Commentary

Admission hyperglycemia in sepsis is associated with poor outcomes: where do we go from here?

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The assessment and management of glucose levels in critical illness is one of the core tenants of supportive care. Both severe hyperglycemia and hypoglycemia are associated with increased morbidity and mortality in several critically ill patient populations as a whole (1,2). Findings from van Vught and colleagues evaluating the relationship between initial blood glucose (BG) value and mortality, as well as changes in the host response, add to the evidence suggesting hyperglycemia is associated with poor outcomes in the subset of critically ill patients with sepsis (3).

The investigators found severe admission hyperglycemia, defined by the investigators as >200 mg/dL, compared to euglycemia (71–140 mg/dL) to be associated with increased 30-day mortality [adjusted hazard ratio, 1.66 (95% CI, 1.24–2.23)], as well as alterations of biomarkers for sepsis, regardless of patient history of diabetes (3). Hyperglycemia has been associated with poor outcomes in other critically ill patient populations, including community-acquired pneumonia, aneurysmal subarachnoid hemorrhage, chronic obstructive pulmonary disease, acute myocardial infarction, or receiving total parenteral nutrition (4). We congratulate the investigators on this finding in the septic patient cohort and look forward to further research undertaken based off of these findings; however, many questions remain. We will attempt to address the following: Will treating the hyperglycemia make a difference in the septic population? Should the diagnosis of diabetes influence target glucose in the critically ill population? What is the safe and effective way to accomplish the targeted glucose value?

Will treating the hyperglycemia make a difference in the septic population?

Hyperglycemia may observationally be a marker of poor outcomes; however it is still unclear if treating the hyperglycemia would influence outcomes. Theses observational analyses cannot evoke causality of the outcomes; therefore they should be viewed as important findings to help identify areas for further research. One randomized controlled trial in septic patients by Brunkhorst and colleagues, entitled The Efficacy of Volume Substitution and Insulin Therapy in Severe Sepsis (VISEP) trial, assessed intensive insulin therapy (goal 80–110 mg/dL) compared to conventional insulin therapy (goal less than 180 mg/dL) in severe sepsis in a multicenter, open-label, two by two factorial that also randomized patients to receive 10% pentastarch or modified Ringer's lactate (5). Patients in severe sepsis were recruited from 18 academic medical center ICUs within 24 hours of admission to the ICU. The trial was suspended prematurely after a safety analysis conducted on 537 patients showed an increase in hypoglycemia (<40 mg/dL) in the intensive insulin therapy group 17% *vs*. 4.1% (P<0.001) in the convention arm. There was no significant difference between mortality or SOFA scores noted between intensive or conventional insulin therapy arms. Since trial was terminated for safety reasons no conclusions can be made on the efficacy of tight glucose control in patient with sepsis.

A definitive prospective analysis is needed to establish BG goals in septic patients. Clinical guidelines generally

recommend critically ill hospitalized patients using insulin therapy should be managed toward a goal glucose value between 140 and 180 mg/dL (6-9). Controversy on the establishment of these goals comes from the heterogeneity of results of analysis comparing "tighter" glucose ranges such as 80–110 mg/dL to more conservative ranges such as 140–180 mg/dL. Randomized trials of different BG goals in critically ill patients have reported mixed results. Mortality was substantially decreased in the intensive BG control arm in 1 randomized trial of surgical ICU patients, increased in the NICESUGAR trial of mixed ICU patients, and resulted in no difference in 3 others (5,10-13).

In these five randomized controlled trials it is clear, attempting to attain a stricter glucose goal with IV insulin therapy results in a higher rate of severe (i.e., <40 mg/dL) hypoglycemia. A post- hoc analysis of the NICESUGAR analysis found an increased incidence of death in either arm (in patients whose death was not attributable to respiratory, arrhythmia, or neurologic causes) associated with severe hypoglycemia (P=0.002) (14). In the observational Lanspa analysis significantly higher rates of severe hypoglycemia (<40 mg/dL) occurred in the cohort of patients who were managed to a goal of 80–110 mg/dL 3.6% *vs.* 2.0%, (P<0.01) (15). Mortality was increased in patients who had at least 1 documented episode of severe hypoglycemia 17.3% *vs.* 10.3% (P<0.01).

Excluded by the investigators in the current analysis were the 60 patients screened initially presenting with a BG value of <70 mg/dL (3). Hypoglycemia, both moderate (i.e., BG <70 mg/dL) and severe (i.e., BG< 40 mg/dL), are linked to poor outcomes in analyses of BG in critically ill patients. It would be interesting to know in the future how admission hypoglycemia in patients with sepsis impacts morbidity, mortality and the host response.

What is the safe and effective way to accomplish the targeted glucose value?

The consistency of the incidence of severe hypoglycemia in the literature evaluating "tight" BG goals in the critically ill should not be viewed as a failure of the theory of euglycemia in the critically ill, but rather the insulin protocols that were used in an attempt to achieve the goal. Intravenous insulin is recommended as first line therapy in the management of hyperglycemia in the ICU, though no major consensus guideline has provided specific recommendations on how best to utilize intravenous insulin (6-9). While there are multiple intravenous insulin protocols that are available in the literature, few have been rigorously evaluated and none have demonstrated both efficacy in the achievement of tight glucose ranges and safety in avoiding hypoglycemic events. An ideal insulin protocol will aggressively monitor patients BG at least hourly, and recommend changes in the infusion rate incorporating not only the patient's current BG, but the previous BG value so that the rate of change can be considered and incorporated into calculating the rate of insulin, ideally avoiding prolonged hypoglycemia (16). If "tight" BG goals are going to be prospectively studied there should be a validation of the efficacy and safety of the IV insulin protocol. Continuous BG monitoring in critically ill patient populations may not be ready for use in clinical practice, but may offer a benefit once validity is established (17).

Before any further clinical outcome studies are commenced on critically ill patients an intravenous insulin protocol capable of effectively achieving therapeutic targets with minimal instances of hypoglycemia should be validated with robust glucometrics. Several software protocols have been developed and may be the most viable option compared to paper-based protocols (18,19) In future trials, validated bedside BG testing using an accurate method of sample assessment such as a bedside blood gas analyzer should be preferred over using a point-of-care-test analyzer (20).

Should the diagnosis of diabetes influence target glucose in the critically ill population?

As baseline diabetic status may impact outcomes regarding critically ill patient's glucose management, further research with a focus on the subsets of patients with and without the diagnosis of diabetes is warranted. A retrospective cohort analysis conducted by Lanspa and colleagues evaluated 3,529 patients in twelve ICUs across eight hospitals using an institutional protocol which allowed providers to choose 80–110 or 90–140 mg/dL for a goal BG level (15). After multivariate analysis there was no significant difference in 30 day mortality between the groups demonstrated based on glucose target alone. When stratified for diabetic status, the multivariate analysis demonstrated that the 90–140 mg/dL glucose target was independently associated with increased risk of mortality in patients without diabetes (P<0.05) but decreased risk of mortality in patients with diabetes (P<0.01) (15). These findings corroborate the theory that in patients with diabetes, adaptation to a chronic hyperglycemic state may occur, and thus patients with diabetes may not benefit from glucose values 80–110 mg/dL.

It would be interesting to see an analysis comparing ICU patients without a history of diabetes treated to a "tight" goal BG of 80–110 mg/dL compared to a conventional arm of 140–180 mg/dL. A similar study can be designed in critically ill patients that carry the diagnosis of diabetes randomized to be managed to a goal BG of either a "tight" arm 90–140 mg/dL or a more conventional 140–180 mg/dL prospectively evaluate the changes in the host response at different glucose values.

In summary, the findings of van Vught and colleagues are a vital part of our ever evolving understanding of glucose management in the critically ill. As technologies such as continuous BG monitoring and fully integrated computerized insulin infusion programs become validated, we can continue to conduct research on the optimization of this facet of supportive care.

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Footnote

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