EDITORIAL

Controlling Glycemic Variability in Non-diabetic Sepsis Patients: A Step toward Precision in Critical Care

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Sepsis is a life-threatening organ failure caused by an aberrant host response to infection, and it remains the leading cause of morbidity and mortality in intensive care units (ICUs) around the world. Despite breakthroughs in supportive treatment, sepsis mortality remains unacceptably high, highlighting the need for new biomarkers and management options to improve outcomes.[1] Dysglycemia, namely, glycemic variability (GV), has emerged as an independent predictor of poor outcomes in critically ill patients, however, it is underutilized in clinical practice.[2] This issue of the IJCCM includes a prospective observational study that highlights the significance of GV as a predictor of in-hospital mortality in non-diabetic sepsis patients, placing it within a broader context of published evidence.[3]

The essential role of GV in critical care stems from its capacity to reflect dynamic glucose changes, which place significant stress on cellular and systemic physiology. Unlike hyperglycemia and hypoglycemia, which are frequently examined separately, GV covers the breadth and amplitude of glucose excursions, offering a more complete picture of metabolic instability. Glycemic variability is critical in sepsis when metabolic derangements are key to the pathogenesis.[4]

The current study investigates the correlation between GV and outcomes in non-diabetic sepsis patients. By focusing on this subgroup, the authors fill a significant gap in previous studies. Non-diabetic patients, who lack the adaptive mechanisms found in diabetic patients, are especially exposed to the negative consequences of glucose variations. The study measured GV using standard deviation (SD), coefficient of variation (CV), and mean amplitude of glycemic excursion (MAGE), and divided patients into low, moderate, and high GV groups. The data show a substantial link between increased GV and in-hospital mortality, the need for mechanical ventilation, renal replacement therapy (RRT), septic shock, and hospital-acquired infections (HAIs).[3] However, no significant link was seen between GV and length of hospital stay, which is consistent with previous studies.[3–8]

The findings are consistent with a mounting amount of research associating GV with worse critical care outcomes. A meta-analysis by Li et al.[5] revealed that septic patients with higher GV had significantly higher mortality rates than those with lower GV. Similarly, Atamna et al.[6] and Yao et al.[7] found robust relationships between GV and ICU mortality, highlighting GV's predictive relevance across many patient populations. Interestingly, although having higher GV, diabetic individuals do not have a similar mortality correlation, most likely due to long-term metabolic adaptations. Hryciw et al.[8] affirm this trend, finding that GV is a significant predictor of fatal outcomes in critically ill patients, with high GV associated with increased mortality rates in a variety of ICU settings. The current study highlights the importance of GV as an independent predictor of poor outcomes, indicating the need for tailored measures to treat GV in ICU patients. The authors found that GV accurately predicts mortality and correlates with comorbidities including mechanical ventilation and organ failure, highlighting its importance in managing critically ill patients.

Glycemic variability's negative consequences on the body are extensively documented. Glycemic fluctuations cause oxidative stress, aggravate inflammatory cytokine release, and impair endothelial function, all contributing to the organ dysfunction seen in sepsis. Furthermore, GV impairs mitochondrial bioenergetics and activates apoptotic pathways, exacerbating cellular damage.[9] These pathways support GV's role as a disease severity measure and possible treatment target. Recent studies have highlighted the role of GV in exacerbating mitochondrial dysfunction in critically ill patients, where even minor glucose fluctuations can initiate significant mitochondrial damage and worsen organ failure.[10]

The study's methodology is notable for its simplicity and practicality, relying on easily available measurements rather than continuous glucose monitoring (CGM). In resource-constrained environments with limited access to advanced techniques, SD, CV, and MAGE provide a viable method for assessing GV. The scientists also eliminated individuals with hypoglycemia, a confounding factor known to independently increase mortality risk, which improved the study's validity. However, the study has limitations. The relatively small sample size (80 patients) and short follow-up

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period (14 days) limit the data' generalizability and may obscure the long-term effects of GV. In addition, dietary components and insulin protocols were not standardized, resulting in variability in glucose management. The lack of CGM, while explained by practical limits, provides a squandered opportunity to gain a more detailed understanding of glucose dynamics. Aside from these issues related to methodology, this study presents important questions for further research. What GV threshold should be utilized to predict bad outcomes in sepsis? Could targeting lower GV enhance survival? If so, what are the potential risks of causing hypoglycemia? How can patient-specific factors, like as baseline metabolic profiles or genetic predispositions, affect GV and its effects on outcomes? Addressing these issues necessitates larger, multicenter studies with different patient populations and longer follow-up periods.

The ramifications of GV go beyond its prognostic value. In clinical settings, GV could guide personalized therapies to reduce glucose swings. Optimal insulin infusion protocols, continuous enteral feeding, and early introduction of CGM in high-risk patients could all be strategies for achieving this. Importantly, these therapies must strike a balance between the benefits of decreasing GV and the hazards of overtreatment, notably hypoglycemia.[11] A recent study by Almagthali et al.[4] emphasizes the need for insulin protocols that balance glycemic control with the prevention of hypoglycemia, demonstrating that overly aggressive glucose management strategies can worsen outcomes in critically ill patients. The broader relevance of GV as a prognostic marker should also be investigated. While this study focuses on non-diabetic sepsis patients, GV may also be worthwhile in other critical care settings, such as acute respiratory distress syndrome (ARDS), cardiac surgery, or traumatic brain injury. Extending study into these areas may uncover new ways to enhance patient outcomes by treating GV throughout various disease processes. A meta-analysis by Rytter et al.[9] revealed that GV is related to poorer outcomes across a wide range of critical situations, implying that monitoring it could improve prognostic accuracy and guide decisions concerning treatment in varied patient populations.

From a resource allocation standpoint, the study provides a cost-effective paradigm for GV monitoring, especially in low- and middle-income countries where advanced technologies are frequently unavailable. Identifying high-risk patients using simple measures allows clinicians to prioritize rigorous monitoring and personalized interventions, maximizing resource utilization while enhancing care quality. Li et al.[5] also highlighted the utility of GV as a cost-effective marker of prognosis in resource-limited settings, recommending its integration into routine clinical practice to improve patient care outcomes.

Despite its potential, incorporating GV monitoring into routine practice presents hurdles. Standardizing measuring techniques across institutions, establishing clinically meaningful thresholds, and teaching healthcare practitioners about GV's importance are all crucial stages. Furthermore, GV evaluation should supplement, not replace, existing biomarkers and grading systems, ensuring a complete approach to sepsis care. Recent advances in CGM technology show promise in resolving some of these problems. Continuous glucose monitoring delivers continuous, real-time data on glucose levels, allowing for dynamic assessments of GV and timely actions. Although currently limited in cost and availability, CGM is expected to become more accessible as technology advances, extending its application in critical care.[12]

This study adds to a growing understanding of the significance of metabolic variability in sepsis therapy. It contradicts the usual emphasis on static glycemic objectives, calling for a more nuanced approach that takes into account the dynamic nature of glucose regulation. The authors open the door for more personalized and precise care regimens in sepsis by identifying GV as a disease severity measure and possible therapeutic target. Glycemic variability is an emerging and important area of focus in critical care. Its ability to reflect dynamic fluctuations in glucose levels in response to systemic physiology offers a new perspective on the intricacies of sepsis etiology and its consequences. This study highlights the potential of GV as a useful marker for assessing disease severity and guiding clinical decision-making. However, its findings emphasize the necessity for more research into the broader applicability and integration of GV monitoring in sepsis management. Incorporating GV into existing treatment frameworks offers a great chance to refine prognostic models, adapt therapeutic approaches more effectively, and improve outcomes for critically ill patients.

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