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REVIEW ARTICLE

Stress Ulcer Prophylaxis in Neurocritical Care

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Abstract Stress ulcer prophylaxis (SUP) with acid-suppressive drug therapy is widely utilized in critically ill patients following neurologic injury for the prevention of clinically important stress-related gastrointestinal bleeding (CIB). Data supporting SUP, however, largely originates from studies conducted during an era where practices were vastly different than what is considered routine by today's standard. This is particularly true in neurocritical care patients. In fact, the routine provision of SUP has been challenged due to an increasing prevalence of adverse drug events with acid-suppressive therapy and the perception that CIB rates are sparse. This narrative review will discuss current controversies with SUP as they apply to neurocritical care patients. Specifically, the pathophysiology, prevalence, and risk factors for CIB along with the comparative efficacy, safety, and cost-effectiveness of acid-suppressive therapy will be described.

Keywords Stress ulcer prophylaxis · Acid-suppressive therapy · Proton pump inhibitors · Histamine-2-receptor antagonists · Gastrointestinal hemorrhage · Adverse drug events · Neurocritical care

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Introduction

Stress ulcer prophylaxis (SUP) with acid-suppressive drug therapy is commonly administered to critically ill patients following neurologic injury for the prevention of clinically important stress-related gastrointestinal bleeding (CIB). Neurologic injury combined with severe physiologic stress has been associated with an increased risk for CIB [1]. These data, however, originate from studies conducted in an era where practices were considerably different than the management strategies of intensive care unit (ICU) patients today. In fact, recent evidence has questioned the value of SUP largely due to the increased observance of adverse effects with acid-suppressive therapy and the perceived decline in the incidence of CIB. This narrative review will describe the pathophysiology, prevalence, and risk factors for CIB along with the comparative efficacy, safety, and cost-effectiveness of acid-suppressive therapy. Using a MEDLINE search for publications from inception to July, 2017, relevant research articles, systematic reviews, and guidelines were extracted and reviewed. In addition, the bibliographies of retrieved articles were scanned to capture any manuscripts that may have been missed with the original search. Within each category, studies with an emphasis on neurocritical care were prioritized, but general ICU patients were also included particularly when data were sparse.

Pathophysiology

The origin of stress ulcers is multifactorial but largely related to reduced splanchnic blood flow, mucosal ischemia, and reperfusion injury that occurs when local blood flow is restored [2]. These changes in the gastric mucosa

may develop within 24 h of injury and are characterized by a constant progression of superficial lesions [3]. Hypersecretion of pepsin and gastric acid might also play a role by disrupting the gastric mucosal barrier. This is commonly observed in patients following neurologic injury and was classically described by Cushing [4]. It was proposed that intracranial lesions (i.e., tumors) stimulated parasympathetic centers of the hypothalamus and the vagal nuclei in the medulla to increase vagal nerve activity. This unopposed parasympathetic stimulation led to abnormal amounts of acid secretion and consequently gastric erosions. Morphologically, however, these ulcers are different than the ones that occur after trauma, shock, or sepsis. Cushing's ulcers tend to be single and deep, thus perforation is common [5]. Ulcers secondary to stress-related mucosal injury in critical illness are diffuse, and the incidence of CIB is relatively low (despite a high prevalence in the critically ill). Gastric acid, therefore, may contribute to injury, but the primary pathophysiologic mechanism leading to CIB is hypoperfusion and reperfusion injury.

Prevalence of Clinically Important Bleeding

The prevalence of CIB is largely confounded by the definition used for CIB, the era when then studies were conducted, the risk factors present in the included patients and the practice standards that were in place at that time. The most common and widely accepted definition used to describe CIB is overt bleeding plus any one of the following within 24 h: a spontaneous decrease in systolic blood pressure by >20 mmHg or >10 mmHg measured on sitting up, an increase in heart rate by >20 bpm, a decrease in hemoglobin by >2 g/dL, and subsequent transfusion after which the hemoglobin did not increase by an appropriate value [6]. The use of definitions that are more consistent with overt bleeding (e.g., hematemesis, coffee ground nasogastric aspirate, melena, etc.) will lead to a higher prevalence of GI bleeding that may not necessarily be clinically relevant.

Neurologic injury has been associated with increases in pepsin and gastric acid secretion, but there are few data describing the prevalence of CIB exclusively in a neuro-ICU population in the modern era [7]. One study utilized the National Inpatient Sample to report inpatient gastrointestinal (GI) bleeding rates in hospitalized patients with acute ischemic stroke [8]. Approximately 4 million patients were included from 2002 to 2011, and the incidence of GI bleeding was 1.24%. Of those with a GI bleed, only 25.7% received a blood transfusion which translates to a substantially lower bleeding rate when a definition more consistent with that used for CIB is considered (calculated rate = 0.32%). Furthermore, rates of full anticoagulation in stroke patients have declined since the Warfarin–Aspirin Recurrent Stroke Study (WARSS) trial demonstrated no difference in the incidence of recurrent ischemic stroke with anticoagulation [9]. GI bleeding rates following spinal cord injury (SCI) range from 2 to 20%, however, these figures originate from studies conducted in the 1980s, an era where high-dose steroids were frequently administered [10–15]. GI complications are more common in patients with SCI at cervical levels compared to those with injuries at lower segments [16]. Patients with traumatic brain injury are another population where a wide range of GI bleeding rates have been reported [17–21]. Similar to SCI, these data are derived from older studies with few using CIB as their outcome measure.

There are two large studies to characterize the prevalence of bleeding in the general ICU population that utilize CIB for their outcome definition. The first study, published in 1994, evaluated 2,252 patients and noted an overall prevalence of CIB of 1.5% [6]. Significant risk factors for CIB were respiratory failure and coagulopathy, and bleeding rates were 0.1, 0.5, 2, and 8.4% in patients with no risk factors, coagulopathy, respiratory failure, or both, respectively. The second study was an international study published in 2015 that reported CIB rates of 2.6% [22]. The median (IQR) time from ICU admission to bleeding was 3 (2–6) days. This study challenges the perception that CIB rates are now insignificant because of advances in critical care practices (e.g., aggressive resuscitation, assessment and restoration of perfusion, early enteral nutrition). It also emphasizes the importance of early identification of at-risk patients since most patients who bled experienced these bleeding events early in their ICU admission. Some ICU patients, however, may experience GI bleeding because of a different pathophysiologic process which exists prior to ICU admission and is not modifiable by the provision of SUP.

Risk Factors

Similar to the data describing the prevalence of CIB, there are few studies describing risk factors for GI bleeding that are specific to the neurocritical care population. These studies are limited by the use of definitions other than CIB to define GI bleeding, small sample sizes, and outdated ICU practices that are no longer considered standard of care (e.g., high-dose steroids).

In 1977, Kamada et al. [20] described a case series of 433 patients with head injury. Seventy-two (17%) experienced GI bleeding with 19 (4.4%) requiring a blood transfusion. Bleeding rates were higher in the patients with more severe head injury. In addition, the incidence of bleeding was higher in the cohort of patients who received

corticosteroids (22 vs 11%, $p < 0.05$). Chan et al. [23] described factors associated with GI complications in 526 patients who underwent neurosurgery for non-traumatic conditions between 1983 and 1987. There were 5 factors identified as independent predictors of GI complications: syndrome of inappropriate antidiuretic hormone, preoperative coma (glasgow coma score [GCS] < 9), postoperative complications (defined as those that resulted in clinical deterioration in the form of major neurologic deficits or operative interventions), age ≥ 60 years and central nervous system (CNS) infection. GI complications became more prevalent when 2 or more risk factors were present. A secondary analysis was performed which was focused on life-threatening complications. In this analysis, preoperative coma was the only independent variable identified. It was recommended that SUP be administered in patients with multiple risk factors or preoperative coma.

Other studies have linked bleeding rates with severity of injury. One study of 51 patients with intracerebral hemorrhage identified hematoma size, septicemia, and lower GCS as independent predictors for GI bleeding [24]. A second study described 165 patients with intracerebral hemorrhage, and GI bleeding was significantly related to surrogate markers for increased intracranial pressure [25]. These included hyperventilation, pupillary asymmetry, loss of cerebral function, decortication, and motor signs on the nonhemiplegic side. Hatton et al. [26] evaluated SUP in 136 neurosurgical ICU patients, and risk factors for bleeding were pentobarbital-induced coma and vasopressor therapy. Finally, Li et al. [27] described 68 patients with severe head injury (GCS ≤ 8) and reported stress ulcer formation to be associated with higher age and increased plasma cortisol levels. Plasma cortisol levels were inversely correlated with GCS.

Several large trials have described risk factors for GI bleeding in generalized ICU patients that use CIB as the primary outcome measure. In a landmark trial that included 2252 ICU patients, respiratory failure (defined as the need for mechanical ventilation for at least 48 h) and coagulopathy (platelet count $<50{,}000/mm^3$, INR > 1.5, or aPTT > 2 times the control value) were identified as independent risk factors for CIB [6]. A follow-up study used data obtained from a randomized controlled trial (RCT) of 1077 mechanically ventilated patients comparing ranitidine with sucralfate to identify protective and predisposing factors associated with bleeding [28]. Factors that were protective were ranitidine administration [relative risk (95% CI), 0.39 (0.17–0.83)] and enteral nutrition [relative risk (95% CI), 0.3 (0.13–0.67)], while maximum serum creatinine was associated with a greater risk for CIB [relative risk (95% CI), 1.16 [1.02–1.32)]. The most recent trials were an international observational study that evaluated risk factors for CIB in 1034 patients across 97 ICU's [22]. Variables associated with CIB [OR (95% CI)] were ≥3 coexisting diseases [8.9 (2.7–28.8)], liver disease [7.6 (3.3–17.6)], renal replacement therapy [6.9 (2.7–17.5)], coagulopathy on day one of ICU admission [5.2 (2.3–11.8)], coagulopathy as a comorbid condition [4.2 (1.7–10.2)], and higher organ failure score [1.4 (1.2–1.5)]. Other risk factors which have been identified in smaller studies, albeit with variable definitions for bleeding, include partial hepatectomy, thermal injury, organ transplantation, alcohol abuse, Helicobacter pylori colonization, ICU length of stay greater than 7 days, SCI, high-dose steroids, and sepsis [1, 29–31].

In summary, the risk for CIB is largely related to severity of illness. Factors that can be used to identify high-risk patients (i.e., those with high severity of illness) include coma (GCS < 9), the use of organ support (e.g., mechanical ventilation, renal replacement therapy), and coexisting diseases (e.g., coagulopathy, liver disease). The prevalence of CIB in low-risk patients is minimal, thus practices of administering SUP in all ICU patients should be discouraged.

Pharmacoepidemiology

There is much variability with practices and beliefs for many aspects of SUP. In a large snapshot study of ICU's in the USA and Canada, SUP was provided to 84% of patients [32]. When stratified by risk for CIB, SUP was administered to 92% of high-risk patients and 71% of low-risk patients. Proton pump inhibitors (PPIs) were the most common agent prescribed (70%) and the use of enteral nutrition did not seem to influence practice (SUP was administered to 93% of high-risk patients who were also receiving tube feeds).

Several survey data exist describing perceptions and beliefs about SUP [33–41]. Collectively, these data show that PPIs are the most common agents used in most parts of the world but beliefs pertaining to indications for SUP, when to discontinue SUP, and concerns for adverse effects with the available medications tend to vary.

Medications for Stress Ulcer Prophylaxis

Studies that are Exclusive to Neurocritical Care

There are few data comparing medications for SUP that are specific to the neurocritical care population [17, 19, 21, 25, 42–46] (Table 1). No studies used CIB as the primary outcome measure, and only three were inclusive of PPI's [25, 42, 44].

One systematic review described benefits and risks of SUP in adult neurocritical care patients [47]. Studies of

Table 1 Trials evaluating stress ulcer medications in neurocritical care patients

Author	Population	Comparison	Primary outcome	Results
PPI vs. H2RA				
Lee et al. [44]	Neurosurgical ICU patients with mechanical ventilation ($n = 60$)	Esomeprazole vs. famotidine	Overt bleeding	Esomeprazole (0%), famotidine (3.3%), p = NS
Liu et al. [25]	Intracerebral hemorrhage ($n = 165$)	Omeprazole vs. cimetidine vs. placebo	Overt bleeding	Omeprazole (15.5%), cimetidine (27.8%), placebo (45.3%), $p = 0.003$
Brophy et al. [42]	Neurosurgical ICU patients with mechanical ventilation or 1 other risk factor ($n = 51$)	Lansoprazole vs. famotidine	Time that gastric pH $\geq$ 4 and residuals were <28 ml	$\geq$80% of pH measurements $\geq$4: Day 1: lansoprazole (36%), famotidine (74%), $p < .05$ Day 2: lansoprazole (79%), famotidine (83%), p = NS
H2RA vs. sucralfate vs. placebo				
Misra et al. [45]	Intracerebral hemorrhage ($n = 141$)	Ranitidine vs. sucralfate vs. placebo	Overt bleeding	Ranitidine (11.1%), sucralfate (14.3%), placebo (23.4%), p = NS
H2RA vs. placebo				
Burgess et al. [17]	Severe head injury defined as GCS $\leq$ 10 ($n = 34$)	Ranitidine vs. placebo	Overt bleeding plus a 5% decrease in hematocrit	Ranitidine (0%), placebo (28%), $p < 0.05$
Chan et al. [43]	Non-traumatic neurosurgical lesions with $\geq$2 risk factors ($n = 101$)	Ranitidine vs. placebo	Symptomatic gastroduodenal lesions	Ranitidine (17.3%), placebo (42.9%), $p < 0.05$
Metz et al. [21]	Severe head injury defined as GCS $\leq$ 10 ($n = 167$)	Ranitidine vs. placebo	Overt bleeding	Ranitidine (3%), placebo (19%)
Reusser et al. [46]	Intracranial lesion caused by trauma or spontaneous hemorrhage requiring neurosurgery plus mechanical ventilation ($n = 40$)	Ranitidine vs. placebo	Overt bleeding	Ranitidine (0%), placebo (0%)
Halloran et al. [19]	Severe head injury defined as inability to obey simple commands ($n = 50$)	Cimetidine vs. placebo	Overt bleeding or guaiac positive gastric aspirates	Cimetidine (19%), placebo (75%), $p = 0.001$

GCS Glasgow coma scale, *H2RA* histamine-2-receptor antagonist, *ICU* intensive care unit, *NS* not significant, *PPI* proton pump inhibitor

adult patients with traumatic brain injury, subarachnoid hemorrhage, intracerebral hemorrhage, ischemic stroke, anoxic brain injury, SCI, CNS infections, or other acute neurologic injuries were eligible for inclusion. There were eight studies identified, and upper GI bleeding rates were lower with SUP compared to placebo [11 vs. 33%, risk ratio (95% CI) = 0.31 (0.2–0.47)], and there was no difference in pneumonia [20 vs. 17%, risk ratio (95% CI) = 1.14 (0.67–1.94)]. All studies, however, were judged as having a high or unclear risk of bias, small sample size, and substantial heterogeneity was noted. Furthermore, five of the eight trials were conducted prior to 1995 and may not reflect modern-day practices. Thus, important considerations with SUP cannot be addressed without inclusion of trials conducted in general ICU patients.

Studies in General ICU Patients

There are 4 RCT's that compare PPI's with H2RA's and utilize clinically important bleeding as the outcome measure [48–51]. (Table 2) All four had relatively small sample sizes with notably different definitions for CIB. Overall, three of the trials did not demonstrate a difference in CIB rates between PPI's and H2RA's, while the fourth reported superiority with omeprazole versus ranitidine (1.7 vs. 31%) [50]. The bleeding rates reported with ranitidine though were much higher than that previously reported in another larger study that was conducted during the same era [52]. Furthermore, the number of risk factors per patient was not equally balanced between the two groups (ranitidine, 2.7 vs. omeprazole, 1.9; $p < .05$).

In light of the small sample sizes with the available trials, five meta-analyses have been published comparing PPI's with H2RA's [53–57]. The first was published in 2009 and evaluated 3 RCT's (569 patients) [57]. CIB rates were lower with PPI therapy [OR (95% CI) = 0.42 (0.2–0.91)]. A second meta-analysis included 7 RCT's (936 patients) and reported no difference in CIB rates between PPI's and H2RA's [pooled risk difference (95% CI) = −0.04 (−0.09 to 0.1)] [56]. A meta-analysis in 2012 included 13 RCT's (8 as fully published articles, 5 as abstracts) and reported an OR (95% CI) of 0.3 (0.17–0.54) in favor of PPI's [55]. These results did not change upon subgroup analysis for various factors such as CIB definition, publication type, or publication year. A fourth meta-analysis was published by Alhazzani et al. [53]. This paper included 14 RCT's (1720 patients) of which 12 trials reported the outcome CIB. The risk ratio (95% CI) for CIB was 0.36 (0.19–0.68) with PPI's compared to H2RA's. An a priori subgroup analysis, however, revealed these findings were largely driven by trials with a high or unclear risk of bias. When the results were limited to those studies with low risk of bias, the risk ratio (95% CI) was 0.60 (0.27–1.35). The most recent meta-analysis was published in 2016 and used the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology to assess quality of evidence [54]. There were 19 eligible RCT's; 14 reported CIB (1,679 patients). The RR (95% CI) in this analysis was 0.39 (0.21–0.71) in favor of PPI's. Similar to the previous meta-analysis, many of the included trials were judged to be at high risk of bias. Subgroup analysis of studies with a low risk of bias reported a RR (95% CI) of 0.60 (0.27–1.35) for the outcome CIB.

Medications for SUP have also been evaluated in observational studies using large national databases. The first utilized the Premier Perspective database and included 35,312 adult ICU patients who were admitted between 2003 and 2008 and required mechanical ventilation for at least 24 h [58]. Using ICD-9 codes to identify study outcomes, the frequency of GI hemorrhage was 5.9% with PPI's and 2.1% with H2RA's ($p < .05$). Upon propensity score adjustment and matching, the risk remained significantly higher with PPIs [OR (95% CI) = 2.24 (1.81–2.76) and OR (95% CI) = 1.95 (1.44–2.65), respectively]. A second study used the Multiparameter Intelligent Monitoring in Intensive Care II (MIMIC II) database and evaluated 686 patients with severe sepsis or septic shock and required mechanical ventilation for at least 48 h [59]. In this analysis, the frequency of GI bleeding was 10% with a PPI vs. 2.3% with an H2RA ($p > .05$). Multivariate analysis revealed the method of SUP (PPI vs. H2RA) was not a significant variable associated with GI bleeding. While these studies provide large sample sizes to evaluate drug therapy for SUP, they are limited by their reliance on ICD-9 coding, the inability to characterize bleeding as clinically important (versus overt) and the potential for indication bias.

Modern-Day Placebo-Controlled Trials

The perception that CIB due to stress ulceration may be decreasing, while recognizing the risks for adverse effects with acid-suppressive therapy may be more prominent, has led to comparisons of SUP (with primarily PPIs) versus placebo. These studies will address the balance between benefit and harm and provide a clearer assessment of the value of SUP.

Faisy et al. [60] compared the rates of clinically important bleeding in a historical observational study. Phase 1 consisted of 736 patients who received SUP (sucralfate or ranitidine), and phase 2 had 737 patients who did not. Approximately 41% of the study cohort required mechanical ventilation. There was no difference in the incidence of clinically important bleeding (1.4 vs. 1.1%,

Table 2 Comparative trials evaluating proton pump inhibitors versus histamine-2-receptor antagonists in general ICU patients

Author	Population	Comparison	Outcome measure	Results
Solouki et al. [51]	Adult and pediatric ICU patients requiring mechanical ventilation for ≥48 h ($n = 129$)	Enteral omeprazole vs. IV ranitidine	Overt bleeding plus: a 20 mmHg decrease in SBP or DBP within 24 h, a 20 beat/minute increase in HR or 10 mmHg decrease in SBP in a standing position, a decrease in Hgb by ≥2g/dL or in Hct by 6% within 24 h, lack of Hgb increase after 2 units PRBC	Omeprazole (1.6%), ranitidine (5.9%), $p > 0.05$
Conrad et al. [48]	Adults ≥16 years old requiring mechanical ventilation for ≥48 h, APACHE II ≥11 and 1 additional risk factor ($n = 359$)	Enteral omeprazole vs. IV cimetidine	At least one of the following: bright red blood per NG not clearing after adjustment and saline lavage for 5–10 min, 8 h of persistent gastro-occult-positive coffee ground material with aspirates every 2 h not clearing with ≥100 mL saline lavage, persistent gastro-occult-positive coffee grounds material over 2–4 h on days 3–14 in three consecutive aspirates not clearing with ≥100 mL saline lavage	Omeprazole (3.9%), cimetidine (5.5%), One-sided 97.5% CI for the difference in rates (−100 to 2.8); non-inferiority margin of 5% met
Kantorova et al. [49]	Adults trauma or surgical patients with projected need for mechanical ventilation >48 h or coagulopathy ($n = 287$)	IV omeprazole vs. IV famotidine vs. enteral sucralfate vs. placebo	Overt bleeding plus one of the following: drop in SBP by ≥20 mmHg or increase in HR by ≥20 beats/min within 24 h, decrease in Hgb by ≥2 g/dL	Omeprazole (1%), famotidine (3%), sucralfate (4%), placebo (1%), $p > 0.05$ for all comparisons
Levy et al. [50]	Adult patients with ≥1 risk factor for GI bleeding ($n = 67$)	Enteral omeprazole vs. IV ranitidine	Hemodynamic instability resulting from hematemesis, coffee ground aspirate, or melena or a decrease in Hgb by ≥2 g/dL plus hemodynamic instability or need for PRBC transfusion	Omeprazole (6%), ranitidine (31%), $p < 0.05$ Imbalance in the number of risk factors per patient was noted (1.9 vs. 2.7, $p < 0.05$)

CI confidence interval, *DBP* diastolic blood pressure, *GI* gastrointestinal, *Hgb* hemoglobin, *Hct* hematocrit, *HR* heart rate, *ICU* intensive care unit, *IV* intravenous, *NG* nasogastric, *PRBC* packed red blood cells, *SBP* systolic blood pressure

respectively). Krag et al. [61] performed a systematic review measuring the effects of SUP versus no prophylaxis on the outcomes all cause mortality, GI bleeding, and hospital-acquired pneumonia using conventional meta-analysis and trial sequential analysis. Twenty trials were included which were published between 1977 and 2004, but only 2 evaluated PPI's. All trials were judged as having a high risk of bias. There was no difference in mortality or hospital-acquired pneumonia between SUP patients and controls, but SUP was associated with a lower risk for bleeding [RR (95% CI) = 0.44 (0.28–0.68)] in the conventional meta-analysis. Trial sequential analysis, however, could not confirm this finding as the adjusted 95% CI was 0.18–1.11. Sasabuchi et al. [62] evaluated the risks and benefits of SUP in patients with severe sepsis in a retrospective study across 526 hospitals in Japan. Using a propensity score matched analysis, 15,651 patients were identified in each group. There was no difference noted in GI bleeding (0.5 vs. 0.6%, $p = .208$) or Clostridium difficile infection (CDI) (1.4 vs. 1.3%), but hospital-acquired pneumonia was higher with SUP (3.9 vs. 3.3%, $p = .012$).

Several RCT's are beginning to emerge comparing pantoprazole with placebo in high-risk patients that evaluate clinically important bleeding and infectious complications. The first trial to be published was the POP-UP study (Pantoprazole or Placebo for Stress Ulcer Prophylaxis), which was conducted in Australia and included patients who were anticipated to be invasively mechanically ventilated for >24 h and receive enteral nutrition within 48 h of admission [63]. There were 214 patients included with no episodes of CIB identified in either group. Furthermore, there were no differences identified in either infective ventilator-associated complications (pantoprazole, 1.9% vs. placebo, 0.9%) or CDI (pantoprazole, 0.9% vs. placebo, 0%). The second trial is called REVISE (Reevaluating the Inhibition of Stress Erosions) and was an international trial conducted in eight Canadian centers, one Saudi Arabian center, and one Australian center. The REVISE pilot study was recently completed which addressed the feasibility of conducting an adequately powered pragmatic trial to determine the safety of withholding SUP, and the impact PPI's had on infectious complications [64]. There were 150 patients included in the pilot, and all a priori feasibility outcomes were achieved. There were no differences in any of the secondary clinical outcomes assessed: CIB (pantoprazole, 6.1% vs. placebo, 4.8%; $p = 1.00$), late ventilator-associated pneumonia (pantoprazole, 20.4% vs. placebo, 14.3%; $p = .583$), or CDI (pantoprazole, 4.1% vs. placebo, 2.4%; p = 1.00). Accompanying the publication of the REVISE pilot was a systematic review of studies that compared PPI's with placebo in critically ill patients. Overall, there was no statistically significant difference between PPI's and placebo in CIB [OR (95% CI) = 0.96 (0.24–3.82)], ventilator-associated pneumonia [OR (95% CI) = 1.45 (0.84–2.50)], or CDI [OR (95% CI) = 2.10 (0.31–14.07)]. Collectively, the REVISE pilot trial and the meta-analysis validate the feasibility for conducting a large RCT (i.e., REVISE) which is currently underway.

There are other large trials currently ongoing evaluating the impact of SUP on clinical outcomes. SUP-ICU (Stress Ulcer Prophylaxis in the Intensive Care Unit) is an international trial comparing 90-day mortality (primary outcome), CIB, pneumonia, and CDI (secondary outcomes) with pantoprazole versus placebo in ICU patients who have risk factors for GI bleeding [65]. As of August, 2017, patient enrollment is 87% complete (goal = 3350 patients) [66]. SIREN (Sup-Icu RENal) is a subanalysis of the SUP-ICU trial designed to clarify whether the subgroup of critically ill patients with dialysis-dependent acute kidney injury benefit from pantoprazole vs. placebo [67]. Finally, PEPTIC (Proton pump inhibitors vs. histamine-2-rEceptor blockers for ulcer Prophylaxis Therapy in the Intensive Care unit) is a cluster-randomized crossover trial comparing in-hospital morality with PPI's versus H2RA's in mechanically ventilated patients [68]. Collectively, these trials will provide a modern-day assessment of the value of SUP, particularly if the benefits gained (i.e., reduced GI bleeding) outweigh the risks for infectious complications.

The Role of Enteral Nutrition

Enteral nutrition may play a role in the prevention of CIB due to stress ulceration, but the data supporting its use are limited. Enteral nutrition has been shown to prevent mucosal ischemia through its effect on splanchnic blood flow [69]. Furthermore, enteral nutrition formulas are typically alkaline and can increase gastric pH, albeit these effects are variable.

There are no prospective data directly comparing enteral nutrition with acid-suppressive therapy for the provision of SUP. Retrospective data do exist, and these studies have produced conflicting results [70]. In an analysis of data obtained from a large RCT comparing ranitidine with sucralfate, enteral nutrition was associated with a lower risk for CIB [RR (95% CI) = 0.3 (0.13–0.67)], but a post hoc analysis revealed benefit with ranitidine (compared to sucralfate), even in patients receiving enteral nutrition [RR (95% CI) = 0.29 (0.1–0.88)] [28]. In contrast, a subgroup analysis of small studies from a meta-analysis comparing H2RA's with placebo found no difference in bleeding rates between the two groups in patients who were receiving enteral nutrition [OR (95% CI) = 1.26 (0.43–3.70)] [71]. Further research is needed to determine the role of enteral

nutrition in the realm of SUP, particularly if medications can be safely discontinued once tube feeds are tolerated.

Adverse Effects of Acid Suppression

The association between acid suppression and infectious complications has been widely described. Acid-suppressive therapy may lead to bacterial overgrowth, delayed gastric emptying, bacterial translocation, decreased mucus viscosity, and changes in normal GI flora. These changes appear to be more prevalent with PPI's versus H2RA's; likely due to their more potent acid-suppressive properties. Alternatively, a second mechanism has been proposed which is related to the immunomodulatory effects of these agents, primarily the PPI's. Specifically, research has demonstrated an association between short-term PPI exposure and impaired neutrophil function and phagocytosis [72, 73]. The latter mechanism is more consistent with the increased risk observed shortly after initiation of therapy.

Pneumonia

The risk for pneumonia with acid-suppressive therapy has been widely studied, but results remain disparate. In the largest RCT conducted to date, there was no difference in pneumonia rates with H2RA's compared to sucralfate [52]. Similarly, the recently published POP-UP trial and REVISE pilot trial reported no statistically significant differences in pneumonia rates between pantoprazole and placebo groups [63, 64].

Several trials have compared pneumonia risk with PPI's versus H2RA's [25, 44, 48–50, 74–77]. In these trials, no difference has been detected with the exception of one trial where the incidence of VAP was greater with PPI therapy (30 vs. 10%, $p = .006$) [75]. The trials evaluating PPI therapy, however, are limited by their sample size and lack of statistical power for the outcome of pneumonia.

The association between pneumonia and acid-suppressive therapy has also been described in several meta-analyses. Five meta-analyses have compared PPI's with H2RA's, while ten have evaluated medications that increase gastric pH versus those that do not [53–57, 61, 71, 78–85]. In the reports that have compared PPI's with H2RA's, no difference in pneumonia rates was noted [53–57]. In the meta-analyses that compare pH-altering mediations with placebo or sucralfate, mixed results exist [61, 71, 78–85]. The most recent meta-analysis was published in 2017 and included 21 RCT's comparing sucralfate and ranitidine [78]. Sucralfate was associated with a reduction in the risk of pneumonia [OR (95% CI) = 0.84 (0.72–0.98)].

In contrast to the results witnessed in RCT's and meta-analyses, several large database studies have shown an increased risk of pneumonia with PPI's compared to H2RA's [58, 86–88]. In a large pharmacoepidemiological cohort study, MacLaren et al. [58] reported higher pneumonia rates with PPI's compared to H2RA's (38.6 vs. 27%, $p < .001$) in 35,312 ICU patients. Statistical significance was maintained after propensity score matching. Bateman et al. [86] reviewed 21,214 cardiac surgery patients, and the relative risk (95% CI) for pneumonia with PPI's was 1.19 (1.03–1.38). Herzig et al. reviewed 63,878 non-ICU patients, and the adjusted odds ratio (95% CI) for pneumonia with acid-suppressive medications was 1.3 (1.1–1.4) [88]. Subgroups analysis revealed a significant association with PPI's [OR(95% CI) = 1.3 (1.1–1.4)] but not H2RA's [OR(95% CI) = 1.2 (0.98–1.4)]. Momosaki et al. [87] evaluated 77,890 acute stroke patients who received either a PPI or H2RA. The unadjusted odds ratio (95% CI) for pneumonia with a PPI was 1.08 (1.02–1.15). Following propensity score matching, however, no difference in pneumonia was noted [OR (95% CI) = 1.1 (0.99–1.21)].

The association between acid-suppressive therapy and pneumonia in patients following acute stroke has been evaluated in several single-center, retrospective cohort studies [89–91]. The first evaluated 335 patients who presented with either ischemic or hemorrhagic stroke over a 10-year period in Japan [89]. The relative risk for pneumonia was significantly greater with a PPI compared to no exposure [RR (95% CI) = 2.07 (1.13–3.62), while no association existed with H2RAs [RR (95% CI) = 1.22 (0.83–1.81)]. Similarly, Herzig et al. [90] evaluated stroke patients (ischemic or hemorrhagic) who presented over a 10-year period in a large academic medical center in Boston, MA. There were 1676 patient admissions evaluated, and the adjusted OR (95% CI) for pneumonia with any acid-suppressive therapy was 2.3 (1.2–4.6)]. This risk was more evident with PPIs [OR (95% CI) = 2.7 (1.4–5.4)] as there was no difference observed in patients who received H2RAs alone [OR (95% CI) = 1.6 (0.8–3.4)]. Finally, Ran et al. [91] reviewed 200 patients with hemorrhagic stroke in China. The adjusted OR (95% CI) for pneumonia was 2.7 (1.2–6.7) for those patients who received a PPI versus no prophylaxis.

Clostridium Difficile Infection

Patients in the ICU are at high risk for CDI, and the prevalence of CDI is approximately double that noted in non-ICU patients [92]. There are numerous studies describing the association with acid-suppressive therapy and CDI in both ICU and non-ICU patients [58, 93–112]. Similar to pneumonia, the risk appears to be greater with PPI's than with H2RA's. In a large pharmacoepidemiological study, the

incidence of CDI with PPI's was 3.8 versus 2.2% with H2RAs ($p < .001$) [58]. Results were similar upon propensity score matching (3.4 vs. 2.6%, $p = .002$). Similarly, one meta-analysis of 23 studies reported a greater risk of hospital-acquired CDI with PPI use [OR (95% CI) = 1.81 (1.52–2.14)] [113].

The association between CDI and PPI use may be related to both intensity and duration of acid-suppressive therapy. In one study, increasing levels of acid suppression were associated with an increased prevalence of nosocomial CDI in a mixed cohort of hospitalized patients [102]. Specifically, the OR (95% CI) for CDI were 1 (reference case), 1.53 (1.12–2.1), 1.74 (1.39–2.18), and 2.36 (1.79–3.11) with no acid suppression, H2RA, daily PPI, and more frequent PPI use, respectively. A second study evaluated if there was a specific duration of PPI therapy where nosocomial CDI became more prominent [94]. Using classification and regression tree analysis, there were 3 tiers of risk identified: ≤2 days of therapy (CDI = 11%), 3–12 days (CDI = 34%), and >12 days (CDI = 100%). In a study of 408 ICU patients, PPI exposure of 2 or more days [OR (95% CI) = 20.3 (1.23–3.36)] and antibiotic use [OR (95% CI) = 2.52 (1.23–5.18)] were independent predictors for nosocomial CDI [95]. This risk may be greater when PPIs and antibiotics are used together [111, 114].

PPI use has also been associated with more severe CDI. One large retrospective study reported an incidence of severe hospital-acquired CDI (according to IDSA guidelines) [115] of 0.21% in patients who received PPIs compared to 0.03% in controls [RR (95% CI) = 6.27 (2.91–13.48) [104]. In addition, the risk for complicated CDI (i.e., severe CDI plus hypotension, shock, ileus, or megacolon) was significantly higher with PPI's [RR (95% CI) = 15.32 (3.6–65.13)]. Finally, acid-suppressive therapy has been associated with recurrent CDI [116]. This risk appears to be recognized more so in studies that were exclusive to PPIs [OR (95% CI) = 1.66 (1.18–2.34)] versus studies that include both PPIs and H2RAs [OR (95% CI) = 1.37 (0.95–1.99)]. The need for acid-suppressive therapy, particularly PPIs, should be strongly critiqued and reassessed once the diagnosis of CDI has been confirmed.

Other Adverse Effects

Case report data and small, retrospective case series have linked H2RA's to thrombocytopenia, but larger studies have failed to report this association [117–121]. In one report describing thrombocytopenia and H2RA's, more than 90% of patients had at least one other risk factor for thrombocytopenia (e.g., sepsis, GI bleeding, renal and hepatic dysfunction) prior to H2RA administration [122]. Case reports have also described H2RA-associated CNS reactions, but these are primarily encountered in elderly patients with end-organ dysfunction [123, 124]. Proper adjustment of dosages based on creatinine clearance estimates is necessary.

Pharmacoeconomics of Stress Ulcer Prophylaxis

The cost-effectiveness of stress ulcer prophylaxis is ultimately determined by the drug acquisition cost and the resultant incidence and costs of all related outcomes (e.g., GI bleeding, pneumonia, CDI). Although the acquisition costs for the medications used for SUP are relatively low, the costs associated GI bleeding, pneumonia, and CDI are profoundly high. These factors must be included in any assessment of value with SUP. When interpreting pharmacoeconomic analyses with SUP, clinicians should evaluate the outcomes and definitions included in the model, the measure used for effectiveness (e.g., GI bleeding, mortality), the assumptions used to determine event rates, all associated costs and the quality of the data used to justify the model.

There are no pharmacoeconomic analysis that are specific for the neuro-ICU population, but four pharmacoeconomic analyses have compared the cost-effectiveness of H2RA's with PPI's in a generalized ICU environment [125–128]. The first was a decision tree model that included sucralfate, famotidine, and various PPI therapies [128]. The primary outcome was cost per bleeding event, and the factors included were drug acquisition costs, consumables and labor for administration, costs associated with CIB and costs to manage the side effects diarrhea, thrombocytopenia, and mental status changes. The most cost-effective regimen was enteral omeprazole at $12,391 per bleeding event avoided. This analysis differs from other pharmacoeconomic analyses in that pneumonia was not included in the model, and the costs associated with adverse drug events (such as diarrhea) were not consistent with other reports. A second analysis compared PPI's with H2RA's, and the primary outcome was cost per averted complication (i.e., bleeding and pneumonia) [125]. In this analysis, cost-effectiveness favored PPI's ($58,700 vs. $63,920 per complication averted). Sensitivity analysis revealed the probability of pneumonia as the most influential factor in the model. Clostridium difficile infection was not included in this model. MacLaren et al. [127] compared the cost-effectiveness of H2RA's versus PPI's measuring effectiveness using survival. Factors included in this model were bleeding, pneumonia, and CDI. Cost-effectiveness favored H2RA's ($6,707 vs. $7,802). Similar to the previous model, the cost and incidence of pneumonia were the most significant drivers for incremental cost. Finally, Hammond et al. [126] compared H2RA's with PPI's using ICU mortality and complication rate as the effectiveness

measure. Factors included in the model were ICU mortality, pneumonia, CDI, and GI bleeding. The costs, complication rates, and mortality rates were $9,039, 17.6%, and 2.5%, respectively, for H2RA's and $11,249, 22%, and 3.34%, respectively, for PPI's. H2RA's, therefore, dominated the model and were the more cost-effective entity.

The disparate results across the four analyses are due to the variation in the complications included in each model, the outcome chosen for effectiveness, and the assumptions used for both outcome prevalence and cost. One consistency, however, was the notable influence pneumonia had on the variability within each model. It is likely that the cost-effectiveness of these agents (or SUP provision in general) will be largely based on whether or not acid suppression is associated with an increased prevalence of pneumonia. All pharmacoeconomic analyses are limited by the quality of evidence that currently exists, thus modern-day, high-quality data are vastly needed to better assess the cost-effectiveness of this therapy.

Summary

SUP is widely used in hospitalized patients with the PPIs being the most commonly sought modality. There are few trials specific to neurocritical care patients pertaining to either risk for CIB or the best mechanism to provide SUP (i.e., PPI or H2RA). Most data are reflective of ICU practices that are not necessarily consistent with today's approach to critical care. The prevalence of CIB is relatively low and appears to be related to severity of illness (e.g., coma), organ support (e.g., mechanical ventilation), and comorbidities (e.g., coagulopathy, liver disease). Collectively, the available evidence does not clearly support superiority of either agent, particularly when only trials with a low risk for bias are considered. PPIs may be associated with a higher risk for infectious complications; this association appears stronger with CDI than with pneumonia. Modern-day, placebo-controlled trials are currently underway which will provide a clearer assessment of the value of SUP considering their potential to reduce CIB but possibly increasing the risk for adverse drug events.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflicts of interest.

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