

JOURNAL CLUB CRITIQUE

# Weighing risks and benefits of stress ulcer prophylaxis in critically ill patients

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## Expanded abstract

### Citation

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### Background

Recent observational studies suggest that bleeding from stress ulceration is extremely uncommon in intensive care unit patients. Furthermore, the risk of bleeding may not be altered by the use of acid suppressive therapy. Early enteral tube feeding (initiated within 48 h of intensive care unit admission) may account for this observation. Stress ulcer prophylaxis may, however, increase the risk of hospital-acquired pneumonia and *Clostridia difficile* infection.

### Methods

**Objective:** A systematic review of the literature to determine the benefit and risks of stress ulcer prophylaxis and the moderating effect of enteral nutrition.

**Design:**

**Data Sources:** MEDLINE, Embase, Cochrane Register of Controlled Trials, and citation review of relevant primary and review articles.

**Study Selection:** Randomized, controlled studies that evaluated the association between stress ulcer prophylaxis and gastrointestinal bleeding. The authors included only those studies that compared a histamine-2 receptor blocker with a placebo.

**Data Extraction:** Data were abstracted on study design, study size, study setting, patient population, histamine-2 receptor blocker and dosage used, incidence of clinically

significant gastrointestinal bleeding, hospital-acquired pneumonia, mortality, and the use of enteral nutrition.

### Results

Seventeen studies (which enrolled 1836 patients) met the inclusion criteria. Patients received adequate enteral nutrition in three of the studies. Overall, stress ulcer prophylaxis with a histamine-2 receptor blocker reduced the risk of gastrointestinal bleeding (odds ratio 0.47; 95% confidence interval, 0.29–0.76;  $P < 0.002$ ; Heterogeneity [ $I^2$ ] = 44%); however, the treatment effect was noted only in the subgroup of patients who did not receive enteral nutrition. In those patients who were fed enterally, stress ulcer prophylaxis did not alter the risk of gastrointestinal bleeding (odds ratio 1.26; 95% confidence interval, 0.43–3.7). Overall histamine-2 receptor blockers did not increase the risk of hospital-acquired pneumonia (odds ratio 1.53; 95% confidence interval, 0.89–2.61;  $P = 0.12$ ;  $I^2 = 41%$ ); however, this complication was increased in the subgroup of patients who were fed enterally (odds ratio 2.81; 95% confidence interval, 1.20–6.56;  $P = 0.02$ ;  $I^2 = 0%$ ). Overall, stress ulcer prophylaxis had no effect on hospital mortality (odds ratio 1.03; 95% confidence interval, 0.78–1.37;  $P = 0.82$ ). The hospital mortality was, however, higher in those studies ( $n = 2$ ) in which patients were fed enterally and received a histamine-2 receptor blocker (odds ratio 1.89; 95% confidence interval, 1.04–3.44;  $P = 0.04$ ,  $I^2 = 0%$ ). Sensitivity analysis and meta-regression demonstrated no relationship between the treatment effect (risk of gastrointestinal bleeding) and the classification used to define gastrointestinal bleeding, the Jadad quality score or the year the study was reported.

### Conclusions

The results of this meta-analysis suggest that, in those patients receiving enteral nutrition, stress ulcer prophylaxis may not be required and, indeed, such therapy may increase the risk of pneumonia and death. However, because no clinical study has prospectively tested the influence of enteral nutrition on the risk of stress ulcer prophylaxis, those findings should be considered exploratory and interpreted with some caution.

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## Commentary

In 1969, Skillman *et al.* [1] reported a clinical syndrome of lethal “stress ulceration” in seven of 150 (5%) consecutive intensive care unit (ICU) patients. These patients had in common respiratory failure, hypotension, and sepsis. Subsequent studies confirmed this finding and two meta-analyses published by Cook *et al.* [2] demonstrated that both histamine-2 receptor blockers (H2RBs) and sucralfate decreased the risk of bleeding from stress ulceration when compared to a placebo. Stress ulcer prophylaxis (SUP) becomes regarded as the standard of care in patients admitted to the intensive Care Unit (ICU), and this intervention is currently endorsed by Surviving sepsis campaign and American Society of Health System Pharmacists (ASHP) guidelines. The universal use of SUP has been reinforced with the adoption of “ventilator bundles.” Currently Joint Commission and the Institute for Healthcare Improvement recommend universal SUP as a core “quality” measure for mechanically ventilated patients.

Although the Agency for Healthcare Research and Quality recommends using SUP only in patients on mechanical ventilation and high bleeding risk from coagulopathies, SUP is used in all critically ill patients and even outside the ICU setting. For example, estimates indicate that approximately 90% of critically ill patients admitted to the ICU receive some form of SUP [3], and up to 52% of non-ICU patients receive SUP [4,5]. SUP is not without risks. Acid suppressive therapy is associated with increased colonization of the upper gastrointestinal tract with potentially pathogenic organisms and may increase the risk of hospital-acquired pneumonia [5]. Furthermore, gastric acid is an important defense against the acquisition of *Clostridium difficile* spores, and the use of acid suppressive therapy has been linked to an increased risk of *Clostridium difficile* infection [6-8]. Thus, understanding risks and benefits of SUP is important. For example, patients receiving enteral alimentation have a lower incidence of stress ulceration than unfed patients [9]. Whether routine SUP in patients who receive enteral feeding is beneficial or harmful is not known.

Marik *et al.* [10] conducted a meta-analysis of 17 randomized clinical trials and postulated that SUP may have no added benefits in ICU patients who receive enteral nutrition. They examined the effect of different SUP regimes on the risk of gastrointestinal bleeding, hospital-acquired pneumonia, and mortality, stratifying the studies based on enteral nutrition.

The meta-analysis included a total of 1836 enrolled between the years 1980 and 2004. Overall, SUP with a H2RB reduced the risk of GI bleeding ( $P < 0.002$ ) but had no effect on mortality. The beneficial effect of SUP was noted only in the subgroup of patients who did not receive enteral nutrition. SUP did not alter the risk of GI

bleeding in patients who received enteral nutrition, and these individuals had higher risk of hospital-acquired pneumonia ( $P = 0.02$ ,  $n = 9$  studies) and mortality ( $P = 0.04$ ,  $n = 2$  studies).

The results of this meta-analysis suggest that SUP may not be beneficial in patients who are fed enterally. The strength of this review article includes the rigorous attempt to identify all relevant RCTs studies, consider and evaluate for possible confounding factors, such as year of publications, definition of gastrointestinal bleeding, quality of randomized controlled trials, and publication bias. Limitations of this article includes lack of homogeneity in patient population, difference in diagnostic criteria used for major end-points, and only three studies had patients with enteral nutrition.

## Recommendation

SUP is beneficial in high risk patients, including those that are on mechanical ventilation and have coagulopathy. SUP may cause unfavorable outcomes, such as hospital-acquired pneumonia and *Clostridium difficile* infection, and clinicians must weigh risks and benefits in low-risk patients, such as those who are not requiring mechanical ventilation or are receiving enteral nutrition.

## Competing interests

The authors declare that they have no competing interests.

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