Chapter 27. Strategies To Prevent Stress-Related Gastrointestinal Bleeding (Stress Ulcer Prophylaxis): Brief Update Review

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Introduction

Stress-related gastrointestinal ulceration is a known complication of critical illness. Disruption of mucosal barriers and gastric acid hypersecretion lead to diffuse shallow mucosal injury and discrete ulcerations in the proximal stomach and duodenum, which in turn can lead to gastrointestinal (GI) bleeding and perforation.1-3 The prevalence of clinically significant bleeding in patients with documented stress ulcers varies from 0.6-15%, and mortality associated with the complication of GI bleeding can be nearly 50%.4-7

Independent risk factors for bleeding include respiratory failure requiring mechanical ventilation for longer than 48 hours and coagulopathy.4,8 Other associated risk factors for mechanically ventilated patients include shock of any cause, renal failure, and burns.8

Several pharmacologic therapies have been studied for the prevention of stress-induced gastrointestinal bleeding, including proton pump inhibitors (PPIs), histamine-2 receptor (H-2) antagonists, sulcrafate, and enteral nutrition. Despite decades of research, significant controversy continues to surround standardization of prophylactic therapy, particularly because of evidence that prophylaxis is associated with pneumonia, inappropriate use, and cost. Independent of prophylactic therapy, rates of clinically significant bleeding have actually declined, likely related to other patient safety practices around management of sepsis and enteral nutrition.9

Multicomponent or “bundled” interventions are becoming increasingly common as a method of improving outcomes by preventing complications in ICU patients. Examples of these approaches include the Surviving Sepsis Campaign,10 which includes stress ulcer prophylaxis and deep venous thrombosis prophylaxis along with evidence-based clinical strategies to improve sepsis outcomes, and the Institute for Healthcare Improvement’s “Ventilator Bundle,” one of the key components of the “100,000 Lives” campaign11 and the Keystone ICU project.12 Given the wide implementation of these bundles, the key issues around stress ulcer prophylaxis involve not only standardization of therapy with the most efficacious agents but also appropriateness of therapy based on risk assessment, and discontinuation of therapy when appropriate.

The 2001 Making Health Care Safer report reviewed evidence on the epidemiology of stress-related GI bleeding, and included an evaluation of two meta-analyses and one large randomized controlled trial (RCT) on the effectiveness of pharmacologic therapies, including H2-antagonists and sucralfate.13-15 Both H2-antagonists and sucralfate were found to be effective at preventing clinically significant GI bleeding in ICU patients, but the overall magnitude of benefit was small. The review found a relatively low incidence of clinically significant stress ulcer-related GI bleeding and a higher cost-to-benefit ratio for low-risk patients. Concern was also raised regarding a possible associated risk of hospital-acquired pneumonia with acid suppression. Therefore, the review concluded that no evidence supported the institution of universal stress ulcer prophylaxis in the ICU. The report recommended considering stress ulcer prophylaxis with either an H2-antagonist or sucralfate for the prevention of GI bleeding in certain high risk ICU
patient populations, including patients with respiratory failure, coagulopathy, renal failure, and/or burns, and considering enteral nutrition for other populations.

**What Is Stress Ulcer Prophylaxis?**

Pharmacologic acid suppressive therapy has been used to prevent stress-induced GI bleeding in the critical care setting. Previous studies have reported decreased rates of bleeding with agents such as H2-antagonists, PPIs, sucralfate, and prostaglandin inhibitors. The practice is to treat at-risk patients prophylactically with appropriate therapy to prevent stress-related gastrointestinal ulceration and bleeding.

**What Is the Context for the Use of Stress Ulcer Prophylaxis?**

Guidelines from the American Society of Health Pharmacists recommend the use of stress ulcer prophylaxis for high risk patients with any of the following conditions: mechanical ventilation >48 hours, coagulopathy (platelet count <50,000 mm³, International Normalized Ratio (INR) >1.5, or Prothrombin Time (PTT) >2× control value), or GI bleeding within the last year; or ≥2 minor risk factors including >1 week ICU stay, sepsis, glucocorticoid therapy, or occult GI bleeding ≥6 days.¹⁶

**What Have We Learned About Stress Ulcer Prophylaxis?**

In the past decade, several systematic reviews have been conducted on stress ulcer prophylaxis. PPIs have increasingly replaced the use of H2-receptor antagonists and sucralfate, despite a limited number of studies evaluating effectiveness in comparison to other agents. Thus, the remainder of this chapter will present a recent review of the literature including specific recommendations based on the evaluation of the evidence.

**Recent Reviews and Systematic Evaluations**

From 2010 to 2011, three systematic reviews compared the effectiveness of acid suppressive therapies,¹³⁻¹⁵ including one systematic review that assessed studies on PPIs.¹⁷

Huang et al.¹⁷ conducted a meta-analysis of 10 RCTs, including 2092 patients, that directly compared H2-antagonists and sucralfate in mechanically ventilated patients. The main outcome measures were rates of clinically important gastrointestinal bleeding, ventilator-associated pneumonia, gastric colonization, and ICU mortality. While there was a trend towards decreased overt bleeding with H2-antagonists compared with sucralfate (OR = 0.87, 95% CI: 0.49 to 1.53), sucralfate was associated with a decreased incidence of ventilator-associated pneumonia (OR = 1.32, 95% CI: 1.07 to 1.64). No difference between the agents was found for mortality (OR = 1.08, 95% CI: 0.86 to 1.34). The authors concluded that H2-antagonists were not more effective in the prevention of overt GI bleeding than sucralfate, but were associated with higher rates of ventilator-associated pneumonia.

Lin et al.¹⁸ evaluated 7 RCTs involving 936 patients that compared H2-antagonists with PPIs. The meta-analysis reported on the incidence of stress-related upper gastrointestinal bleeding, pneumonia, and ICU mortality. The review found no strong evidence that PPIs were significantly different from H2-antagonists in the prevention of overt or clinically important upper GI bleeding (pooled risk difference -0.04, 95% CI: -0.09-0.01), pneumonia, or ICU mortality.

Marik et al.¹⁹ evaluated the effect of H2-antagonists compared with placebo, with specific attention to the role of enteral nutrition as an effect modifier. The review found H2-antagonists...
reduced the incidence of clinically significant GI bleeding, but only in patients not receiving enteral nutrition. In patients receiving enteral nutrition, H2-antagonists did not affect the risk of GI bleeding; however, this finding is based on only three trials enrolling a total of 262 patients. The possibility that enteral nutrition may have a protective effect on patients’ baseline risk of stress ulceration implies that routine acid suppressive therapy may not be necessary even in patients with traditional risk factors. This finding, while exploratory, is certainly worthy of further study.

These systematic reviews suggest that acid suppressive therapy, while effective in preventing stress-related mucosal bleeding, is also associated with significant risks, including pneumonia. PPIs, though widely used, do not appear to be superior to H2-antagonists in preventing clinically significant GI bleeding.

No New Studies for Effectiveness of Acid Suppressive Therapy for Stress Ulcer Prophylaxis

To date, no additional RCTs or large scale observational or cohort studies of adequate quality have evaluated the effectiveness of pharmacologic acid-suppressive therapy for stress ulcer prophylaxis, apart from those included in the recent systematic reviews discussed above.

PPI Use and Misuse Have the Potential for Harm

The only PPI that is FDA-approved for stress ulcer prophylaxis is omeprazole immediate-release suspension. Overall, data demonstrate that PPIs are becoming the preferred agents of choice for prophylaxis, despite no clear evidence that these agents are superior to H2-receptor antagonists or placebo. Widespread use of PPIs, and inappropriate use, is common in hospitalized patients and is associated with significant cost. A survey of trauma ICUs found that the majority of patients continued stress ulcer prophylaxis after leaving the ICU. In a retrospective chart review over a 3 month period, Wohlt found 357 patients received stress ulcer prophylaxis in the ICU and 80% continued therapy following transfer out of the ICU. In 60% of these cases, the authors judged that the therapy was continued inappropriately. Approximately 25% of patients were discharged from the hospital with inappropriate therapy, at a total cost of $13,973.

Several RCTs and systematic reviews have noted the association between acid suppressive agents, specifically proton pump inhibitors and H2-receptor antagonists, and risk of nosocomial pneumonia, community-acquired pneumonia and enteric infections, specifically Clostridium difficile. The risk of hospital-acquired pneumonia extends to patients taking PPIs outside of the ICU. A cohort study of 63,878 non-ICU patients demonstrated that PPI use was associated with development of hospital-acquired pneumonia. Inappropriate continuation of acid suppressive therapy, particularly PPIs, after discharge from the ICU therefore can have adverse short-term effects for patients.

Costs and Implementation

Effective prevention of stress ulcer-related bleeding involves implementing methods to both increase rates of appropriate prophylaxis and decrease inappropriate prophylaxis. Much of the literature on increasing prophylaxis rates derives from studies of bundled approaches to ICU preventive practices. The Keystone ICU Project, which ranks as one of the most successful patient safety interventions of the past decade, used a “ventilator bundle” of five practices to
improve safety of mechanically ventilated patients, including stress ulcer prophylaxis. This project was remarkably successful at preventing hospital-acquired infections and improving other safety outcomes in the ICU, and also successfully increased stress ulcer prophylaxis rates. Another successful approach to increasing prophylaxis was described by Krimsky et al, who implemented a similar bundle approach incorporating several ICU prophylactic measures, including stress ulcer prophylaxis. The implementation method emphasized team communication, used prompts to providers to address the evidence-based measures on a daily basis, and used a “data wall” to provide real-time feedback. This approach resulted in nearly 100% adherence to bundle use.

Evidence on efforts to control inappropriate prophylaxis use is limited. Coursol and Sanzari described the implementation of an ICU algorithm with specific indications according to guidelines on appropriate use, length of therapy, and cost. The algorithm was associated with a reduction in inappropriate use of prophylaxis and costs.

Evidence on the cost of prophylaxis as it relates to implementation is also lacking. The cost of acid suppressive therapy varies, with H2-receptor antagonists being less expensive than PPIs. Decreasing inappropriate PPI use could likely be cost-saving for hospitals.

Conclusions and Comment

Acid suppressive therapy (H2-receptor antagonists and PPIs) and sucralfate are effective in the prevention of bleeding from stress-related gastric ulceration in ICU patients. PPIs are widely used, but are more expensive and no more effective than H2 receptor antagonists. Both types of acid suppressive therapy appear to be used inappropriately, often being continued after patients are discharged from the ICU. This practice raises safety concerns given the association between acid suppressive therapy and pneumonia. While relatively strong evidence indicates that rates of appropriate prophylaxis can be improved through the use of bundled approaches to ICU prophylaxis, evidence on how to limit inappropriate prophylaxis is lacking. Further research in this area is required in order to determine how to target prophylaxis most effectively to patients who will receive the most benefit, while avoiding prophylaxis when it is not required. A summary table is located below (Table 1).

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<th>Table 1, Chapter 27. Summary table</th>
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<td><strong>Scope of the Problem Targeted by</strong>&lt;br&gt;<strong>the PSP (Frequency/Severity)</strong></td>
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References


