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Inpatient glycemic control and community-acquired pneumonia outcomes in the pre-COVID-19 era: reviewing the evidence to pave the road for future studies

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Over the past several decades, our understanding of inpatient glycemic control has grown, and paradigms of management have shifted with results of key studies such as the Leuven Surgical Trial in 2001 and NICE-SUGAR trial in 2009.[1 2] Inpatient glycemic targets in society guidelines, including the 2012 Endocrine Society recommendations and the Surviving Sepsis Campaign, significantly changed to a more liberal glycemic range as a result of the NICE-SUGAR results.[3 4] Despite these advances, gaps exist in our knowledge, including more precise evaluations of inpatient glycemic targets and whether hyperglycemia is associated with or potentially causes unfavorable clinical outcomes in hospitalized patients.

In this issue of the journal, Barmanray *et al* report the findings of a thorough and methodical systematic review and meta-analysis of observational studies on associations of inpatient glycemic control and community-acquired pneumonia (CAP) prior to the COVID-19 pandemic.[5] They note that inpatient hyperglycemia was associated with in-hospital mortality and intensive care unit (ICU) admission, while the presence of diabetes (irrespective of glycemic control) was not. This systematic review provides key insights into the likely relationship between inpatient hyperglycemia and CAP outcomes, and also highlights several important gaps in our knowledge of inpatient glycemic management.

This study importantly adds to the literature on the association between hyperglycemia and hospital outcomes, as such analyses are limited. A review of literature by an Endocrine Society task force noted that intensive glycemic control might be linked to decreased risk of infection in hospitalized persons with diabetes.[6] Of note, studies that included patients with stress hyperglycemia or hyperglycemia from previously unrecognized diabetes were not part of this analysis. Additionally, a retrospective study of the Veterans Affairs database found an association between increasing mean glucose and mortality in critically ill patients hospitalized with sepsis or pneumonia.[7]

Delving further into the impact of hyperglycemia, Barmanray *et al* demonstrate that an acutely elevated blood glucose portends a poor inpatient outcome more so than having underlying diabetes.[5] The authors describe the pathophysiologic mechanism between hyperglycemia and infection, and suggest that chronic non-glycemic effects of diabetes may not play a role in the acute setting. Prior research has similarly suggested that hyperglycemia in patients without diabetes leads to increased mortality and poorer functional status than in those with diabetes.[8 9] The underlying reason for this connection is not clearly understood, though we hypothesize that hyperglycemia in individuals without a known diagnosis of diabetes hospitalized for reasons such as CAP may be considered a stress response, initially raising the threshold for therapeutic antihyperglycemic interventions. With essential time to pharmacologically lower hyperglycemia potentially being lost, known detrimental effects of hyperglycemia on the immune system may prevent effective treatment of infection including CAP. Alternatively, inpatient hyperglycemia could be just a marker of infection severity. Though only future prospective interventional trials will be able to delineate whether non-diabetic hyperglycemia impacts inpatient

outcomes, we believe that proactive and early management of stress hyperglycemia should be implemented in patients without diabetes, similarly to the innate attention devoted to glycemic control in patients with diabetes.

The publication by Barmanray *et al* also reminds us of the challenge in defining evidence-based inpatient glycemic targets. While 17 studies examining the relationship between hyperglycemia and CAP outcomes were identified by the authors, significant heterogeneity existed in definitions of hyperglycemia. For example, a glucose of 126–180 mg/dL was considered 'mild hyperglycemia' in one study but would qualify as 'severe hyperglycemia' in another. Similar heterogeneity also applies to the Leuven Surgical Trial and NICE-SUGAR trial, two landmark studies on critically ill patients that shaped inpatient guidelines. The glycemic target comparisons are slightly different, particularly in the 'conventional' glycemic groups, with the Leuven patients having a target of 180–200 mg/dL and NICE-SUGAR having a target of <180 mg/dL. Additionally, no large randomized controlled trials have examined non-critically ill patients (which comprise the vast majority of hospitalized patients) nor an inpatient glycemic target of 110–140 mg/dL.

Lastly, as this systematic review and meta-analysis evaluated CAP outcomes prior to COVID-19, we must examine the newest data derived from the CAP studies conducted during the pandemic. Though not a universal finding, it appears that the majority of studies reporting on COVID-19 pneumonia and glycemic control noted a significant association between hyperglycemia and poor hospital outcomes,[10–12] similar to the findings by Barmanray *et al*. A potential factor introducing bias is that patients with more severe COVID-19 pneumonia likely received glucocorticoids, which may in turn have worsened glycemic control. With regard to the studies looking at the impact of underlying diabetes, there seems to be a consistent association with the presence of diabetes, independent of glycemic control, portending an increased risk of severe COVID-19 pneumonia and death.[13–15] This is in contrast to the findings of Barmanray *et al* that diabetes alone was not associated with CAP mortality or ICU admission in the pre-COVID-19 era.

We have gained new insights on diabetes, glycemic control, and outcomes in hospitalized patients with pneumonia during the COVID-19 pandemic. The systematic review and meta-analysis on pre-COVID-19 CAP and glycemic control highlights both the extent and the limitations of our knowledge. Furthermore, prospective studies on alternate glycemic targets, such as 110–140 mg/dL, can improve the precision and confidence of our consensus guidelines. We hope the manuscript by Barmanray *et al*, as well as the scientific community's recent experience with the COVID-19 pandemic, further catalyzes clinical research in inpatient diabetes management.

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