

Stress ulcer prophylaxis in critically ill patients: review of the evidence

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KEY WORDS

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ABSTRACT

Critically ill patients are at risk of developing stress ulcers in the upper digestive tract. Multiple risk factors have been associated with the development of this condition, with variable risk of association. Decades of research have suggested the benefit of using pharmacologic prophylaxis to reduce the incidence of clinically important upper gastrointestinal bleeding, with no reduction in overall mortality. It has been the standard of care to provide prophylaxis to patients at risk. Options for prophylaxis include: proton-pump inhibitors, histamine₂-receptor antagonists, or sucralfate. The choice of prophylaxis depends on multiple factors including the presence of risk factors, risk for nosocomial pneumonia, and possibly cost.

Introduction Stress ulcer-related gastrointestinal (GI) bleeding was first described in 1969.¹ Subsequently, a large case series that described this condition in further details was published.^{2,3} Over the last few decades, the use of stress ulcer prophylaxis (SUP) has been a controversial topic in the care of critically ill patients. There are still questions concerning diagnosis, risk factors for bleeding, and need for and choice of prophylactic agents. The aim of this review was to explore current controversies and questions. Do we need to use SUP in critically ill patients? Which patients will benefit from SUP? Are there differences in the efficacy of various drug classes?

Definitions Several definitions have been used to describe different forms of stress ulcer bleeding; we present those that are used in the published literature. Occult bleeding is usually defined as a positive guaiac test on fecal sample without overt GI bleeding; overt bleeding is defined as hematemesis, coffee ground emesis, melena, or bloody nasogastric aspirate; clinically important bleeding (CIB) is usually defined as overt bleeding plus one of the following 4 features in the absence of other causes: a spontaneous drop of systolic or diastolic blood pressure of 20 mmHg or more within 24 hours of upper GI bleeding,

an orthostatic increase in pulse rate of 20 beats per minute and a decrease in systolic blood pressure of 10 mmHg, a decrease in hemoglobin of at least 2 g/dl (20 g/l) in 24 hours or transfusion of 2 U packed red blood cells within 24 hours of bleeding.³

Incidence and clinical implications of gastrointestinal bleeding in critically ill patients There is a variation in the estimates of incidence due to a lack of standardization of the definition of stress ulcer-related GI bleeding and the heterogeneity of risk of bleeding among patients. The incidence of “mucosal injury” based on endoscopic studies was as high as 75%–100%, frequently observed within 24 hours of admission to the intensive care unit (ICU).^{2,4} Occult bleeding incidence ranges from 15% to 50%.⁵ The incidence of overt bleeding is 5% to 25% among critically ill patients who do not receive prophylaxis.^{6,7} However, overt bleeding does not necessarily translate into CIB.⁸ In the 2 large prospective cohort studies, the incidence of CIB was observed to be 1.5% and 3.5%.^{3,9} The mortality in those patients was significantly higher when compared with patients who did not bleed (48.5% vs. 9.1%).⁹

The incidence of bleeding was also recorded in other populations. In a retrospective review of

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TABLE 1 Incidence of clinically important gastrointestinal bleeding among critically ill patients in cohort studies

Study	Type	Population	Number of patients	Incidence	All cause mortality	Attributed mortality	Increase in ICU length of stay
Zandstra ⁴¹	prospective cohort study	MVP	167	0.6%	NA	NA	NA
Cook ⁹	prospective cohort study	critically ill patients in medical ICU	2252	1.5%	49%	NA	NA
Cook ³	prospective cohort study	MVP	1666	3.5%	NA	30%	3.8 days
D'Ancona ¹¹	prospective cohort study	postcardiac surgery	11,058	0.3%	22.5%	NA	NA
Faisy ¹⁴	observational study	medical and surgical ICU	737	1.1%	75%	NA	NA
Andersson ¹²	prospective cohort study	postcardiac surgery	6119	0.3%	6%	NA	NA
Bruno ⁴²	prospective cohort study	oncology in ICU	100	1%	NA	NA	NA

All the studies included critically ill patients in either surgical (postcardiac surgery) or medical ICU.

Abbreviations: ICU – intensive care unit, MVP – mechanically ventilated patients, NA – data not available

526 nontrauma neurosurgery patients in Hong Kong, the prevalence of overt GI bleed and CIB was 6.8% and 2.8%, respectively. Most of the patients with overt GI bleed received histamine₂-receptor antagonist (H₂RA) for prophylaxis.¹⁰ Two prospective cohort studies in cardiac surgery patients included 11,508 and 6186 patients and found the incidence of clinically important GI bleed to be 0.3% and 0.8%, respectively.^{11,12} It appears that the incidence of stress ulcer-related GI bleed has decreased over the years. In studies published before 1999, the incidence of CIB was between 2% to 6% in patients not receiving prophylaxis.¹³ However, in studies published since 2001, the incidence of CIB has been reported to range between 0.1% and 4% with or without prophylaxis.^{12,14,15} This is probably related, in part, to better overall ICU care and use of appropriate prophylactic therapy.⁵ Increasing use of enteral feeding also may have contributed to the reduced incidence.¹⁶ The above cohort studies are summarized in **TABLE 1**.

What are the risk factors for bleeding? A large prospective cohort study involving critical care patients showed that respiratory failure (need for mechanical ventilation for at least 48 hours) and coagulopathy (platelet count <50,000/cubic millimeter, international normalized ratio >1.5, or activated partial thromboplastin time >2 times the upper limit of normal) were the only factors associated with increased risk of CIB. Of 847 patients who had one or both risk factors, 3.7% developed CIB, while only 0.1% of 1405 patients without either of those risk factors developed CIB.⁹ In a subsequent prospective multicenter cohort study of 874 patients in the ICU, 79 patients (9%) developed overt GI bleeding (the incidence of CIB was not reported in this study).¹⁷ In that second study, several factors were found to be

associated with increased risk of overt bleeding in multivariate analysis: acute hepatic failure, nasogastric tube placement for over 5 days, history of alcohol abuse, chronic renal failure, and a positive *Helicobacter pylori* serology.¹⁷ In mechanically ventilated patients, acute renal failure was associated with increased risk of bleeding in a multivariate analysis performed during yet another study.¹⁸ Other factors that have been associated with increased risk of bleeding include: severe head or spinal cord injury, thermal injury involving more than 35% of the body surface area, major surgery (lasting more than 4 hours), high-dose corticosteroids, and acute lung injury.^{13,19} The risk factors for GI bleeding based on the above observational studies are summarized in **TABLE 2**.

What to use? Histamine₂-receptor antagonists vs. placebo Cook et al.⁸ conducted a meta-analysis that included 10 randomized clinical trials (RCTs) comparing H₂RA therapy to placebo: H₂RA therapy was superior to placebo in reducing the risk of CIB (odds ratio [OR], 0.44, 95% confidence interval [CI], 0.22–0.88). Messori et al.²⁰ conducted another meta-analysis that identified 5 RCTs with a total of 398 patients comparing ranitidine (but not other H₂RAs) with placebo and observed no statistically significant difference between the 2 groups (OR, 0.72; 95% CI, 0.3–1.7). The authors concluded that ranitidine is not superior to placebo for SUP. It is possible, however, that the lack of significant effect simply was due to small number of patients (imprecision) and to the fact that not all relevant studies were included in that analysis (i.e., only English language and only published studies). Recently, a systematic review comparing H₂RA with placebo and including 1836 patients from 17 RCTs reported significant results (OR, 0.47; 95% CI, 0.29–0.76; *P* < 0.002).¹⁶ Of note, all 3 meta-analyses did not

TABLE 2 Risk factors for stress-induced ulcer bleeding multivariate analysis

Risk factors	Cook et al. ⁹ (OR)	Ellison et al. ^{17a} (OR)
MV >48 hours	15.6 ^b	NS
coagulopathy	4.3 ^b	NS
hypotension	NS	NS
acute hepatic failure	1.6 (NS)	6.7 ^b
chronic renal failure	1.6 (NS)	3 ^c
prolonged NG tube placement	NS	2.6 ^b
history of alcohol abuse	not reported	2.2 ^c
<i>Helicobacter pylori</i>	not reported	1.9 ^c

a reported outcome was overt gastrointestinal bleeding

b $P < 0.001$

c $P < 0.05$

Abbreviations: NG – nasogastric, MV – mechanical ventilation, NS – nonsignificant, OR – odds ratio

show a statistically significant increase in the risk of nosocomial pneumonia with H₂RA treatment when compared with placebo (OR, 1.25; 95% CI, 0.78–2.00; OR, 1.10; 95% CI 0.45–2.66; and OR, 1.53; 95% CI 0.89–2.61; respectively).

Histamine₂-receptor antagonists vs. sucralfate

Cook et al.⁸ conducted a meta-analysis of 4 RCTs comparing sucralfate to H₂RA and found no statistically significant difference between the 2 interventions (OR, 1.28; 95% CI, 0.27–6.11).

A subsequent large multicenter, randomized, blinded, placebo-controlled trial that compared sucralfate with ranitidine in 1200 mechanically ventilated patients, found lower risk of CIB on ranitidine (1.7% vs. 3.8%; relative risk (RR), 0.44; 95% CI, 0.21–0.92; $P = 0.02$),²¹ with a number needed to treat estimate of 47. A recently published meta-analysis included 10 RCTs with a total of 2092 patients, although there were only 3 RCTs where CIB was an outcome. The authors did not report the pooled OR for this outcome, as there was significant heterogeneity between the studies. For overt bleeding, the results of 6 RCTs indicated no difference (OR, 0.87; 95% CI 0.49–1.53).²² Interestingly, the risk of nosocomial pneumonia was higher in patients treated with H₂RA (OR, 1.32; 95% CI, 1.07–1.64).²² This is consistent with the results of previous meta-analyses that showed a trend toward an increased risk of pneumonia with H₂RA compared with sucralfate use.^{8,20}

Proton-pump inhibitors vs. histamine₂-receptor antagonists

Two recently published meta-analyses summarized the data available on this subject, but reached different conclusions. The first meta-analysis by Pongprasobchai et al.²³ included a total of 569 patients from 3 RCTs. The overall incidence of CIB was lower in the group receiving proton-pump inhibitors (PPIs) when compared with the H₂RA group, 3.5% and 8% respectively (OR, 0.42; 95% CI, 0.20–0.91).²³ The rate of

CIB in the H₂RA group was higher than previously reported in the literature; this was related to the very high event rate in one of the included studies (31% in the H₂RA arm vs. 6% in the PPI arm).²⁴ A more recent meta-analysis included 936 patients from seven RCTs and reported no difference in the rate of CIB between PPI and H₂RA (risk difference of 0.04; 95% CI, –0.09 to 0.01; $P = 0.08$).²⁵ Significant heterogeneity was observed when all 7 studies were included ($I^2 = 66\%$), and this was reduced after excluding the study with the high event rate²⁴ ($I^2 = 26\%$). With the exclusion of this study, the analysis continued to indicate no significant difference (OR, 0.48; 95% CI, 0.21–1.08; $P = 0.08$). We have conducted a more up to date meta-analysis that included 1274 patients from 10 RCTs and found that PPIs were more effective in preventing CIB (RR, 0.36; 95% CI, 0.19–0.67).²⁶ The reason for the discrepancy between this and the previous meta-analysis²⁵ is possibly the choice of summary statistic. Risk difference was the only summary statistic that demonstrated insignificant results in the previous meta-analysis²⁵ (i.e., if the OR or RR were used to summarize the treatment effect of all 7 studies, the results would have been statistically significant). In our meta-analysis, the *a priori* defined subgroup analysis suggested that choice of drug delivery route (oral vs. parenteral) and dosing (once vs. twice a day) does not affect the results.²⁶ All 3 meta-analyses did not show a statistical significant difference in the rate of nosocomial pneumonia.^{23,25,26}

Enteral feeding In animal models, enteral alimentation has been demonstrated to protect the gastric mucosa from stress-related gastric mucosal damage.²⁷ There are no RCTs comparing enteral feeding to H₂RA or other SUP drugs. A recent meta-analysis comparing H₂RA and placebo for SUP looked into a subgroup of studies where most patients (>50%) received enteral feeding. In this subgroup, H₂RA did not change the risk of bleeding (OR, 1.26; 95% CI, 0.43–3.7). More importantly, mortality was higher in the H₂RA group in those studies (OR, 1.89; 95% CI, 1.04–3.44; $P = 0.04$).¹⁶ These findings were, however, derived from only 3 RCTs (2 for mortality), of which 2 were unblinded. According to the authors, these results, suggesting that GI prophylaxis with H₂RA may be harmful among patients receiving enteral feeding, could be only considered preliminary. The questions of SUP among patients receiving enteral nutrition remains open.

In summary, the last decade has provided clinicians with a considerable amount of data on relative efficacy of different drugs, but the choices remain diverse with H₂RA therapy being the most commonly used drug (FIGURE 1) both in the United States and in Europe.^{28–32} The results of systematic reviews on comparative RCTs are summarized in TABLE 3.

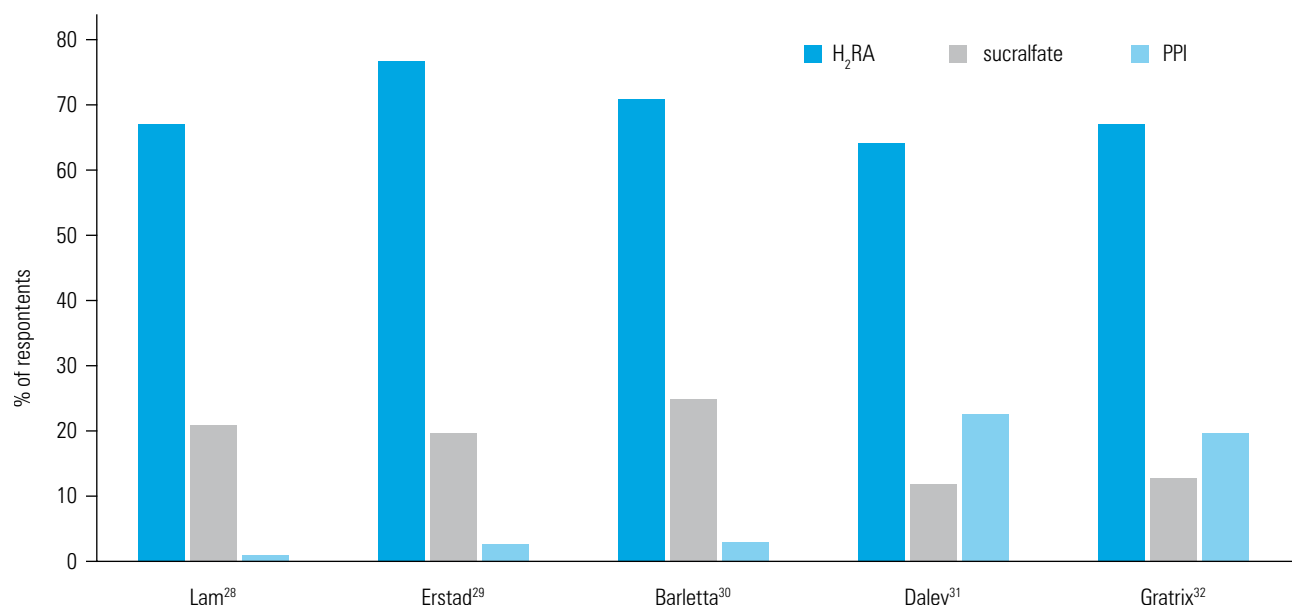


FIGURE 1 Recent surveys on stress ulcer prophylaxis use in the intensive care unit
Abbreviations: H₂RA – histamine₂-receptor antagonist, PPI – proton-pump inhibitor

Is acid suppression safe? None of the previous clinical trials and meta-analyses demonstrated the benefit of SUP in reducing mortality or ICU length of stay, neither comparing them with placebo or between different agents.

Thus, the relevant questions include not only the effect of different drugs on bleeding, but also on ventilator-associated pneumonia (VAP) and, more recently, questions surrounding the effect of H₂RA and PPI on the incidence of *Clostridium difficile*.³³

There have been numerous studies that questioned the safety of acid suppression, particularly from PPI therapy, also in the hospital setting. To some degree, those concerns may be applicable to the critically ill population. Studies suggest that PPI therapy may be associated with increased

risk of hospital acquired pneumonia.³⁴ The proposed mechanism includes an increase of gastric pH promoting the growth of bacteria in the stomach (particularly duodenal gram-negative bacilli) with esophageal reflux and aspiration of gastric contents leading to airway colonization or pneumonia. There are also concerns about increasing the risk of *Clostridium difficile* associated colitis³³ and apprehension that for patients taking clopidogrel, the efficacy of platelet inhibition may be reduced by PPI therapy with an increased risk of cardiovascular events.³⁵ Indeed, the Food and Drug Administration has warned that omeprazole, esomeprazole, and cimetidine should not be prescribed concomitantly with clopidogrel.³⁶ There is concern that these recommendations have not been transparent³⁷ and do not place sufficient

TABLE 3 Summary of meta-analyses on stress ulcer prophylaxis

Comparison	Meta-analysis	Number of patients (studies)	CIB measure of effect (95% CI)
H ₂ RA vs. placebo	Cook et al. ⁸	(10)	OR 0.44 (0.22–0.88)
	Messori et al. ²⁰	398 (5)	OR 0.72 (0.3–1.7)
	Marik et al. ¹⁶	1836 (17)	OR 0.47 (0.29–0.76)
sucralfate vs. placebo	Cook et al. ⁸	54 (1)	OR 1.26 (0.12–12.87)
	Cook et al. ⁸	(4)	OR 1.28 (0.27–6.11)
H ₂ RA vs. sucralfate	Huang et al. ²²	172 (3)	data were not pooled due to significant heterogeneity between 3 randomized clinical trials
PPI vs. H ₂ RA	Pongprasobchai et al. ²³	569 (3)	OR 0.42 (0.20–0.91)
	Lin et al. ²⁵	(7)	RD –0.04 (–0.09 to 0.01)
	Alhazzani et al. ²⁶	1274 (11)	RR 0.36 (0.19–0.67)
H ₂ RA vs. placebo (in studies where >50% of patients were receiving enteral nutrition)	Marik et al. ¹⁶	1836 (17)	OR 1.26 (0.43–3.70)

Abbreviations: CI – confidence interval, CIB – clinically important bleeding, H₂RA – histamine₂-receptor antagonists, RD – risk difference, RR – relative risk, others – see TABLE 2 and FIGURE 1

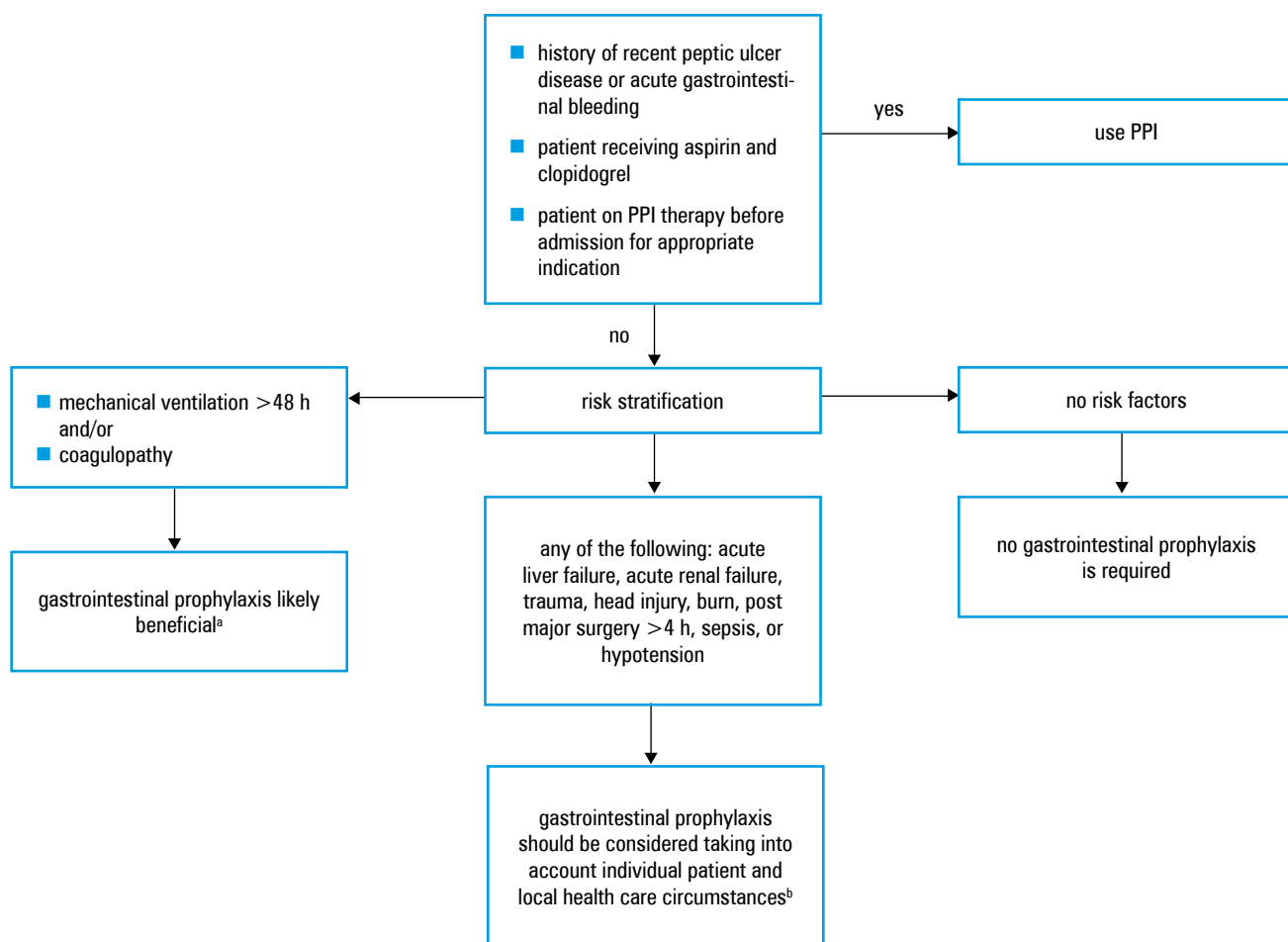


FIGURE 2 Our approach to stress ulcer prophylaxis in critically ill patients

a PPI appears to be more effective than H₂RA

b PPI appears to be more effective than H₂RA, but consider individual patient and local health care setting circumstances including the risk of ventilator-associated pneumonia (likely lowest with sucralfate), *Clostridium difficile* infection (likely highest with PPI), presence of enteral feeding (possibly lower benefit), and cost

Abbreviations: see TABLE 2 and FIGURE 1

weight on RCT evidence, which suggests that PPI therapy reduces the risk of upper GI bleeding in patients taking clopidogrel without increasing the risk of cardiovascular events.^{38,39} Other joint guidelines from the American College of Cardiology, the American Heart Association, and the American College of Gastroenterology recommend PPI therapy for those on clopidogrel with high risk of bleeding.⁴⁰ Most of the observational studies have shown that PPI therapy is preferentially prescribed to those that have multiple comorbidities, and observational data on the harms of PPI therapy may simply relate to this confounding factor.³⁴ Nevertheless, the possibility that acid suppressive therapy may be associated with clinically significant adverse events in a small number of patients cannot be excluded. As both drugs have very short half-lives, taking them with a large time gap between drugs (e.g., morning and night) may theoretically decrease the chance of interaction. Preferential use of pantoprazole in this situation is not supported by high-quality evidence.³⁸ The systematic reviews of PPI vs. H₂RA showed no increase in the risk of nosocomial pneumonia, but if both

drugs increase the risk this may explain the above observation. There was also no increased risk of nosocomial pneumonia in the systematic reviews of H₂RA vs. placebo but these analyses were underpowered for detecting a modest increase in these events. The overall effect is thus not entirely clear, but lack of harmful effect is not proven. Similar comment may apply to another potential undesirable effect of acid suppression in critically ill patients – *Clostridium difficile* infection. As gastric acid is important in eliminating ingested bacteria from the digestive tract, it is biologically plausible that raising the pH of the stomach may result in an increased load of pathogenic microbes and subsequent infections. No data are available from critically ill population, but indirect evidence derived from observational studies, both hospital and population based, suggest an increased risk of such infections especially in those taking PPIs (OR associated with PPI use was 1.96, 95% CI, 1.28–3.00 compared with OR associated with H₂RA of 1.40, 95% CI, 0.85–2.29).³³ Acid suppression is therefore best limited as prophylaxis to those at high risk of developing stress ulceration.

Our approach to stress ulcer prophylaxis among critically ill patients

The use and choice of the prophylactic agent is not straightforward and involves multiple steps. As we attempted to describe above, the indiscriminate use of SUP in all patients admitted to critical care setting is not warranted and may be harmful. On the basis of the available evidence, we propose the following course of action. First, the risk for bleeding should be considered in each patient and use of prophylaxis may not be appropriate for those at low risk. The risk of GI bleeding seems to be highest in mechanically ventilated patients or those with coagulopathy. In the absence of those risk factors presence of renal failure, liver failure, hypotension, sepsis, or other risk factors mentioned above may justify this intervention. The use of enteral feeding was not tested in an RCT; to our knowledge the only evidence available is derived from a subgroup analysis of 3 small RCTs with poor methodological quality. Also, it is not clear whether the site of feed infusion (stomach vs. distal to pylorus) affects the overall effect, as the data from comparative studies are lacking.

The choice of drug class remains difficult: moderate quality of evidence supports the use of PPI over H₂RA to lower bleeding events, with no evidence of increased risk of nosocomial pneumonia and no change in mortality. Moderate-to-high quality evidence support the use of H₂RA over sucralfate to prevent bleeding at the potential expense of increased risk of nosocomial pneumonia. The majority of studies were conducted prior to the era of widespread VAP prevention, so one of the factors influencing the decision may be the rate of VAP in an individual institution. For instance, the rate of VAP reported in 2010 in ICUs in Ontario was less than 5 per 1000 ventilator days (Safer Healthcare Now program), which should not alter the choice of drug for SUP.

FIGURE 2 summarizes our approach to the use of GI prophylaxis in the ICU. It follows that one may be inclined to forgo or limit pH increase (and thus either not use any SUP or use H₂RA rather than PPI, and use once a day rather than twice a day medication) in patients with a lower risk of bleeding, fed enterally, and in the setting of a higher risk of nosocomial pneumonia and *Clostridium difficile* infections. In contrast, the presence and severity of bleeding risk factors, lack of enteral nutrition, and epidemiological settings of low pneumonia and *Clostridium difficile* risk may result in the decision to use more vigorous pH-altering interventions.

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Profilaktyka stresogenego wrzodu trawiennego u chorych w stanie krytycznym – przegląd dostępnych danych

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SŁOWA KLUCZOWE

krwawienie ze stresogenego wrzodu trawiennego, leczenie zubożniające, chorzy w stanie krytycznym, zapobieganie krwawieniu z górnego odcinka przewodu pokarmowego

STRESZCZENIE

U chorych w stanie krytycznym istnieje ryzyko rozwoju stresogenego wrzodu trawiennego zlokalizowanego w górnym odcinku przewodu pokarmowego. Scharakteryzowano wiele czynników ryzyka w różnym stopniu związanych z rozwojem tej choroby. Wyniki badań prowadzonych od dziesięcioleci sugerują, że profilaktyka farmakologiczna może mieć korzystny wpływ na zmniejszenie częstości występowania istotnego klinicznie krwawienia z górnego odcinka przewodu pokarmowego, lecz pozostaje bez wpływu na umieralność. Rutynowo stosuje się taką profilaktykę u zagrożonych chorych. Opcje terapeutyczne to m.in. inhibitory pompy protonowej, antagoniści receptora histaminowego H₂ i sukralfat. Dobór strategii profilaktycznej zależy od wielu czynników, m.in. od obecności czynników ryzyka, zagrożenia rozwojem szpitalnego zapalenia płuc oraz, potencjalnie, od kosztów leczenia.

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