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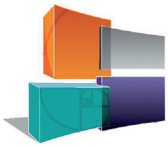

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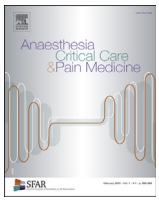

Editorial

Prophylaxis for stress related gastrointestinal bleeding in the ICU: Should we adjust to each patient's individual risk?

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Clinicians worldwide administer stress ulcer prophylaxis (SUP) in 80 to 90% of critically ill and injured patients [1,2], although the incidence of overt stress-related gastrointestinal bleeding (SRGIB) is low (0.6 to 6%), and varies with diagnostic definition, the prophylaxis prescribed, and the studied population [3,4]. The use of SUP is based on evidence gained from randomised trials performed over the past four decades, and most guidelines recommend the use of either histamine H_2-receptor antagonists (H_2RAs) or proton-pump inhibitors (PPIs) in intensive care unit (ICU) patients who are at risk of developing SRGIB [5,6].

The pathophysiology of SRGIB is not fully elucidated [7]. The stomach is normally protected by a layer of alkaline mucus gel that forms a physical barrier to hydrogen ion backward diffusion and traps bicarbonate. The bicarbonate neutralises gastric acid adjacent to the stomach wall. This barrier may be broken down by increased concentrations of refluxed bile salts or uremic toxins, which are common in critically ill patients [8]. Hypersecretion of acid due to excessive gastrin stimulation by parietal cells has been detected in patients with head trauma [9]. Stress related ulcers may be less related to acid secretion, than to decreased mucosal blood flow, ischaemia and reperfusion injury in ICU patients [7].

The identification of patients at risk of developing SRGIB (Fig. 1) is based on characteristics relating to the severity of acute (e.g., shock, respiratory failure, head trauma, thermal injury) and chronic illness (e.g., renal dysfunction, liver disease, coagulopathy), the use of certain drugs, such as anticoagulants, antiplatelet agents or NSAIDs, and therapeutic interventions, namely mechanical ventilation lasting 48 h or more, renal-replacement therapy, and extra-corporeal life support [3,4,10,11].

Recently, the Stress Ulcer Prophylaxis in the Intensive Care Unit (SUP-ICU) Trial group reported on a large randomised, placebo-controlled, clinical trial evaluating a single dose of pantoprazole (40 mg) given as a bolus intravenous injection once daily from the time of randomisation until ICU discharge or death [12]. The primary endpoint was death up to 90 days after randomisation. The main inclusion criteria were patients 18 years or older who were admitted to the ICU for an acute condition and had at least one risk factor for SRGIB, including shock, use of anticoagulant agents at curative dose, renal-replacement therapy, mechanical ventilation (expected to last $>$ 24 hours), any history of liver disease, or any history of or ongoing coagulopathy (platelets below 50×10^9/L, or INR above 1.5, or prothrombin time above 20 s). A total of 3298 patients were included and received either pantoprazole or placebo for a median of 4 days (interquartile range, 2 to 9 days in both groups). There was no significant difference between groups in the rate of the primary outcome (31.1% and 30.4%, for pantoprazole and placebo respectively). The endpoint of clinically important GI bleeding was part of a composite outcome measure, and no statistical testing on this outcome alone was carried out due to the lack of adjustment for multiple comparisons; numerically, however, the rates were 2.5% in the pantoprazole group vs 4.2% in the control group (Relative Risk (RR) 0.58; 95% confidence interval (CI) 0.40–0.86). In this trial, the authors did not mandate diagnostic endoscopy to assess the source of bleeding and were therefore unable to differentiate between stress ulcers and other causes of gastro-intestinal bleeding.

Importantly, a recent network meta-analysis that included 57 randomised controlled trials (RCTs) and a total of 7293 patients, compared various SUP strategies [5]. SRGIB was reported in 31 trials, accounting for a total of 5283 patients. The network meta-analysis showed moderate quality evidence that PPIs were probably more effective for preventing clinically important gastrointestinal bleeding than H2RAs (odds ratio (OR) 0.38; 95% CI: 0.20, 0.73], sucralfate (OR 0.30; 95% CI: 0.13, 0.69), and placebo (OR 0.24; 95% CI: 0.10, 0.60). Furthermore, in this meta-analysis, PPIs were the most effective prophylactic strategy for SUP, with best estimates of the impact of PPIs on clinically important bleeding suggesting an absolute reduction of 1.6% relative to placebo, with a CI of 0.8–1.9%. These findings are similar to the 1.7% difference observed in the study by Krag and colleagues [12]. The network meta-analysis also found moderate-quality evidence suggesting that none of the management options differed significantly with regards to the risk of death from all causes [5]. This is also in agreement with the findings in the RCT by the SUP-ICU group. The 2 studies however show contrasted results concerning the incidence of pneumonia: the network meta-analysis suggested an absolute increase of 3.1% with PPIs vs. no

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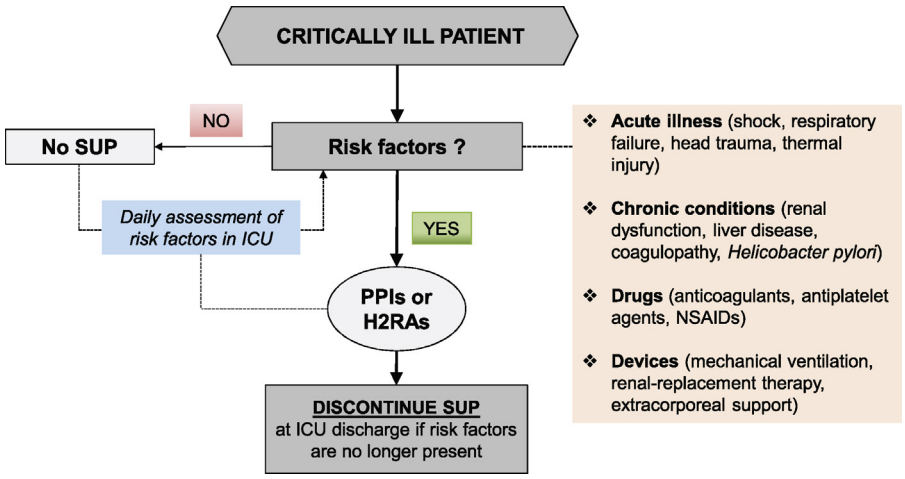

Fig. 1. Decisional algorithm for stress ulcer prophylaxis in critically ill patients in the intensive care unit. PPIs: protonpump inhibitors; H2RAs: histamine H2-receptor antagonists; SUP: stress ulcer prophylaxis; NSAIDS: non-steroidal anti-inflammatory drugs.

prophylaxis, with a CI ranging from 0.3% fewer events to 8.5% more events [5], whereas the greater-quality SUP-ICU RCT demonstrated no difference between the 2 groups (even though no statistical comparison was carried out for the same reasons as for the bleeding outcome) [12]. A previous conventional meta-analysis performed by our group (assessing direct comparisons in a smaller number of trials but yielding higher quality results than the network approach) had previously also concluded there was no increase in the incidence of nosocomial pneumonia in ICU patients receiving PPIs versus H2RAs [13].

A frequent question is whether a patient who is receiving enteral nutrition also requires pharmacological SUP. Enteral administration of nutrients buffers gastric acid, induces prostaglandin production, and enhances regional perfusion, optimising mucosal energy and intramucosal pH [14]. Enteral nutrition may provide protection against ischaemic bleeding and increase gastric pH to a greater extent than acid suppression does. It may thus theoretically reduce the risk of SRGIB during critical illness [15]. Only low-level evidence exists addressing this issue. An exploratory post-hoc analysis using data from a randomised trial suggested that enteral nutrition independently reduced SRGIB (RR 0.30, 95% CI, 0.13–0.67) in 1077 critically ill patients who were mechanically ventilated for more than 48 hours [16]. Furthermore, an observational study of 526 patients in a burn ICU found that the incidence of upper gastrointestinal bleeding was lower among patients who received enteral nutrition alone as compared to patients who received H2RAs without early enteral nutrition (3.3% vs. 8.3% respectively) [17]. In a recent systematic review and meta-analysis that included seven RCTs (n = 889 patients), the authors showed no statistically significant differences in SRGIB incidence rates between patients receiving SUP or not, and no effect on overall mortality [18]. Interestingly, the difference in SRGIB was of the same magnitude as in a secondary analysis of the SUP-ICU trial, keeping in mind that patients were not randomised according to enteral nutrition administration (5.6% vs. 7.5% for SUP vs control group, with an absolute difference of 1.9%)[12]. However, with only 889 patients, the meta-analysis was likely not powered enough to show statistical significance in such small differences. In view of all the available published data, it thus seems appropriate to continue SUP in at-risk patients receiving enteral nutrition.

A further question that arises in SUP is when should prophylaxis be discontinued. Two studies have reported continued prophylaxis without an appropriate indication in approximately 60% of patients transferred from the ICU to a medical unit, and similar findings in approximately 35% of patients subsequently discharged home [19,20]. We propose that patients receiving SUP should be reassessed daily, and as soon as their clinical condition improves, discontinuation of SUP should be considered, usually upon discharge from the ICU (Fig. 1).

In conclusion, given the low incidence of clinically important SRGIB in the ICU, the consistent 1.6%–1.9% absolute reduction in clinically important bleeding attributable to SUP but the absence of a resulting decrease in mortality, clinicians may or may not decide to start such prophylaxis in the ICU setting. However, when electing to do so, especially in light of new and high-quality evidence for an absence of PPI-related adverse events (notably infectious ones), we suggest starting a PPI. Such SUP should be reserved for seriously ill patients who are at high risk for developing this SRGIB. Furthermore, PPI treatment should be re-evaluated daily in critically ill patients and stopped as soon as the bleeding risk has decreased, or at the latest, upon ICU discharge. The role of enteral feeding in SUP requires further study.

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Authors' contributions

AD, JPQ participated in the literature search; AD, JPQ, AB and MB analysed and interpreted the data; AD, JPQ drafted the manuscript; AB, MB revised the manuscript critically for important intellectual content; all authors approved the final manuscript for publication.

Disclosure of interest

The authors declare that they have no competing interest.

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