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REVIEW

Prevention of stress-related ulcer bleeding at the intensive care unit: Risks and benefits of stress ulcer prophylaxis

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Abstract

Stress-related mucosal disease is a typical complication of critically ill patients in the intensive care unit (ICU). It poses a risk of clinically relevant upper gastrointestinal (GI) bleeding. Therefore, stress ulcer prophylaxis (SUP) is recommended in high-risk patients, especially those mechanically ventilated > 48 h and those with a manifest coagulopathy. Proton pump inhibitors (PPI) and, less effectively, histamine 2 receptor antagonists (H2RA) prevent GI bleeding in critically ill patients in the ICU. However, the routine use of pharmacological SUP does not reduce overall mortality in ICU patients. Moreover, recent studies revealed that SUP in the ICU might be associated with potential harm such as an increased risk of infectious complications, especially nosocomial pneumonia and *Clostridium difficile*-associated diarrhea. Additionally, special populations such as patients with liver cirrhosis may even have an increased mortality rate if treated with PPI. Likewise, PPI can be toxic for both the liver and the bone marrow, and some PPI show clinically relevant interactions with important other drugs like clopidogrel. Therefore, the agent of choice, the specific balance of risks and benefits for individual patients as well as the possible dose of PPI has to be chosen carefully. Alternatives to PPI prophylaxis include H2RA and/or sucralfate. Instead of routine SUP, further trials should investigate risk-adjusted algorithms, balancing benefits and threats of SUP medication in the ICU.

Key words: Proton pump inhibitors; *Clostridium difficile*; Intensive care unit; Gastrointestinal hemorrhage; Stress; Histamine H2 antagonists; Risk assessment; Pneumonia; Physiological; Sucralfate

Core tip: To prevent gastrointestinal (GI) bleeding due to stress-related mucosal disease, critically ill patients are often routinely treated with proton pump inhibitors (PPI) or histamine 2 receptor antagonists (H2RA) for stress ulcer prophylaxis (SUP) in the intensive care unit (ICU). While major GI bleeding is currently rare in the ICU, SUP has not improved the overall survival of ICU patients in large clinical trials. Moreover, PPI and H2RA pose significant risks including toxicity, drug-drug-interactions

and infectious complications (*e.g.*, nosocomial pneumonia or *Clostridium difficile*-associated diarrhea). Instead of routine SUP, risk-adjusted algorithms may better balance benefits and threats of SUP in the ICU.

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INTRODUCTION

The gastric mucosa is sensitive to both hemodynamic changes and inflammatory signals in critical illness. The term stress-related mucosal disease (SRMD) has been introduced to describe the resulting mucosal damage ranging from single lesions to multiple gastric ulcers that may lead to major bleeding complications in critical ill patients[1].

With proton pump inhibitors (PPI) and histamine 2 receptor antagonists (H2RA) potent options for pharmacological prophylaxis of such lesions are available. Both are able to decrease the risk of a bleeding event effectively[2] and are usually well tolerated. However, pharmacological stress ulcer prophylaxis (SUP) in the intensive care unit (ICU) has not translated into a mortality benefit in prospective trials. Thus, recently, some intensivists have expressed concerns about the safety of SUP, especially with respect to infectious complications.

EPIDEMIOLOGY

SRMD, as defined by clinical, endoscopic or histological characteristics, is present in most critically ill patients[3]. However, only a few patients experience overt bleeding complications. The fraction of ICU patients with SMRD-related gastrointestinal (GI) bleeding has been reported to be as high as 17% in earlier trials and in patients without prophylaxis[4,5] but has remarkably decreased at present to rates as low as 1% or below[2,6,7].

PATHOPHYSIOLOGY

In most critically ill patients, the gastric mucosal blood flow is impaired. Reasons include systemic hemodynamic changes (hypotension and/or vasopressor therapy) and/or local alterations, *e.g.,* reduced splanchnic blood flow because of positive end-expiratory pressure in mechanical ventilated patients[8]. In addition to the ischemic tissue damage itself, hypoperfusion leads to a reduced production of several protective mechanisms that exist in a healthy stomach (Figure 1)[4]. The latter include various components such as mucus, phospholipids, bicarbonate, trefoil factor family peptides and heat-shock proteins[9]. For example, gastric ischemia/reperfusion in an experimental rat model led to an inhibition of both cyclooxygenase and lipoxygenase pathways, resulting in lower prostaglandin levels (especially PGE2), lower bicarbonate levels and decreased gastric mucosal defense[10,11]. Moreover, two important molecular regulators of vascular tension are dysregulated in critical illness. While the production of the vasodilator nitric oxide is reduced, the level of endothelin-1, a strong vasoconstrictor, is significantly increased[12,13]. This shift can further harm the mucosa.

While these mechanisms can cause mucosal damage, they are often insufficient by themselves to cause major ulcerations and gastric bleeding. A crucial component for overt damage is the presence of gastric acid. Without acid, mucosal damage is only minimal. In animal models of gastric ischemia, the addition of acid increased the damage by factor of ten[12]. This provides the rationale for the use of acid-suppressive drugs such as PPI or H2RA for pharmacological prophylaxis.

MORTALITY RISK OF STRESS ULCER-RELATED BLEEDING

An acute bleeding episode due to a stress ulcer is associated with an increased risk of death in the ICU. In a large prospective trial by Cook *et al*[14] the mortality of patients with stress ulcer bleeding was 49% compared to 9% in those without an episode of GI bleeding. This latter figure, however, appears unusually low for a general ICU population, raising the concern that related co-factors (*e.g.,* co-morbidities, medication) might have affected the mortality risk of ICU patients who experienced bleeding.

Moreover, the patients in this study mainly underwent cardiovascular surgery and only 1.6% presented with sepsis, provoking the question whether the numbers can be extrapolated to other settings of critical illness[14]. Nonetheless, a more recent study by the same authors using multivariate analysis for adjustment showed an increased relative risk (RR) of 1 to 4 (dependent on the model used) as well as an extension of the ICU stay by up to eight days in ICU patients with GI hemorrhage[15].

In contrast to these findings, in a more recent study including 1034 patients in 97 ICUs, GI bleeding was not associated with an increased mortality in multivariate analysis after adjusting for severity of comorbidity, other organ failure and age[7], in line with two meta-analyses reported in 2012 and 2013[2,16]. However, these recent studies all reported a very low incidence of stress ulcer-related bleeding due to effective pharmacological and non-pharmacological prophylactic measures, which may not allow proper assessment of true mortality risk.

RISK FACTORS FOR STRESS ULCER-RELATED BLEEDING

Multiple investigations have been conducted to identify patients at risk for stress ulcer-related bleeding. A

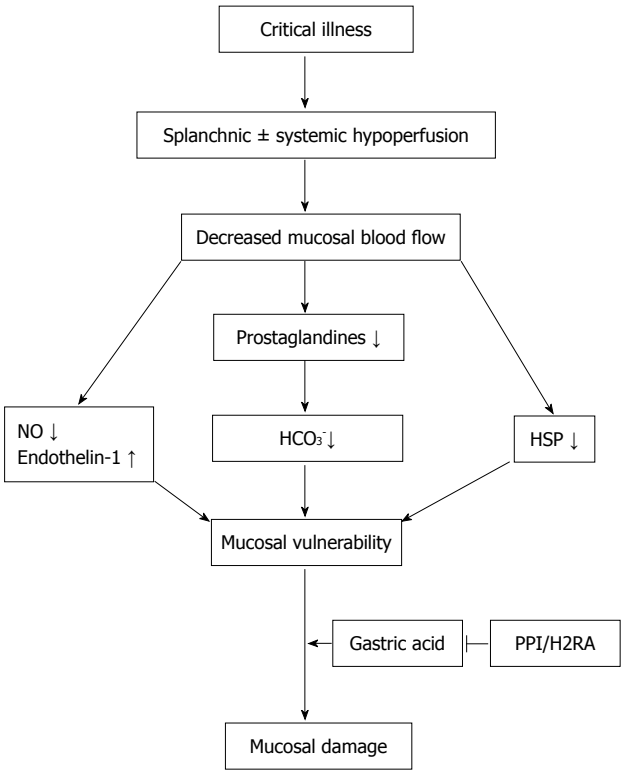

Figure 1 Pathophysiology of stress-related mucosal disease and rationale for the routine use of proton pump inhibitor/histamine 2 receptor antagonists at the intensive care unit. NO: Nitric oxide; PPI: Proton pump inhibitor(s); H2RA: Histamine 2 receptor antagonists; HSP: Heat-shock proteins; HCO_3^-: Bicarbonate.

large, prospective multicenter trial of 2252 ICU patients was able to identify at multiple regression two main risk factors: mechanical ventilation (OR = 15.6; $P < 0.001$) and coagulopathy (OR = 4.3; $P < 0.001$). In the absence of both risk factors the bleeding rate was as low as 0.1%[14]. A smaller, earlier trial came to the same conclusion[17]. A more recent inception cohort study ($n = 1034$) identified the presence of more than three or more comorbidities (OR = 8.9; 95%CI: 2.7-28.8), liver disease (OR = 7.6; 95%CI: 3.3-17.6); use of renal replacement therapy (OR = 6.9; 95%CI: 2.7-17.5); a coexisting (OR = 5.2; 95%CI: 2.3-11.8) or acute coagulopathy (OR = 4.2; 95%CI: 1.7-10.2) and higher SOFA-score (OR = 1.4; 95%CI: 1.2-1.6) as significant risk factors after multivariate analysis. Interestingly, mechanical ventilation was not associated with an increased risk of GI bleeding in this trial[7].

Other risk factors with a lower degree of evidence include patients with severe head trauma, those who have had extended surgeries with operation times exceeding 4 h as well as patients with acute kidney or hepatic failure, sepsis, hypotension, a history of gastrointestinal bleeding, high-dose corticosteroids, burn patients, advanced age and male sex[1,3,17,18]. This wide spectrum of suggested risk factors has prompted the rather unselected use of pharmacological SUP in the ICU setting, resulting in the routine use of PPI and/or H2RAs in > 80% of critically ill patients as reported in in many observational studies[6,7].

INDICATIONS FOR PHARMACOLOGICAL PROPHYLAXIS

While SRMD-related bleeding can have severe clinical impact, acid-suppressive medication effectively decreases bleeding rates as demonstrated by multiple meta-analyses on this topic[19-22]. Although the quality of the available data has been criticized[23], both national and international guidelines recommend stress ulcer prophylaxis (SUP) in critically ill patients with sepsis and other risk factors[24,25].

In our ICU, patients with at least one of the following risk factors are recommended to receive pharmacological ulcer prophylaxis based upon current evidence: Mechanical ventilation, coagulopathy, history of an upper gastrointestinal bleeding within the past 12 mo, severe sepsis or septic shock, or cardiogenic shock. Additionally, we consider ulcer prophylaxis for the following patients based on weaker evidence: burn patients, those with cranio-cerebral injury, acute renal failure, known peptic ulcer disease, those post kidney or liver transplantation and patients taking non-steroidal anti-inflammatory drugs (NSAID) or high-dose glucocorticoids. The algorithm that we propose for SUP in the ICU is presented as Figure 2.

However, it is mandatory to frequently re-evaluate the individual indication both during and after ICU stay. Buckley *et al*[26] could show that 14.4% of patients in an ICU received acid suppression without proper indication, which resulted in unnecessary risk of side effects (see below) and unnecessary costs (> 200000 dollar annually in the study hospital).

While prophylaxis effectively decreases the risk of stress ulcer-related bleeding, it is important to stress that no single trial and/or meta-analysis has been able to convincingly demonstrate a benefit regarding survival. Outside an ICU or even in outpatients, very little evidence supports the use of stress ulcer prophylaxis; for instance, patients with cardiovascular diseases who have concomitant newly prescribed with the oral anticoagulant dabigatran may be at lower risk for severe GI bleedings if PPI are administered[27]. Without a proper indication or a clear high-risk assessment, SUP should be discontinued, because it might cause unnecessary harm (see below) as well as costs[22].

PHARMACOLOGICAL PROPHYLAXIS

If a stress ulcer prophylaxis is necessary, different options are available: Options include the acid-suppressing drugs, PPI and H2RA, or the mucosa-protective agent sucralfate. Sucralfate is a reasonable option and reduces the risk of stress ulcer-related bleeding. However, a large trial revealed its inferiority to H2RA[28], so that an acid-suppressive medication is preferred for SUP.

There are several trials and meta-analyses comparing PPI to H2RA. Most of them favor PPI with respect to reduction of bleeding rates (Table 1). Regarding mortality, no analysis has been able to show a significant difference. Currently, PPI are the agents of choice in SUP.

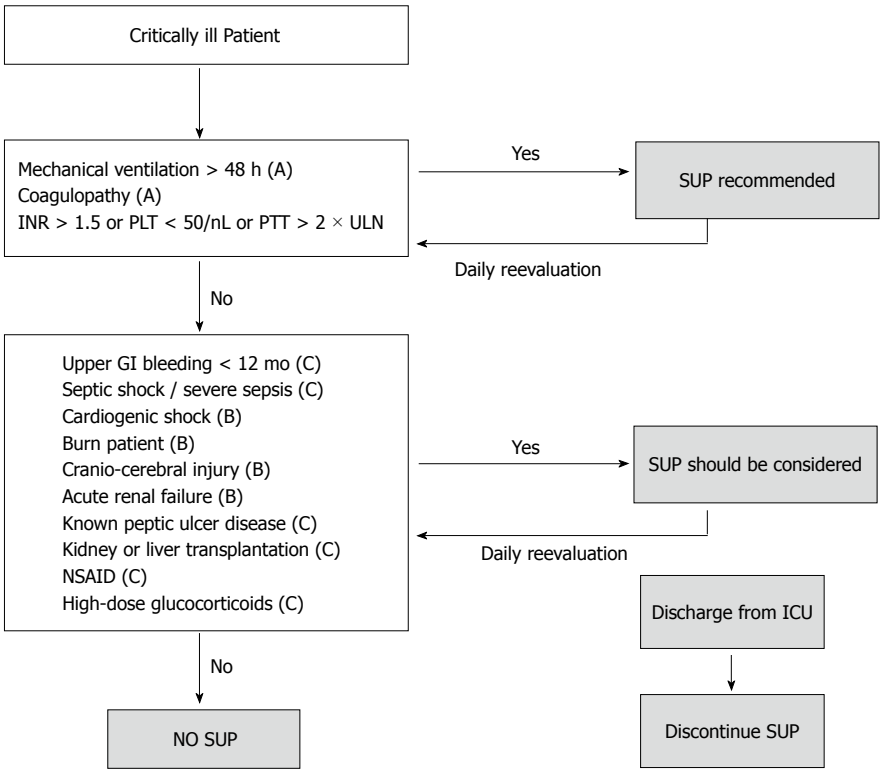

Figure 2 Proposed algorithm for stress ulcer prophylaxis. For the different indications for SUP, the level of evidence is provided [A: Multiple randomized trials or meta-analysis, B: Single randomized or large non-randomized trial(s), C: Expert opinion or retrospective studies]. GI: Gastrointestinal; ICU: Intensive care unit; INR: International normalized ratio; NO: Nitric oxide; NSAID: Nonsteroidal anti-inflammatory drugs; PLT: Platelets; PTT: Partial thromboplastin time; SUP: Stress ulcer prophylaxis.

Table 1 Efficacy of proton pump inhibitor compared to histamine 2 receptor antagonists at the intensive care unit

Meta-analysis	*n*	Risk reduction (bleeding)	Risk reduction (mortality)
Alhazzani *et al*[2]	1720	RR = 0.36 (95%CI: 0.19-0.67)	RR = 1.01 (95%CI: 0.83-1.24)
Pongprasobchai *et al*[59]	569	OR = 0.42 (95%CI: 0.20-0.91)	n/a
Barkun *et al*[60]	1587	OR = 0.30 (95%CI: 0.17-0.54)	OR = 1.19 (95%CI: 0.84-1.68)
Lin *et al*[61]	936	RD = 0.04 (95%CI: 0.09-0.01)	RD = 0.00 (95%CI: 0.04-0.05)

n/a: Not assessed; *n*: Patients included in the meta-analysis; RR: Relative risk; OR: Odds ratio; PPI: Proton pump inhibitor(s); RD: Risk difference.

ADVERSE EVENTS

Gastric acid is a natural physiological barrier against ingested pathogens. Pharmacological acid suppression alters this barrier significantly. Subsequently, it is associated with gastric and duodenal bacterial overgrowth[29]. This effect is stronger in patients receiving PPI than in those taking H2RA[30]. The loss of this natural barrier may lead to intestinal (*e.g., Clostridium difficile*-associated diarrhea), but also to extra-intestinal infections (*e.g.,* pneumonia, possibly *via* retrograde microaspiration). In addition, both PPI and H2RA potentially affect leucocyte function: Experimental studies have shown an effect of these drugs on both phagocytosis by neutrophils itself and the acidification of the phagolysosome in neutrophils necessary to kill its contents[31,32].

As the effects of acid-suppressing drugs may render patients susceptible for infections, two main complications have to be considered: *Clostridium difficile*-associated diarrhea (CDAD) and pneumonia. In outpatients and patients on standard care wards, it has been shown that PPI increase the risk of both significantly[6,33-44]. Additionally, experiments in mice suggest that acid suppression favors intestinal colonization with multi-resistant bacteria such as Vancomycin-resistant *Enterococcus faecium* (VRE) or multi-resistant *Klebsiella pneumonia*[45].

In the setting of SUP in the ICU, the data are controversial (Table 2). Two meta-analyses failed to show any effect on the rate of nosocomial and/or ventilator-associated pneumonia[2,16]. However, only seven of the original studies included reported on pneumonia. In contrast, a small (n = 137) but prospective and randomized trial showed a strong increase in ventilator-associated pneumonia within the PPI group compared to placebo (36.4% *vs* 14.1%, $P < 0.001$)[46].

A retrospective study from our group found a significant association of PPI with pneumonia only by univariate but not by multivariate analysis[6]. A prevalence study including over 10000 patients from 17 countries identified SUP as an independent risk factor for infections[47]. Thus, the role of acid suppression as a risk factor for pneumonia is unclear but remains likely. Larger randomized prospective

Table 2 Acid suppression as a risk factor for pneumonia at the intensive care unit

Acid suppression as a risk factor for		Pneumonia
Barkun *et al*[16]	Meta-analysis	OR = 1.05 (95%CI: 0.69-1.62)
Alhazzani *et al*[2]	Meta-analysis	RR = 1.06 (95%CI: 0.73-1.52)
Khorvash *et al*[6]	Randomized controlled trial	14.1% without *vs* 36.4% with PPI, $P < 0.001$
Buendgens *et al*[6]	Retrospective cohort study	OR = 1.28 (95%CI: 0.95-1.73)

OR: Odds ratio; RR: Relative risk; PPI: Proton pump inhibitor.

trials are warranted to resolve this issue.

The main infection route of *C. difficile* is *via* ingestion of its spores and its vegetative forms. While the spores are naturally resistant to acid, the vegetative form is normally killed by acid in the stomach. If the stomach pH is raised above 5, *Clostridia* species show drastically improved survival. Given that the stool of infected individuals contains tenfold more vegetative forms than spores, this might explain an association of PPI and H2RA with CDAD[48].

Although no prospective data is available on this matter for critically ill patients, studies suggest an association between pharmacological SUP and CDAD in the ICU (Table 3). A small case-control study showed a positive association between the duration of PPI therapy and the risk of CDAD[49]. A retrospective study with 3286 ICU patients demonstrated PPI as an independent risk factor for CDAD by multivariate analysis (OR = 3.11; 95%CI: 1.11-8.74), comparable to the risk for CDAD associated with the use of fluoroquinolones or third-generation cephalosporins. Moreover, in this trial an ICU-onset CDAD was associated with an increased mortality (OR = 1.59; 95%CI: 1.06-2.41)[6]. Another recent study from Canada revealed a significant association with CDAD recurrence rates and continuation of PPI therapy (OR = 1.5; 95%CI: 1.1-2.0), similar to antibiotic reexposure (OR = 1.3; 95%CI: 0.9-1.7)[50].

Patients with liver cirrhosis appear to pose a population particularly prone to adverse effects of SUP. A prospective study including 272 patients with cirrhosis found the use of PPI to be an independent risk factor for overall mortality by multivariate analysis in those patients (HR = 2.3; 95%CI: 1.3-4.3)[51]. Reasons for this might be an increased risk of spontaneous bacterial peritonitis in addition to higher rates of pneumonia and CDAD[52-54].

Drug-drug-interactions are another concern for using PPI, especially in ICU patients. An important possible interaction exists between the antiplatelet agent clopidogrel and various PPI. In 2009, a study reported increased cardiovascular events in patients taking both clopidogrel and PPI[55]. The antiplatelet agent clopidogrel is a prodrug, dependent on the enzyme CYP2C19. *In vitro* PPI inhibit CYP2C19 and potentially inhibit clopidogrel. It remains unclear if this experimental finding is of clinical

Table 3 Proton pump inhibitor as a risk factor for *Clostridium difficile*-associated diarrhea at the intensive care unit

PPI as a risk factor for		*Clostridium difficile*-associated diarrhea (OR, 95%CI)
Barletta *et al*[49]	Case control study	1.14 (1.02-1.27)
Buendgens *et al*[6]	Retrospective cohort study	3.11 (1.11-8.74)

OR: Odds ratio; PPI: Proton pump inhibitor.

importance, since the patients with concomitant use of PPI and clopidogrel might have had a higher intrinsic risk due to greater age and more cardiovascular risk factors. In order to overcome this potential interaction, independent ingestion times, the use of pantoprazole (a PPI with low interaction potential) and/or replacing clopidogrel with ticagrelor, which is not a prodrug, have been suggested.

Other side effects of PPI potentially relevant for critically ill patients include toxicity to liver or bone marrow and hypomagnesaemia. The latter has resulted in a recent warning from the Food and Drug Administration of the United States[56]. Osteopenia, another known association, seems less important acutely in ICU patients[57]. It is currently unknown if those adverse effects affect the prognosis of patients in an ICU.

ENTERAL NUTRITION

With regard to the potential adverse effects of SUP as described above, potential alternatives have been discussed. One should also keep in mind that both PPI and H2RA do not have a direct effect on the SRMD pathophysiology of reduced blood flow and altered balance between vasoconstrictors and dilatators (Figure 1). Enteral nutrition, in contrast, potentially has a positive impact on both[58]. Enteral nutrition could therefore be a viable alternative to pharmacological SUP. However, no prospective data is available on this subject. A meta-analysis of data available on 1836 patients disclosed that in presence of enteral nutrition a pharmacological SUP did not significantly change the risk of stress ulcer-related bleeding. Interestingly, in those patients that were enterally fed and treated with SUP the risk of pneumonia was increased (OR = 2.81; 95%CI: 1.2-6.6) compared to patients on parenteral nutrition. In this subgroup, even an increase in mortality was observed[21]. Therefore, the role of enteral nutrition in SUP should be further explored in randomized prospective trials.

CONCLUSION

Critically ill patients often develop gastrointestinal lesions due to altered perfusion of the gastric mucosa, reduced protective mucosal factors and increased gastric acid, rendering them at risk for GI bleeding due to SRMD or ulcers. Pharmacological SUP is performed in the majority of ICU patients at present, with PPI or H2RA effectively preventing GI bleeding. However, this common practice

is currently debated, due to the fact that SUP does not significantly improve mortality of ICU patients, while acid suppression poses relevant risks. Specifically, nosocomial pneumonia and *Clostridium difficile* associated diarrhea are potential serious complications of SUP. Thus, SUP should follow a clear algorithm balancing risks and benefits (Figure 2). Alternative strategies like enteral feeding or restricting SUP to the early phase of ICU treatment or to patients with an exceptional high-risk profile deserve evaluation in prospective randomized trials.

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