

We No Longer Need to Stress Ulcer Prophylaxis in the Critically Ill

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Abstract

Preventing stress gastropathy has been a mainstay in the management of critically ill patients for decades. A landmark trial in 1994 identified the most significant risk factors for stress gastropathy as mechanical ventilation for greater than 48 h and primary coagulopathy. Since this study's publication more than two decades ago, the incidence of clinically significant gastrointestinal bleeding secondary to stress gastropathy has significantly declined. In addition, the most widely used agents for prophylaxis have been associated with an increasing number of adverse effects, including myocardial infarction, *Clostridium difficile* infection, osteoporosis, and ventilator associated pneumonia. As the incidence of significant bleeding decreases and the knowledge about prophylaxis-related adverse events increases, it is necessary to revisit current clinical practice. Major practice changes, including early aggressive fluid resuscitation and development of dynamic markers for volume status, have reduced the likelihood for prolonged hypoperfusion states. Additionally, the recognition of the importance of enteral nutrition early in the ICU stay encourages mesenteric perfusion and reduces risk for development of ischemic damage. Contemporary studies have failed to replicate significant rates of gastrointestinal bleeding, likely in part due to these advances in care. Recent studies, including a pilot randomized trial, are questioning the necessity of pharmacologic prophylaxis in the modern era, with undetectable rates of gastrointestinal bleeding in enrolled patients. Patients with risk factors for stress gastropathy who demonstrate no evidence of splanchnic hypoperfusion may not benefit from receiving stress ulcer prophylaxis and tolerance of enteral nutrition may be used as a surrogate marker for adequate perfusion. Overall there is a lack of high quality data supporting stress ulcer prophylaxis in the modern era.

Keywords: Stress ulcer prophylaxis; Gastrointestinal bleeding; Proton pump inhibitor; Nutrition

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Review

Preventing stress gastropathy has been a mainstay in the management of critically ill patients for decades. Stress gastropathy occurs when the mucosal barrier of the gastrointestinal (GI) tract is compromised and can no longer block the detrimental effects of hydrogen ions and free radicals [1]. The main cause of stress gastropathy in the intensive care unit (ICU) is mucosal ischemia due to splanchnic hypoperfusion, which may be caused by shock or changes in intra-thoracic pressure (i.e., during mechanical ventilation), and can result in clinically significant GI bleeding (CSGIB) [1]. This bleeding is associated with significant morbidity and mortality; therefore, it is considered standard of care to

provide stress ulcer prophylaxis (SUP) to patients who are at risk of stress gastropathy [2]. Cook et al. conducted a landmark trial in 1994 identifying the most significant risk factors for stress gastropathy as mechanical ventilation for greater than 48 h (odds ratio: 15.6) and primary coagulopathy (defined as INR > 1.5 or platelets < 50,000 or aPTT greater than twice the upper limit of normal; odds ratio: 4.3). The prevalence of CSGIB at the time of this landmark trial was 1.5% with use of SUP [3]. Over the past decades, the incidence of CSGIB has significantly declined [4]. In addition, the most widely used agents for SUP, proton pump inhibitors (PPI), have been associated with an increasing number of adverse effects, including myocardial infarction, *Clostridium difficile* infection, osteoporosis and ventilator associated

pneumonia [5]. As the incidence of CSGIB decreases and the knowledge about SUP-related adverse events increases, it is necessary to revisit the role of SUP in the ICU in current clinical practice.

The decrease in CSGIB in recent years may be attributed to the improved management of critically ill patients. One of these advancements is early goal directed therapy (EGDT), which promotes aggressive early fluid resuscitation in septic patients. The increase in recognition and early treatment of sepsis has likely impacted a reduction in stress ulcers through avoidance of hypoperfusion [6]. Additionally, improved technologies to assess fluid status and responsiveness in all patients with shock, which include monitors such as Vigileo® and Lidco® for stroke volume variation and pulse pressure variation, have improved recognition of fluid responsiveness and need for resuscitation. A retrospective chart review conducted in the medical/surgical ICU in 2003 showed no reduction in CSGIB with the use of SUP [7]. A further randomized control trial of 1473 at-risk trauma/surgical ICU patients confirmed these results [8]. Neither study evaluated the role of early enteral nutrition.

Another major change in practice over the past decades is the promotion of early enteral nutrition in the critically ill. Nutrition has been recognized as not just adjunctive therapy to provide exogenous fuels but as treatment to help attenuate the metabolic response to stress and prevent cellular injury [9]. Improvement in the clinical course of a critically ill patient can be expedited with early enteral nutrition, which is advocated in the ASPEN/SCCM guidelines [9]. Tolerance of enteral nutrition in the ICU is dependent on adequate gut perfusion, thereby demonstrating that the patient is not experiencing splanchnic ischemia. Furthermore, enteral nutrition may independently provide prophylaxis against stress gastropathy by increasing intragastric pH, similar to medication therapies, and providing cytotoxin protection [1,4,5]. A retrospective chart review evaluated the incidence of CSGIB in intubated surgical/trauma ICU patients tolerating enteral nutrition without pharmacological prophylaxis, finding no benefit to pharmacologic SUP [10]. A further randomized trial conducted in 2016 evaluated CSGIB amongst intubated patients receiving enteral nutrition (EN). Prophylactic

pantoprazole demonstrated no benefit to mechanically ventilated patients who received enteral nutrition [11].

Finally, a pilot randomized control trial was recently conducted by Cook and colleagues to evaluate the safety of withholding SUP. No difference was found in the CSGIB rate between those that received pantoprazole versus placebo. Although this study was not powered to determine a difference in CSGIB based on contemporary rates of bleeding, it is hypothesis generating, and larger scales studies are currently enrolling [12,13].

Much of the current literature evaluates patients in whom mechanical ventilation is the primary risk factor for stress gastropathy. Although this was determined to be the strongest risk factor for CSGIB (odds ratio 15.6) in the original analysis by Cook and colleagues, it must be noted that those at risk due to coagulopathy are distinctly lacking from contemporary studies. Patient selection for minimizing the use of SUP is a very important parameter that has been discerned throughout the years. Patients with neurologic injury or traumatic brain injury have been seen as a risk factor, but the above studies included these patients and did not show a change in the rates of CSGIB. ASHP guidelines also considers patients with thermal injury involving >35% of body surface area as a risk factor. These patients have been evaluated in several studies that have concluded that enteral nutrition was able to decrease overt bleeding and no additional pharmacologic prophylaxis was needed [14,15]. In the overall assessment of stress ulcer prophylaxis in today's healthcare system, there may be reason to believe that certain patients, particularly those in the medical and surgical ICU, may not benefit but instead could be introduced to increased risk with current treatment options. The collection of data does lend credence to the theory that, with advances in clinical practice, there may no longer be benefit to SUP in our highest risk patients admitted to the surgical and medical ICU. In conclusion, the prevalence of clinically significant bleeding has decreased from 1.5% in 1994 to as low as 0.6% in 2016, due to significant advancement in ICU care. Patients with risk factors for stress gastropathy who demonstrate no evidence of splanchnic hypoperfusion may not benefit from receiving stress ulcer prophylaxis. Tolerance of enteral nutrition may be the surrogate marker for adequate perfusion as seen in the studies discussed above. Overall there is a lack of high quality data supporting SUP in the modern era.

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