Stress ulcer prophylaxis in the intensive care unit

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Purpose of review
Stress ulcer prophylaxis (SUP) is considered standard of care in the majority of critically ill patients in the ICU. In this review, we will present the current evidence for the use of SUP in ICU patients, including data on the prevalence of gastrointestinal bleeding and the balance between benefits and harms of SUP.

Recent findings
The prevalence of overt gastrointestinal bleeding in critically ill patients is in the area of 5%. Consistent risk factors for gastrointestinal bleeding have been identified, but indications for SUP vary considerably. SUP is used in three out of four critically ill patients, most frequently in the form of proton pump inhibitors. A recent systematic review of SUP vs. placebo or no prophylaxis in critically ill patients highlights the lack of evidence supporting the use of SUP. Importantly, data suggest potential harm, including increased risk of nosocomial infections and cardiovascular events.

Summary
The prevalence of gastrointestinal bleeding in critically ill patients in the ICU is low, the prognostic importance is ambiguous, and SUP is widely used. The balance between benefits and harms of SUP is unknown, and clinical equipoise exists. High-quality randomized controlled trials and systematic reviews assessing benefits and harms of SUP in ICU patients are highly warranted.

Keywords
acid suppressants, gastrointestinal bleeding, risk factors, side-effects, stress ulcer prophylaxis

INTRODUCTION

Critically ill patients in the ICU are at risk of developing stress-related mucosal damage [1]. The pathophysiology is not completely understood, but it has been hypothesized that stress ulcerations are caused by decreased mucosal blood flow, ischaemia and reperfusion injury, and hence are less related to acid secretion than peptic ulcers [2▪▪]. The majority of stress ulcerations are superficial and asymptomatic, but the ulceration can progress and erode larger vessels resulting in overt gastrointestinal bleeding [3].

To prevent gastrointestinal bleeding in critically ill patients, stress ulcer prophylaxis (SUP) was introduced more than 40 years ago [4]. Different agents for prevention of gastrointestinal bleeding have been used through the years. Initially, antacids and later sucralfate were the preferred agents, but with the introduction of histamine-2-receptor antagonists (H2RAs) the opportunity of intravenous administration became available. In a randomized controlled trial (RCT) from 1998, a significantly lower incidence of gastrointestinal bleeding in patients receiving H2RA compared with sucralfate was reported [5]. Later on, proton pump inhibitors (PPIs) were introduced and today the vast majority of prescribed SUP is H2RA or PPI [6▪▪,7]. Today, SUP is recommended in international guidelines and is standard of care in the majority of critically ill patients in ICUs worldwide [8,9▪]. However, in recent years, the evidence base for SUP in critically ill patients has been questioned, and clinical equipoise exists [10▪▪,11▪].

In this review, we will present current data on gastrointestinal bleeding and SUP in critically ill patients in the ICU.

THE PREVALENCE OF GASTROINTESTINAL BLEEDING IN CRITICALLY ILL PATIENTS

The reported prevalence of gastrointestinal bleeding among the general ICU population varies between 2 and 5% which may be because of heterogeneous

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KEY POINTS

- The prevalence of gastrointestinal bleeding in critically ill patients is low and not all gastrointestinal bleedings are because of conditions prevented by acid suppressants.
- A high number of ICU patients are prescribed acid suppressants but it remains unresolved whether stress ulcer bleedings are prevented by these drugs.
- Acid suppressants may increase the risk of pneumonia and *C. difficile* infections – conditions associated with increased mortality.
- Recent systematic reviews have not been able to confirm improved outcome in patients receiving SUP.
- Benefits and harms of SUP are unknown and prophylaxis should not be used routinely until firm evidence from high-quality trials and systematic reviews is available.

populations, varying definitions of gastrointestinal bleeding, and difficulties in diagnosing stress ulcers [1,6▪▪,12▪▪,13,14]. Importantly, the reported estimates often include all conditions resulting in gastrointestinal bleeding, and not solely stress ulcer and other bleedings prevented by acid suppressants. In a cohort study by Cook *et al.* [15] stress ulceration was identified as the sole source of gastrointestinal bleeding by endoscopy in less than 50% of the patients, suggesting that sources of gastrointestinal bleeding not prevented by SUP are frequent.

Data from a recent international mixed ICU cohort showed a prevalence of overt gastrointestinal bleeding of 4.7%, and 2.6% of clinically important gastrointestinal bleeding [6▪▪]. Consequently, the prevalence of gastrointestinal bleeding in today's ICU patients seems relatively low.

RISK FACTORS FOR GASTROINTESTINAL BLEEDING IN CRITICALLY ILL PATIENTS

Most guidelines distinguish between high-risk and low-risk patients when prescribing SUP, and several studies have sought to identify factors predicting gastrointestinal bleeding [8,16]. A landmark multicentre, prospective cohort study by Cook *et al.* from 1994 ($n = 2252$) highlighted mechanical ventilation at least 48 h [odds ratio (OR) 15.6] and coagulopathy (OR 4.3) as major risk factors for gastrointestinal bleeding in critically ill patients [17], and today these risk factors are widely accepted [9▪]. However, almost half of the patients (48.5%) included in this study were cardiovascular surgical patients with an all-cause mortality of less than 10% [17]. This is in contrast to mixed ICU populations as of today with reported mortality rates of 25–35% [6▪▪,18,19]. This may partly explain why recently published observational studies have not been able to confirm that mechanical ventilation consistently is a risk factor for gastrointestinal bleeding [6▪▪,12▪▪]. Additionally, proposed risk factors for gastrointestinal bleeding, including acute kidney injury, hepatic failure, acute and chronic disease severity, and coagulopathy have been confirmed in recent studies [6▪▪,12▪▪,20▪▪]. Severe head or spinal injury, burn injury, long lasting surgery, high-dose corticosteroids and acute lung injury have also been identified as risk factors for gastrointestinal bleeding, but the evidence supporting these findings is weak, as a result of a high risk of systematic and random errors [16,21,22▪,23]. Finally, it has been suggested that enteral feeding decreases the risk of gastrointestinal bleeding [24]. However, this was not confirmed in a recently published systematic review of RCTs of SUP with PPI or H2RA vs. placebo/no control [10▪▪]. Despite the ambiguous evidence of enteral nutrition on the risk of gastrointestinal bleeding, studies reveal that clinicians takes enteral nutrition into account, when prescribing or discontinuing SUP [9▪,25].

THE PROGNOSTIC IMPORTANCE OF GASTROINTESTINAL BLEEDING IN CRITICALLY ILL PATIENTS

Gastrointestinal bleeding among ICU patients is considered a serious condition which has been estimated to result in a 1–4 times increased risk of mortality and an excess length of ICU stay of 4–8 days [1,26▪]. A recent international cohort study confirmed a crude association between clinically important gastrointestinal bleeding and increased mortality, but when adjusting for age, disease severity, and comorbidities the association was no longer statistically significant, indicating that the excess mortality largely is explained by confounding [6▪▪]. High-quality RCTs assessing mortality as the primary outcome measure are needed to confirm this finding [11▪].

STRESS ULCER PROPHYLAXIS

Epidemiology

Acid suppressants are the most frequently prescribed off-label drugs in the ICU, and prophylaxis of stress ulcers the most frequent indication [27▪]. PPI is more frequently used than H2RA in most countries, with pantoprazole being first choice PPI [9▪,12▪▪]. Acid suppressants are used in 75% of all ICU patients [9▪,25], indications for prescribing

SUP vary considerably [9▪,25], and inappropriate use appears to be common [7]. In a 2014 US survey, respondents indicated that a median of 90% of their ICU patients were started on SUP while in the ICU [25], and another recent survey concluded that around 22% of patients prescribed SUP met no criteria for appropriate SUP prescription [7]. Farley *et al.* [28] recently reported that 63% of patients initiated on acid suppressants at ICU admission were discharged from the ICU without discontinuation of the drug, and in 39% acid suppressants were inappropriately continued at hospital discharge. Apart from increased cost for the patient there is a risk of interactions and long-term side-effects related to continued use of acid suppressants [29,30].

Benefits of stress ulcer prophylaxis

For years RCTs have sought to provide evidence for a clinical benefit of SUP with H2RA or PPI compared with placebo or no prophylaxis [31–33]. A systematic review with meta-analysis and trial sequential analysis (TSA) assessed the existing evidence in 2014 [10▪▪]. Twenty trials comparing H2RA ($n = 20$ trials) or PPI ($n = 2$ trials) with placebo or no prophylaxis were included. All included trials had high risk of bias, and the risk of random error (as assessed by TSA) was high. The conventional meta-analysis and TSA showed no statistically significant difference in all-cause mortality at longest follow-up. Even though the conventional meta-analysis indicated an increased risk of gastrointestinal bleeding in the placebo/no prophylaxis group, the TSA highlighted the high risk of a spurious finding (random error because of repetitive testing), as the cumulative sample size only reached 22% of the required sample size. Consequently, it was concluded that the quantity and quality of evidence supporting the use of SUP is low.

PPI and H2RA have also been compared with each other in several RCTs and meta-analyses [31,34▪▪,35,36]. The most recent meta-analysis (14 trials) by Alhazzani *et al.* [34▪▪] found that PPI was more effective than H2RA in reducing both clinical and overt gastrointestinal bleeding. However, the clinical relevance of this finding may be questioned as long as there is no evidence that PPIs or H2RAs are superior to placebo.

Harms of stress ulcer prophylaxis

Pneumonia

An observational study from 2014 assessing 35 312 mechanically ventilated adult patients receiving either PPI or H2RA found an increased risk of pneumonia in patients receiving PPI as compared with those receiving H2RA [12▪▪]. However, earlier systematic reviews of RCTs evaluating the risk of nosocomial pneumonia in patients receiving SUP do not support this finding [24,34▪▪,37,38]. A recent systematic review of RCTs comparing PPI or H2RA to placebo/no prophylaxis showed no difference in the risk of pneumonia between PPI and H2RA [10▪▪]. Importantly, SUP with PPI vs. placebo has only been assessed in high risk of bias trials with a very limited number of patients [31,33,39], thereby challenging interpretation of harm associated with use of SUP [10▪▪,11▪].

Clostridium difficile infection

Clostridium difficile infection is associated with increased mortality and excess length of ICU stay in critically ill patients [26▪]. As gastric acidity may be protective against infections, treatment with acid suppressants is hypothesized to increase the risk of *C. difficile* infections [40]. No RCTs have assessed the association between treatment with PPI or H2RA and *C. difficile* infection in critically ill patients in the ICU [10▪▪]. A recently published observational study in critically ill patients assessed the association between treatment with acid suppressants and adverse outcome [12▪▪]. The authors concluded that critically ill patients requiring mechanical ventilation and receiving PPI have a higher risk of *C. difficile* infection than patients receiving H2RA. Apart from the observational design, the study is hampered by the absence of data comparing SUP with placebo/no prophylaxis. The hypothetically increased risk of *C. difficile* infection in patients receiving acid suppressants is supported by observational data outside the ICU, as aggregate data in patients using acid suppressants for other indications than SUP (39 studies including 313 000 patients) suggest an increased risk of *C. difficile* infection in patients receiving PPI (OR 1.74, 95% confidence interval 1.47–2.85).

Cardiovascular events

An increased risk of cardiovascular events in patients receiving PPI has been suggested, and possible mechanisms leading to this have been investigated [41–45]. It has been hypothesized that the combination of clopidogrel and PPI results in increased risk of adverse cardiac events, but data on this are ambiguous [41,44,45]. An observational study of 56 406 patients points at an increased risk of cardiovascular events in non-ICU patients treated with PPI independent of treatment with clopidogrel [42]. However, research assessing the association

between PPI and cardiovascular events in critically ill patients is weak and high-quality data are needed before drawing conclusions.

CONCLUSION

The prevalence of gastrointestinal bleeding in critically ill patients in the ICU is low, the prognostic importance is ambiguous, and SUP is widely used. Not all gastrointestinal bleedings are because of conditions prevented by acid suppressants and it remains unresolved whether stress ulcer bleedings are prevented by SUP. Importantly, the balance between benefits and harms of SUP is unknown, and clinical equipoise exists.

We recommend that SUP is not used routinely, as there is no firm evidence for benefit or harm. High-quality RCTs and systematic reviews assessing benefits and harms of SUP are highly warranted.

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Conflicts of interest

There are no conflicts of interest.

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