Don't Stress about Ulcer Prophylaxis

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A common medical doctrine is that critically ill patients require stress ulcer prophylaxis (SUP) to prevent gastrointestinal bleeding (GIB) caused by mucosal ischemia from physiologic stress. Withholding or de-escalating SUP in a patient at risk for GIB may be perceived as medical misconduct or a failure to meet benchmark performance measures. SUP is so ingrained in practice that many intensive care units (ICUs) have admission order sets that specify automatic initiation of SUP. Unfortunately, the inadvertent consequence of improvident SUP in the ICU is the spread of this practice to patients without an indication for SUP. The declining rate of GIB and the association between acid suppression and infectious complications have generated skepticism regarding SUP. Two years ago in this journal, Yamashita and Duffett argued in favour of and against SUP in a Point Counterpoint debate.[1,2] My purpose here is to highlight additional considerations, including key findings of recently published studies, to emphasize the ongoing clinical dilemma of SUP.

The 2 most commonly quoted risk factors for stress-related GIB are mechanical ventilation and coagulopathy. These risk factors are derived from an observational study of 2252 ICU patients, in which investigators requested that SUP be withheld unless a patient had head injury, extensive thermal burns, transplant, or a recent peptic ulcer or GIB; ultimately, 674 patients received SUP and 1578 did not.[3] The presence of hypotension trended toward a significant association with GIB. The primary indication in 54.8% of the patients was cardiovascular disease or surgery, for which medical practices have evolved from primarily anticoagulation and surgery to noninvasive interventional radiologic techniques. Few patients had a diagnosis of central nervous system injury, sepsis, head injury, or multiple trauma. Noninvasive ventilation was not routinely used at the time of publication. Therefore, the results of this study must be considered in the context of the population evaluated, the exclusion of patients with potential risk factors, and changes in medical practices since its publication. Fast forward to today and the recent publication of a meta-analysis of 8 studies (116 497 patients), which showed that coagulopathy, shock, and chronic liver disease were associated with clinically important GIB, but mechanical ventilation was not.[4] Those favouring SUP will note that most of the included studies used SUP, so these parameters should be considered risk factors when SUP is administered, whereas opponents of SUP will highlight the lack of consistency across the studies and question whether "established" risk factors are truly known.

While goals of therapy focus on mortality, clinically important GIB, and infectious complications, SUP is commonly prescribed with little concern about the advantages and disadvantages of particular agents. The histamine-2 receptor antagonists (H2RAs) are commonly employed on the basis of a randomized, double-blind study of 1200 mechanically ventilated patients, which showed a lower rate of clinically significant GIB with ranitidine than with sucralfate (1.7% versus 3.8%, $p = 0.02$).[5] However, a recent meta-analysis that included this study found no difference in clinically important GIB between H2RAs and sucralfate, but less pneumonia with sucralfate.[6] Of note, most of the included studies involved administration of H2RAs by infusion and/or dose adjustment to achieve gastric pH values above 3.5–4, both of which may alter the gastrointestinal microbiome to enhance infection risk to a greater extent than conventional, intermittent H2RA administration. The results of a recent meta-analysis suggest lower GIB with proton pump inhibitors (PPIs) than H2RAs[7]; however, the results were driven by 2 studies with methodological flaws. In contrast, pharmacoepidemiologic analyses found lower rates of pneumonia and *Clostridioides difficile* infection with H2RAs, which again suggests that the extent of acid suppression contributes to microbiome disturbances.[8,9] More recently, a randomized, double-blind, placebo-controlled study found lower rates of clinically important GIB with pantoprazole (2.5% versus 4.2%, relative risk 0.58, 95% confidence interval 0.4–0.86).[10] Although infectious complications and the primary outcome of 90-day mortality were similar between groups, a post hoc analysis showed higher mortality rates with pantoprazole in the most severely ill patients (i.e., those most likely to have risk factors for GIB).[11] Taken together, these data confound the choice of which class of agents is preferred for SUP and highlight

the need to define which outcomes are most important. Although GIB is associated with prolonged ICU stay and additional costs, no study has shown a mortality benefit with SUP. The risk of infectious complications and the unexplainable higher rate of mortality in the post hoc analysis of the most recent study[11] generate uncertainty surrounding the routine practice of SUP.

The decline in stress-related GIB over the past few decades may be explained, in part, by more effective SUP strategies or by contemporary medical practices (such as aggressive hemodynamic resuscitation) that limit mucosal ischemia. Early administration of enteral nutrition may offer GIB protection to the extent that the effectiveness of pharmacologic SUP is minimized.[12] At the very least, tolerance to enteral nutrition suggests that gastrointestinal reperfusion has occurred, whether or not risk factors for GIB remain present. The duration of SUP has been shortened substantially, with the most recent study suggesting about 4 days of therapy, which coincides with when GIB is most likely to occur after ICU admission.[10] Unfortunately, real-world practice does not reflect this trend, as 25% of patients unnecessarily continue to receive SUP after hospital discharge. The argument for or against SUP should not focus on the universal adoption or abandonment of the practice but instead on how to rationalize appropriate use to optimize GIB prevention while limiting exposure and minimizing adverse consequences. Rather than discontinuing therapy, the safer practice model is to limit SUP orders to 2–3 days, with longer durations necessitating a new order by the prescriber. In the study of risk factors, the rate of GIB was substantially higher in the cohort that received SUP (16.3% versus 1.5%).[3] Some may argue that this suggests SUP is ineffective, when really it reflects selection bias, with clinicians being more likely to provide SUP to patients perceived to be at higher risk of GIB. Pending studies and new guidelines may resolve some uncertainties but in the meantime it is important to understand the clinical equipoise surrounding SUP and to ensure appropriate SUP therapy, while dispelling the belief that SUP is a rite of passage in the ICU.

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