP.

RISK FACTORS FOR CLINICALLY IMPORTANT BLEEDING

Critically ill patients are at risk as CIB develops due to stress ulceration because of physiologic stress leading to impaired mucosal defense mechanisms and mucosal ischemia (4). In a large observational study of 2,252 ICU patients, respiratory failure (defined as the need for mechanical ventilation for at least 48 hr) and coagulopathy (platelet count, < 50,000/mm^3; international normalized ratio, > 1.5; or a partial thromboplastin time, > 2 times the control value) were identified on multivariate analysis as independent risk factors for CIB (2). A follow-up study sought to identify both predisposing and protective factors that were associated with bleeding using data obtained from a large randomized controlled trial (RCT) comparing ranitidine with sucralfate (5). In this study, 1,077 mechanically ventilated patients were evaluated and independent risk factors found for bleeding were maximum serum creatinine (relative risk, 1.16; 95% CI, 1.02–1.32), and factors associated with less bleeding risk were ranitidine administration (relative risk, 0.39; 95% CI, 0.17–0.83) and enteral nutrition (relative risk, 0.30; 95% CI, 0.13–0.67). The role of enteral nutrition as a method for SUP has been raised (6–8). Unfortunately, there are no prospective RCTs directly comparing enteral nutrition with drugs used for SUP. Post hoc analyses from the preceding trial revealed benefit with ranitidine (over sucralfate), even in patients who received enteral nutrition (relative risk, 0.29; 95% CI, 0.1–0.88) (5). In contrast, a meta-analysis of small studies evaluating the effects of histamine 2 receptor antagonists (H2RAs) versus placebo found no benefit in terms of lower bleeding rates with H2RAs in the subgroup of patients who received enteral feeds (odds ratio [OR], 1.26; 95% CI, 0.43–3.70) (9). Given challenges interpreting subgroup analyses, the role of enteral nutrition as a method of SUP requires further evaluation.

A very recent international observational study evaluated risk factors for CIB among 1,034 patients from 97 ICUs (3). Variables associated with CIB on multivariate analysis (OR and 95% CI) were as follows: greater than or equal to three coexisting diseases (8.9 and 2.7–28.8), liver disease (7.6 and 3.3–17.6), use of renal replacement therapy (6.9 and 2.7–17.5), coagulopathy on the first day of ICU admission (5.2 and 2.3–11.8), coagulopathy listed as a comorbid condition (4.2 and 1.7–10.2), and higher organ failure score (1.4 and 1.2–1.5).

Other risk factors have been identified in smaller studies or in subpopulations of critically ill patients. Although results are variable and the strength of inference for many of these risk factors is weak, the following has also been documented: spinal cord injury, traumatic brain injury (Glasgow Coma Score, ≤ 10), thermal injury (body surface area, > 35%), sepsis, partial hepatectomy, hepatic or renal transplantation, major trauma (Injury Severity Score, ≥ 16), alcohol abuse, *Helicobacter pylori* colonization, ICU length of stay more than 1 week, occult or overt bleeding for more than or equal to 6 days, and high-dose corticosteroids (10–13).

EFFICACY OF ACID SUPPRESSION FOR SUP

Increasing Use of Proton Pump Inhibitors (PPIs)

The utilization of PPIs for SUP in North America has recently increased. An observational study in 2013 documented that PPIs were used in 70% of ICU patients when compared with previous reports of 23% in 2002 and 3% in 1998 (14–16). Similarly, PPI use has become more prominent in other parts of the world. In a recent survey of intensivists representing 97 ICUs in 11 countries, 66% (64/97) stated that PPI was the preferred SUP agent, and 31% (30/97) used primarily H2RA (17). This may be due to the superiority of PPIs for achieving and maintaining a gastric pH of greater than 4, which is a historical target for SUP due to minimization of gastric acid-mediated fibrinolysis (18–20). This trend may also reflect the RCT evidence suggesting lower CIB rates with PPIs compared with H2RAs (21) and guidelines such as the 2012 Surviving Sepsis Campaign update, which suggest using PPIs rather than H2RAs for SUP (22).

RCTs

Several RCTs have been conducted comparing PPIs versus H2RAs (18, 23–35) but only four have been fully published using CIB as the primary endpoint (18, 27, 29, 33). All four had relatively small sample sizes and three were single center

investigations (27, 29, 33), notably differing in their criteria for CIB. The first RCT ($n = 67$) was published in 1997 and evaluated omeprazole versus ranitidine in adult ICU patients with at least one risk factor for stress-related mucosal bleeding (29). The frequency of CIB was lower with omeprazole versus ranitidine, 6% (2/32) versus 31% (11/35), respectively ($p < 0.05$). However, these results are limited by a greater number of risk factors in the ranitidine group (2.7 vs 1.9 per patient; $p < 0.05$), an association between the number of risk factors and the development of a CIB, and the higher than expected frequency of CIB with ranitidine (31% in comparison to 1.7% identified in a much larger trial of high-risk patients conducted at a similar time) (36). A subsequent larger ($n = 287$), placebo-controlled RCT in adult trauma (70%) and surgical (30%) ICU patients found no difference in the frequency of CIB with omeprazole (1%, 1/72), famotidine (3%, 2/71), sucralfate (4%, 3/69), or placebo (1%, 1/75) ($p > 0.05$ for all comparisons) (27). The largest ($n = 359$) and only multicenter RCT comparing a PPI versus a H2RA was published by Conrad et al (18). This phase III, non-inferiority trial suggested that omeprazole was non-inferior to cimetidine for the prevention of CIB, with a frequency of 3.9% (7/178) versus 5.5% (10/181), respectively. The criterion for non-inferiority in this trial was the upper bound of an one-sided CI for the difference in bleeding rates less than 5%. One additional RCT has been recently published, enrolling 129 patients, which showed no difference in CIB rates with use of omeprazole versus ranitidine (1.6% [1/61] vs 5.9% [4/68]) amongst ICU patients in a single center in Tehran (33).

Meta-Analyses

Four meta-analyses comparing PPIs and H2RAs have been conducted in the past 7 years (**Table 1**) (21, 37–39). Pooled results are limited by the risk of bias of the original RCTs, and variable statistical approaches were used (e.g., risk difference vs OR or risk ratio [RR], fixed effects vs random effects model). Also, trials evaluating PPIs versus H2RAs differed in many aspects that likely influenced outcomes but were not always accounted for, including the study population, SUP regimen (dose, route, and frequency), and the definition of gastrointestinal bleed.

A meta-analysis in 2013 incorporating 14 RCTs summarized the results of 12 RCTs on the outcome of CIB (21). The RR for CIB was 0.36 (95% CI, 0.19–0.68) with PPIs compared with H2RAs; however, an a priori subgroup analysis revealed that these findings were driven by trials with a high or unclear risk of bias. ICU type (surgical vs medical/mixed), route of PPI administration (enteral vs parenteral), PPI administration schedule (once daily vs more than once daily), and geographic location of studies (non-Asian vs Asian) did not influence the findings. However, limiting the analysis to RCTs judged to be of low risk of bias ($n = 3$), the results were not significant (RR, 0.60 [0.27–1.35]). Barkun et al (37) evaluated 13 RCTs in a meta-analysis and reported an OR of 0.3 (95% CI, 0.17–0.54) with PPIs compared with H2RAs. These results did not significantly change upon subgroup analysis for gastrointestinal bleed definition, publication type, or publication year. In contrast, Lin et al (38) reported no difference between PPI and H2RA in a meta-analysis of seven RCTs (pooled risk difference, –0.04 [–0.09 to 0.1]). Finally, Pongprasobchai et al (39) included three RCTs in a meta-analysis and reported a lower frequency of CIB with PPIs (OR [95% CI], 0.42 [0.2 to 0.91]).

Krag et al (40) recently evaluated the effect of SUP versus no prophylaxis, using both conventional meta-analysis and trial sequential analysis techniques. Twenty trials were included whereby SUP consisted of either an H2RA (20 trials) or a PPI (two trials). Conventional meta-analysis revealed a significant reduction in gastrointestinal bleeding in patients treated with SUP (relative risk, 0.44; 95% CI, 0.28–0.68), but this was not significant using trial sequential analysis (adjusted 95% CI, 0.18–1.11). All included RCTs were considered to be at high risk of bias. Like other meta-analyses, this one found no mortality benefit to using SUP versus no SUP in ICU patients (relative risk, 1.00; 95% CI, 0.84–1.2).

Large Observational Studies

Most recently, two retrospective cohort studies were published utilizing large databases to evaluate the prevalence of gastrointestinal bleeding (per *International Classification of Diseases,* 9th Edition [ICD-9] classification) amongst ICU patients who received a H2RA or PPI (41, 42). Utilizing the Premier Perspective database, MacLaren et al (41) conducted the largest analysis to date, including 35,312 adult patients admitted to the ICU between January 1, 2003 and December 31, 2008, who required mechanical ventilation for at least 24 hours. The majority of patients received a PPI (62% vs 38% for H2RA utilization). Interestingly, and contrary to available meta-analyses, the frequency of gastrointestinal hemorrhage was higher in the PPI group (5.9% vs 2.1%; $p < 0.05$), and the risk remained significantly higher after propensity score adjustment (OR, 2.24; 95% CI, 1.81–2.76) and after matching (OR, 1.95; 95% CI, 1.44–2.65). A subsequent analysis used the Multiparameter Intelligent Monitoring in Intensive Care II (MIMIC II) database and included 686 adult patients with severe sepsis (42%) or septic shock (58%) requiring mechanical ventilation for at least 48 hours at the Beth Israel Deaconess Medical Center between 2001 and 2008 (42). The frequency of gastrointestinal bleeding was higher amongst patients who received a PPI (10% compared to 2.3% for H2RAs; $p > 0.05$); however, multivariate analysis revealed that the method of SUP (H2RA vs PPI) was not associated with the frequency of gastrointestinal bleeding. The inherent limitations of these studies, including outcomes reliant on ICD-9 coding, the inability to ascertain bleeding severity (i.e., overt vs clinically important), and potential indication bias rendering it difficult to fully adjust for confounding, underscore how observational studies are best viewed as hypothesis-generating and how large RCTs are needed to address these controversies.

ADVERSE EFFECTS OF ACID SUPPRESSION

Concerns have been raised about the association between non-judicious acid suppression and increased risk of bacterial

TABLE 1. Meta-Analyses Evaluating Proton Pump Inhibitors Versus Histamine-2-Receptor Antagonists for Stress Ulcer Prophylaxis in Critically Ill Adult Patients

Citation	Inclusion Criteria	Results	Comments
Alhazzani et al (21)	RCT comparing any PPI vs any H2RA (regardless of drug, dose, or route) and published prior to March 2012 14 trials (five as abstracts only) *n* = 1,720 patients	Results reported as pooled RR (95% CI) Clinically important bleeding: (12 trials/1,614 patients); RR, 0.36 (0.19 to 0.68); *p* = 0.002 Overt bleeding: (14 trials/1,720 patients); RR, 0.35 (0.21 to 0.59); *p* < 0.0001 Pneumonia: (eight trials/1,100 patients); RR, 1.06 (0.73 to 1.52); *p* = 0.76 Mortality: (eight trials/1,196 patients); RR, 1.01 (0.83 to 1.24); *p* = 0.91 ICU length of stay (reported as mean difference [95% CI]): (five trials/555 patients); −0.54 d (−2.2 to 1.13); *p* = 0.53	Significant study heterogeneity and treatment effect lost with pooled RD RD, −0.03 (−0.05 to 0.00) I^2 = 66% Cochrane Risk of Bias tool revealed three trials at low risk (five unclear/six high risk) Treatment effect not present amongst subset of trials with low risk of bias (*n* = 3) RR, 0.60 (0.27 to 1.35) Other subgroup analyses did not change results
Barkun et al (37)	RCT comparing any PPI vs any H2RA (regardless of drug, dose, or route) and published prior to September 2011 13 trials (five as abstracts only) *n* = 1,587 patients	Results reported as pooled OR (95% CI) Clinically significant bleeding: (13 trials/1,587 patients); OR, 0.30 (0.17 to 0.54) Pneumonia: (seven trials/1,017 patients); OR, 1.05 (0.69 to 1.62) Mortality: (eight trials/1,260 patients); OR, 1.19 (0.84 to 1.68) Days in ICU (reported as weighted mean difference [95% CI]): (three trials/339 patients); −0.12 (−1.9 to 1.66)	Cochrane Risk of Bias tool revealed only one trial with low risk (11 unclear/one high risk) Results did not change upon sensitivity analyses for: Definition of bleeding included: OR, 0.39 (0.19 to 0.77) Fully published trials (vs abstracts): OR, 0.35 (0.18 to 0.68) Year of publication (2002–2009 vs 1993–2001): OR, 0.41 (0.2 to 0.83)
Lin et al (38)	RCT and quasi-RCT comparing any PPI vs any H2RA (regardless of drug, dose, or route) and published prior to May 30, 2008 Seven trials (two as abstracts only) *n* = 936 patients	Results reported as pooled risk difference (95% CI) Upper gastrointestinal bleed (seven trial/936 patients); RD, −0.04 (−0.09 to 0.01); *p* = 0.08 Pneumonia: (six trials/905 patients); RD, 0 (−0.04 to 0.05); *p* = 0.86 ICU mortality: (three trials/569 patients); RD, 0.02 (−0.04 to 0.08); *p* = 0.50	Jadad score revealed three of the seven trials were of poor quality Sensitivity analysis: Removing Levy et al (29) study reduced heterogeneity (I^2) from 66% to 26% and reduced overall difference between groups. RD, −0.02 (−0.05 to 0.01); *p* = 0.19 Subgroup analyses: Trials that reported balanced patient characteristics at baseline: RD, −0.01 (−0.04 to 0.01); *p* = 0.34 Probability of ventilation need of > 48 hr as entry criterion RD, −0.02 (−0.05 to 0.01); *p* = 0.24 Year of publication (before 2000 vs after) RD, −0.11 (−0.21 to −0.01); *p* = 0.03
Pongprasobchai et al (39)	RCT of adult ICU patients with mechanical ventilation > 48 hr or coagulopathic, published prior to mid-Jan 2008 Three trials *n* = 569 patients	Results reported as pooled OR (95% CI) Clinically important bleed (three trials/569 patients); OR, 0.42 (0.20 to 0.91) Pneumonia: (three trials/569 patients); OR, 1.02 (0.59 to 1.75)	Authors comment that exclusion of Levy et al (29) trial would negate statistical significance

H2RA = histamine 2 receptor antagonist, OR = odds ratio, PPI = proton pump inhibitor, RCT = randomized controlled trial, RD = risk difference, RR = risk ratio. *Clostridium difficile* not included as an outcome variable in the included trials therefore not reported in the meta-analyses.

infections, namely *Clostridium difficile* infection (CDI) and pneumonia. Gastric acid plays an important role as a defense mechanism against ingested organisms and prevents bacterial colonization (43). Decreased gastric acidity (through administration of acid suppression) may lead to bacterial overgrowth, delayed gastric emptying, bacterial translocation, decreased gastric mucus viscosity, and normal gastrointestinal flora changes, which may impair gastric host defenses (44, 45). The rate of gastric bacterial overgrowth has been shown to be higher with PPIs compared with H2RAs possibly as a result of greater gastric acid inhibition (46). Alternatively, a second hypothesis has been proposed for the perceived risk in infectious complications, particularly with the PPIs, which is related to their immunomodulatory effects (47–49). One study of healthy volunteers demonstrated impaired neutrophil function and decreased bactericidal activity following a single dose of omeprazole (49). Other studies have suggested that short-term PPI exposure may diminish the expression of adhesion molecules on neutrophils, impair transmigration to inflammatory sites, and decrease microorganism phagocytosis (50). Further research is required in this area.

C. difficile Infection

Numerous studies have suggested that acid suppression, primarily PPIs, is a risk factor for nosocomial CDI (41, 51–67). Although most studies enrolled a range of hospitalized patients, there are a few studies that are specific to ICU patients(41, 53, 54, 68, 69). In a large, pharmacoepidemiologic cohort study of mechanically ventilated patients, CDI occurred more frequently in patients who received PPIs compared with H2RAs (adjusted OR, 1.29; 95% CI, 1.04–1.64) (41). A second retrospective study conducted in 3,286 medical ICU patients also revealed PPI use as an independent risk factor for CDI (OR, 3.11; 95% CI, 1.11–8.74) (54). A third study, which used the MIMIC II database, examined duration of PPI exposure as a potential risk factor for CDI and reported a significant increase in CDI when PPI duration was 2 or more days (OR, 2.03; 95% CI, 1.23–3.36) (53). However, other smaller studies have failed to establish this association (68, 69). H2RAs have not been linked to CDI in studies that are specific to critically ill patients, but in other settings, this association has been found in observational studies, albeit apparently attenuated in magnitude compared with PPI administration (59, 70, 71).

Pneumonia

The risk of pneumonia associated with acid suppressive medications in critically ill patients remains controversial. In the largest RCT to date, no difference in ventilator-associated pneumonia (VAP) was observed between ranitidine and sucralfate (36). RCTs have also evaluated pneumonia rates with PPIs and H2RAs (18, 23, 24, 27–30, 34, 35). Significant differences have not been noted with the exception of one small study where a three-fold increase in VAP was observed with pantoprazole (24).

Meta-analyses of RCTs comparing H2RAs with PPIs (Table 1) (21, 37–39) have not identified a significant difference in pneumonia rates. Several meta-analyses have been published comparing medications that increase gastric pH (either H2RAs or antacids) with those that do not directly affect gastric pH (sucralfate or placebo); results are disparate (**Table 2**) (9, 40, 72–78).

Despite the absence of RCT data clearly showing that SUP increases the risk of pneumonia, several large pharmacoepidemiologic studies have continued to fuel the debate, showing an increased risk of pneumonia with PPIs compared with H2RAs (41, 79, 80). MacLaren et al (41) reported a higher risk for pneumonia with PPI exposure in adult patients requiring mechanical ventilation (OR, 1.2; 95% CI, 1.03–1.41). Bateman et al (79) evaluated cardiac surgery patients and the relative risk for pneumonia with PPIs (vs H2RAs) was 1.19 (95% CI, 1.03–1.38). Finally, Herzig et al (80) reviewed 63,878 non-ICU patients and found a significant association between PPIs and pneumonia (OR, 1.3; 95% CI, 1.1–1.4) but not H2RAs (OR, 1.2; 95% CI, 0.98–1.4).

Thrombocytopenia

The literature describing the relationship of H2RA prescription and thrombocytopenia is limited to case reports and small retrospective case series (81, 82). Several large analyses have failed to report this association (83–87). The proposed mechanism for this interaction is direct bone marrow suppression and hapten formation (82). Of note, hapten formation can take several days; therefore, thrombocytopenia that develops shortly after H2RA initiation is unlikely to be related (88). In one review of patient reports describing H2RA-induced thrombocytopenia, more than 90% had at least one other documented risk factor for thrombocytopenia, such as sepsis or gastrointestinal bleeding, prior to H2RA administration (82). Case reports have also described thrombocytopenia secondary to PPIs, although as with H2RA case reports and case series, a causal relationship cannot be inferred (89–91).

PHARMACOECONOMICS OF SUP

Although most acquisition drug costs are relatively low compared with other resource consumption in the ICU, the widespread use of SUP around the world over a patient's ICU stay underscore the need for rigorous economic evaluation. The overall cost-effectiveness of SUP is determined by prescribing prevalence, the acquisition costs of various agents, and their impact on outcomes (including the prevalence, attributable morbidity and mortality, and cost of each outcome). In terms of outcomes, rates of pneumonia may be higher than rates of CIB and CDI. The attributable morbidity and mortality may be greater from pneumonia and CDI than CIB. Interpreting pharmacoeconomic analyses requires carefully critiquing the outcomes and definitions considered in the model, the measure used for effectiveness, the assumptions and quality of the data used to formulate those assumptions, the costs associated with each outcome, and the costing perspectives taken (e.g., hospital and societal).

TABLE 2. Meta-Analyses of Studies Reporting Pneumonia Risk With Medications That Increase Gastric pH (H2RAs and Antacids) Versus Medications That Do Not (Sucralfate or Placebo)

Citation	Inclusion Criteria	Results	Comments
Krag et al (40)	RCTs comparing either H2RA or PPI with placebo or no prophylaxis seven trials 1,008 patients	Results reported as pooled RR (95% CI). Random effects model used if heterogeneity detected ($I^2 > 0$) Any SUP vs no SUP: Fixed effect RR, 1.16 (0.84–1.58); $p = 0.28$; $I^2 = 19\%$ Random effects RR, 1.23 (0.86–1.78)	Subgroup analysis of H2RA vs PPI showed no increased risk of ventilator-associated pneumonia with PPIs.
Eom et al (74)	Observational and RCTs that investigated the association between acid suppressive medications and pneumonia (both community and hospital-acquired) Eight observational trials: Five trials/1,900,621 patients (CAP) Three trials/64,737 patients (HAP) 23 RCT's/3,640 patients	Results reported as pooled OR (95% CI) for observational studies and relative risk (95% CI) for RCTs. Observational studies assessing PPIs OR, 1.27 (1.11–1.46) Observational studies assessing H2RAs OR, 1.22 (1.09–1.36) RCTs assessing H2RAs RR, 1.22 (1.01–1.48)	Subgroup analyses: Trial type and methodologic quality: In the RCTs, the risk for pneumonia with H2RAs was significant only in low quality studies. (RR, 1.35 [1.1–1.67]) Pneumonia rates were not higher with H2RAs in high-quality studies. (RR, 0.96 [0.65–1.43]) Type of pneumonia (observational trials): CAP: Risk with PPI: OR, 1.34 (1.14–1.57) Risk with H2RA: OR, 1.19 (0.99–1.42) HAP: Risk with PPI: OR, 1.04 (0.58–1.88) Risk with H2RA: OR, 1.24 (1.05–1.47)
Marik et al (9)	RCT comparing any H2RA with placebo nine trials/1,157 patients	Results reported as pooled OR (95% CI) OR, 1.53 (0.89–2.61); $p = 0.12$	Increased risk of pneumonia observed in subgroup who received enteral nutrition OR, 2.81(1.2–6.56); $p = 0.02$
Huang et al (75)	RCTs of adult patients projected to require mechanical ventilation for at least 48 hr comparing H2RA and sucralfate 10 trials, eight of which evaluating ventilator associated pneumonia (2,004 patients)	Results reported as pooled OR (95% CI) OR, 1.32 (1.07–1.64); $p = 0.011$	Subgroup analysis conducted using early- vs late-onset pneumonia. Higher pneumonia rates with H2RA only observed with late-onset pneumonia. OR, 4.36 (2.09–9.09); $p < 0.001$
Messori et al (76)	RCTs evaluating ranitidine and sucralfate Ranitidine vs placebo: three trials/311 patients Ranitidine vs sucralfate: eight trials/1,825 patients	Results reported as pooled OR (95% CI). Control group (placebo or sucralfate) vs ranitidine each evaluated separately Ranitidine vs placebo: OR, 1.1 (0.45–2.66); $p = 0.84$ Ranitidine vs sucralfate: OR, 1.51 (1.00–2.29); $p = 0.05$	Methodologic quality score (10 max) = 6 for ranitidine vs placebo and 5.6 for ranitidine vs sucralfate
Cook et al (73)	RCTs of medications used for SUP (H2RA, sucralfate, antacids) compared with each other or an untreated control group 57 trials, 27 of which evaluating nosocomial pneumonia: H2RA vs placebo: eight trials Sucralfate vs H2RA: 11 trials	Results reported as common OR (95% CI). H2RA vs placebo: OR (95% CI) = 1.25 (0.78–2.00) Sucralfate vs H2RA OR (95% CI) = 0.78 (0.6–1.01)	Comparison of sucralfate vs H2RA or antacid: OR, 0.79 (0.65–0.96). Comparison of sucralfate vs antacid: OR, 0.8 (0.56–1.15)

(*Continued*)

TABLE 2. (*Continued*). Meta-Analyses of Studies Reporting Pneumonia Risk With Medications That Increase Gastric pH (H2RAs and Antacids) Versus Medications That Do Not (Sucralfate or Placebo)

Citation	Inclusion Criteria	Results	Comments
Cook et al (72)	RCTs of medications used for SUP (H2RA, sucralfate, antacids) eight trials: pH altering drugs vs placebo/control: four trials/338 patients Sucralfate vs pH altering drugs: four trials/252 patients	Results reported as common OR (95% CI). pH altering drugs vs placebo/control OR, 0.42 (0.16–1.1) Sucralfate vs pH altering drugs OR, 0.55 (0.28–1.06)	No significant effect on the rate of pneumonia in patients receiving therapy titrated to gastric pH of 3.5 or greater.
Tryba (77)	RCTs and non-randomized studies H2RA vs placebo or non-pH altering agents: three trials/704 patients Sucralfate vs H2RA or antacids: six trials/488 patients	Results reported as incidence and typical OR (95% CI) H2RA vs placebo/non-pH meds: 7.7% vs 4.2% (OR, < 1) H2RA/antacids vs sucralfate: 37.8% vs 18.1% (OR, < 1)	Large differences in pneumonia rates across two comparisons. Meta-analysis included studies with pirenzepine which is no longer used.
Tryba (78)	All studies comparing sucralfate with H2RAs or antacids Sucralfate vs H2RA: five trials/440 patients Sucralfate vs antacids: four trials/338 patients	Results reported as incidence and typical OR (95% CI) Sucralfate vs H2RA: 18.4% vs 34.4%; OR, 0.498 (0.316–0.783) Sucralfate vs antacids: 14.6% vs 29.3%; OR, 0.402 (0.235–0.687)	Only included studies evaluating clinically important bleeding whereas previous meta-analysis included all macroscopic bleeding

CAP = community acquired pneumonia, HAP = hospital-acquired pneumonia, H2RA = histamine 2 receptor antagonist, OR = odds ratio, PPI = proton pump inhibitor, RCT= randomized controlled trial, RR = risk ratio, SUP = stress ulcer prophylaxis.

There are three reports comparing the cost-effectiveness of H2RAs with PPIs (92–94). The first was a decision-tree model that included various PPI regimens, famotidine and sucralfate, and measured the cost per bleeding event avoided for high-risk patients (94). Factors included in the model were drug acquisition costs, consumables and labor costs, costs associated with CIB, and costs to evaluate diarrhea, thrombocytopenia, and mental status changes. The most cost-effective regimen was enteral omeprazole ($12,391 per bleeding event avoided). Although this was the first pharmacoeconomic analysis to assess adverse drug events (ADEs), the costs used to represent these ADEs were not consistent with those reported in other studies, and the costs associated with pneumonia were not included. The second evaluation compared PPIs with H2RAs in high-risk ICU patients whereby the main outcome was cost per complication event averted (92). The complications included in the model were bleeding and pneumonia. In this analysis, cost-effectiveness favored PPIs ($58,700 vs $63,920 per complication averted). These findings were most influenced by the prevalence of pneumonia in each group. A third publication examined the cost-effectiveness of H2RAs and PPIs in mechanically ventilated adult patients, using mortality as the effectiveness outcome (93). Factors included in the decision tree were bleeding, pneumonia, and CDI; factors most strongly influencing these results were the probability and resultant cost of pneumonia. Overall, the associated cost of SUP with an H2RA was $6,707 with a mortality of 3.8%. The cost of providing SUP with a PPI was $7,802 with a mortality of 3.8%. An incremental cost per survival was not calculated since both components (i.e., cost and survival) were dominated by H2RAs and the model favored H2RAs.

There are several factors contributing to the disparate results of published pharmacoeconomic analyses. These include the outcome chosen for effectiveness, the complications included in the model, and assumptions regarding the prevalence and costs of bleeding and pneumonia. For example, Barkun et al (92) estimated bleeding rates of 1.3% for PPIs and 6.6% for H2RAs, and pneumonia rates of 10.3% for both agents. By contrast, MacLaren and Campbell (93) estimated bleeding rates (calculated based on data provided) were 1.5% for PPIs and 4.1% for H2RAs, and pneumonia rates as 23.5% for PPIs and 19.1% for H2RAs. Both analyses identified pneumonia as the predominant factor that influenced the results, despite

TABLE 3. Recommendations From Published Evidence-Based Guidelines

Organization	Method for Evaluating Quality of Evidence	Indications for SUP	Preferred Modality
American Society of Health-System Pharmacists 1999 (10)	Category A: Levels I+, I, and I- Category B: Levels II+, II, and II- Category C: Levels III+, III, IV+, IV, and V Category D: expert opinion	Coagulopathy or need for mechanical ventilation for more than 48 hr (LOE = C) History of gastrointestinal ulceration or bleeding within 1 yr of admission (LOE = D) Patients with at least two of the following: sepsis, ICU stay of > 1 wk, high-dose corticosteroids, occult bleeding lasting 6 d or more (LOE = D) ICU patients with: Glasgow Coma Score ≤ 10 (LOE = B) Thermal injuries to > 35% body surface area (LOE = B) Partial hepatectomy (LOE = C) Multiple trauma with ISS ≥ 16 (LOE = D) Hepatic failure (LOE = D) Spinal cord injury (LOE = D) Hepatic or renal transplantation (LOE = D)	The choice among antacids, H2RA, and sucralfate should be made on an institution-specific basis.(LOE = A) This choice should take into account concerns for administration, adverse drug event profile and total costs (LOE = D) Insufficient data on misoprostol or PPIs are available to allow any recommendation with these agents.
Eastern Association for the Surgery of Trauma 2008 (12)	Level of recommendations derived from Class I, II, and III evidence. Level I: strongest evidence for effectiveness and represent principles of patient management that reflect a high degree of clinical certainty. Level II: moderate degree of clinical certainty Level III: degree of clinical certainty is not established.	Level I: Mechanical ventilation Coagulopathy Traumatic brain injury Major burn injury Level II: Multi-trauma Sepsis Acute renal failure Level III ISS > 15 High-dose steroids In selected populations, no prophylaxis is necessary	Level I: There is no difference between H2RAs, cytoprotective agents and some PPIs. Antacids should not be used. Level II: Aluminum containing compounds should not be used in patients on dialysis. Level III: Enteral feeding alone may be insufficient.
Surviving Sepsis Campaign 2012 (22)	GRADE	We recommend SUP using H2RAs or PPIs be given to patients with severe sepsis/septic shock who have bleeding risk factors. (grade 1B) We suggest patients without risk factors should not receive SUP. (grade 2B)	We suggest the use of PPIs rather than H2RAs. (grade 2C)
Danish Society of Intensive Care Medicine and the Danish Society of Anesthesiology and Intensive Care Medicine 2014 (95)	GRADE	We recommend not using SUP routinely for adult critically ill patients in the ICU (grade 1C) There is insufficient evidence to make any recommendation on SUP and nutrition. There is insufficient evidence to make any recommendation on SUP in ICU subpopulations: trauma, burn septic, and cardiothoracic patients.	We suggest using PPIs when SUP is indicated in adult critically ill patients in the ICU. (grade 2C)

GRADE = Grading of Recommendations Assessment, Development and Evaluation, H2RA = histamine-2-receptor antagonist, ISS = Injury Severity Score, LOE = level of evidence, PPI = proton pump inhibitor, SUP = stress ulcer prophylaxis.

these discordant assumptions, and it is likely that overall cost-effectiveness of these agents will be determined by whether and if so, how much, these agents increase the risk of pneumonia. More research comparing PPIs and H2RAs is necessary to generate robust evidence for future pharmacoeconomic studies to inform practice and policy.

RECOMMENDATIONS FROM PUBLISHED EVIDENCE-BASED GUIDELINES

Table 3 summarizes the recommendations of some organizations regarding the use of SUP in critically ill patients (10, 12, 22, 95). Overall, guidelines are in agreement that SUP should only be provided to critically ill patients with risk factors for CIB. The Danish guidelines explicitly recommend not using SUP routinely for critically ill adult patients in the ICU (grade 1C; strong recommendation, low level of evidence) (95). With regards to SUP agent selection, the 2012 Surviving Sepsis Campaign update and the 2014 Danish Society of Intensive Care Medicine and the Danish Society of Anesthesiology and Intensive Care Medicine are the most recent (22, 95). Both organizations provide a grade 2C recommendation (weak recommendation, low level of evidence) for the use of PPIs rather than H2RAs when SUP is indicated in critically ill patients.

In light of recent data published postrelease of these guidelines, and with due consideration of the adverse effect profile of SUP (particularly the growing concern about CDI), and the uncertain economic impact of PPIs, H2RAs, or no SUP, these recommendations will need to be revisited in the future as more trial data emerge. Comparing pantoprazole to placebo, one pilot RCT has been completed in Australia (Pantoprazole Or Placebo for Ulcer Prophylaxis) (96), a second pilot trial has been completed in Canada, Saudi Arabia, and Australia (Re-evaluating the Inhibition of Stress Erosions) (97), and a large RCT is underway in Europe (Stress Ulcer Prophylaxis in the Intensive Care Unit) (98). These studies will provide current data regarding the baseline prevalence of CIB along with the clinical benefit and potential harms of SUP with pantoprazole. Additionally, useful research would address the pharmacologic agent of choice, the impact of enteral nutrition, the role of SUP in patients receiving noninvasive ventilation, and the suitable timing of SUP discontinuation.

CONCLUSION

SUP is considered for critically ill patients typically upon evaluation of their risk for CIB. The risk for CIB appears to be related to the overall severity of illness, the use of organ-support (e.g., mechanical ventilation and renal replacement therapy), and coexisting diseases (e.g., coagulopathy and liver disease). Currently, when considering only the trials at low risk of bias, the available evidence does not clearly support superiority of either PPIs or H2RAs but PPI appears to be the dominant drug class used worldwide today. Available evidence does not consistently show increased infectious complications with acid suppression, although the association may be stronger for *C. difficile* than pneumonia. The relationship between acid suppressive therapy and infectious complications may be the primary factor that determines overall cost-effectiveness. It is doubtful that SUP will be cost-effective in patients at low risk for clinically important bleeding. Widespread administration of SUP to critically ill patients is now being reevaluated, given questions about decreasing baseline gastrointestinal bleeding rates, the potential infectious complications of SUP, and concerns about the risk-benefit and cost-effectiveness of SUP.

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