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EDITORIAL COMMENT

Strategies to Reduce CICU Critical Illness-Related Complications

Adding Information to an (Almost) Evidence-Free Zone*

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Stress-related gastrointestinal (GI) ulcers are reported to occur in 1.5 to 2.6% of patients admitted to medical and surgical intensive care units (ICUs) and in 0.5% of patients in cardiac surgical ICUs.[1-3] Stress ulcer prophylaxis (SUP) with either proton pump inhibitors (PPIs) or histamine-2 receptor blockers (H2RBs) have been shown to reduce the risk of upper GI bleeding and are prescribed in 73 to 81% of critically ill patients.[2,4] This benefit may in part be offset by an increase in the associated risks of ventilator-associated pneumonia (VAP) and *Clostridium difficile infections*.[5,6] Whether inferences about the efficacy and safety of SUP are transferrable to the cardiac ICU (CICU) patients remains unclear. The American Heart Association's Scientific Statement on Prevention of CICU Complications suggest that SUP "is not necessary for low-risk patients in the CICU," but that it may be reasonable for patients "with multiple risk factors for GI bleeding" which may include shock, acute kidney injury requiring renal replacement therapy, the provision of mechanical ventilation, coagulopathy, and/or use of anticoagulants/antiplatelets agents.[7] The statement also acknowledges the very limited CICU-based data for this practice suggestion and that existing data are largely derived from studies performed in medical and surgical ICU settings. Recently, the PEPTIC (Proton Pump Inhibitors vs Histamine-2 Receptor Blockers for Ulcer Prophylaxis Treatment in the Intensive Care Unit) trial, which enrolled nearly 27,000 patients, reported no differences in 90-day all-cause mortality among patients randomized to H2RB vs PPI ($P = 0.054$), but a lower incidence of clinically important upper GI bleeding among medical and surgical ICU patients receiving PPI (1.3%) compared to H2RB (1.8%).[1] Notwithstanding, the comparative effectiveness of these SUP medications in the CICU setting remains unclear. The proportionally higher use of dual antiplatelet agents, anticoagulants, and fibrinolytics, as well as the frequency of cardiogenic shock-associated congestion and hypoperfusion, and temporary mechanical circulatory support devices may suggest that more robust gastric acid suppression with a PPI would be warranted, but high-quality evidence is lacking.[7]

In this issue of *JACC: Advances*, Banna et al[8] performed a multicenter retrospective cohort study using the Vizient database to identify 11,552 adult patients admitted to over 650 hospitals in 47 U.S. states with a primary diagnosis of acute myocardial infarction who also received invasive mechanical ventilation. The analysis compared outcomes between patients treated with a PPI vs H2RBs. The authors reported no difference in the risk of adjusted all-cause in-hospital mortality (OR: 0.97; 95% CI: 0.89-1.06). In a secondary analysis, H2RBs were associated with more ventilator-free days (incidence rate ratio: 0.83; 95% CI: 0.81-0.84; $P < 0.001$) and a lower incidence of VAP (3.1% vs 4.0%; adjusted OR: 0.80; 95% CI: 0.64-0.997; $P = 0.047$). No differences

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were observed in the incidence of *Clostridium difficile infections*.

The strengths of the study include the relatively large population from a robust multicenter database and it appropriately excluded patients undergoing cardiac surgery, with a preintubation upper or lower endoscopic procedure, and/or known GI bleeding. In an effort to mitigate the potential for residual confounding, a sensitivity analysis using inverse probability weighting also showed no difference in mortality. Finally, the authors should be congratulated for seeking to validate ICU evidence in a CICU population that may have a different risk of upper GI bleeding compared to patients admitted to a general ICU with sepsis or trauma.[9]

The results of the study should be interpreted with caution in light of its limitations. First, the study does not contain information on concurrent enteral nutrition which may modulate the risk of both VAP and stress ulcers.[10] Second, the study does not provide information on labs, hemodynamics, or in-hospital medication timing (or dosing). Thus, little is known about the number of concurrent antiplatelet agents, anticoagulants, or number of intravenous vasoactive agents—all of which may be associated with the risk of GI bleeding.[11] Third, there was a higher rate of postintubation endoscopies and blood product transfusions in the PPI cohort. Ostensibly, more intense acid suppression with a PPI could be beneficial in patients receiving antiplatelet agents and anticoagulants, thus the higher rate may signal the potential for residual confounders.[12] This issue is best highlighted by the higher mortality associated with PPI use among CICU patients in the PEPTIC study[1]; however, ancillary analysis with more robust laboratory and peri-operative surgical information showed no difference in outcomes between cardiac surgical patients treated with H2RB vs PPIs who were enrolled in the PEPTIC study in Canada.[13] The database did not directly contain the incidence of postintubation upper GI bleeds or stress ulcers. Finally, this study was likely underpowered for all-cause mortality given that PEPTIC enrolled nearly double the number of patients.

What are the implications for clinical practice? Foremost, the results suggest that either PPIs or H2RBs are reasonable first-line agents for SUP among patients with an acute myocardial infarction who require invasive mechanical ventilation. The study may point to differences in safety with a higher risk of VAP and mechanical ventilation duration among patients receiving PPI—important endpoints which could logically be a sequela of more efficacious gastric acid suppression.[6] It should be noted, however, that neither ventilator-associated conditions nor length of stay were meaningfully different in the PEPTIC study. Collectively, we would propose that either a PPI or H2RBs are reasonable for CICU SUP with the provision that clinicians recognize that there may be some subgroups at higher risk of upper GI bleeding (eg, prior GI bleeding, triple therapy, multisystem organ failure, and/or profound cardiogenic shock) in whom it may be reasonable to favor PPIs.

While traditional randomized controlled trials addressing this question may be unlikely given the need for large sample sizes and likely modest effects, validating general ICU best practices, including preventions of critical illness-related complications, may be well suited to pragmatic electronic medical record embedded trials. In the interim, observational studies could explore the associations between SUP strategies stratified by intensity and duration of antiplatelet therapy, anticoagulant use, vasoactive inotropic scores, and risk of mortality using validated CICU/ICU risk scores. Moreover, whether the concurrent enteral nutrition mitigates upper GI bleeding or raises VAP risk is worthy of investigation.

The authors should be congratulated for this important observational study. With the growing acuity and complexity of patient care in contemporary tertiary CICUs, it is incumbent on the cardiac critical care community to not only help identify optimal treatment strategies but also to reduce the risks associated with critical care admission and life-sustaining therapies. The study addresses this latter need and may serve as the foundation for future CICU-based SUP studies.

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