Management of Hyperglycemia in Critically Ill Patients

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Hyperglycemia is a common complication of critical illness, regardless of a history of diabetes mellitus. It has an estimated prevalence of approximately 40% in hospitalized patients. Initially, hyperglycemia was presumed to be an adaptive stress response that was beneficial to survival. However, over the past 2 decades, understanding of this disease process has improved, with several studies showing that hyperglycemia is associated with increased mortality and morbidity.

**Pathophysiology of Stress Hyperglycemia**  
Stress hyperglycemia is caused by several endogenous and exogenous factors. In an observational study, ICU patients with newly diagnosed hyperglycemia had significantly higher mortality (31%) compared with patients with known diabetes (10%) or normoglycemia (11.3%). Stress hyperglycemia usually is defined as an increase in blood glucose above 200 mg/dL in the presence of acute illness. Resolution typically occurs after appropriate treatment of the underlying illness. However, if hyperglycemia is left untreated, it can lead to acute kidney injury, sepsis, critical illness polyneuropathy, respiratory failure, and decreased wound healing. Prudent understanding of blood glucose goals and effective glycemic control is essential for appropriate management and optimization of patient outcomes.

**Adverse Effects Associated With Stress Hyperglycemia**  
There are various physiologic complications of hyperglycemia. Osmotic diuresis leads to dehydration, which may impair renal function and worsen hyperglycemia. The DCCT (Diabetes Control and Complications Trial) revealed that maintaining normoglycemia slowed the progression of nephropathy in individuals with type 1 diabetes. In the landmark 2001 trial conducted by Van den Berghe et al (Leuven 1), surgical ICU patients randomized to a blood glucose target of...
80 to 110 mg/dL had a decreased incidence of renal replacement therapy compared with those randomized to conventional glucose control.\textsuperscript{18}

Elevations in blood glucose cause mitochondrial injury and endothelial dysfunction, suppressing immunity and leading to an increased risk for infection.\textsuperscript{13-15} In an observational study, patients undergoing elective surgery who were hyperglycemic (blood glucose >220 mg/dL) on postoperative day 1 had a 3-fold higher rate of infection.\textsuperscript{19} A recent retrospective analysis showed that orthopedic trauma patients with a mean blood glucose greater than 220 mg/dL had a 7-fold increase in the risk for infection.\textsuperscript{20} Data also suggest that patients with stress hyperglycemia, especially those in the post-cardiothoracic surgery population, are at an increased risk for wound infection.\textsuperscript{21,22} Additionally, skin graft failure in burn patients has been associated with uncontrolled hyperglycemia.\textsuperscript{23} Overall, risk for infection is highly correlated with hyperglycemia and occurs across multiple populations.

Stress hyperglycemia also is associated with increased risk for critical illness polyneuropathy (CIP). The pathogenesis of CIP is not well understood, but cytokine release is a presumed cause.\textsuperscript{24-26} A prospective ICU-based study by Nanas et al revealed an independent association between CIP and elevated blood glucose.\textsuperscript{26} Similarly, a retrospective analysis by Bercker et al correlated increased daily peak blood glucose with acute respiratory distress syndrome in patients with CIP.\textsuperscript{27} Patients with CIP also were found to have prolonged mechanical ventilation time and longer ICU stays. Hyperglycemia appears to play a role in CIP severity as well.\textsuperscript{24,25,28} A 1991 prospective study found that increases in blood glucose were associated with decreases in electrophysiological peripheral nerve function in critically ill patients.\textsuperscript{29} Of the patients studied, 30% had clinical manifestations of CIP, including difficulty in mechanical ventilation weaning.

All of these complications can increase mortality. In a retrospective analysis of nearly 260,000 ICU admissions, mortality correlated with increasing blood glucose, independent of baseline disease severity.\textsuperscript{26} Even moderate hyperglycemia during an ICU stay has been associated with higher mortality.\textsuperscript{5} In a recent meta-analysis, a statistically significant reduction in overall mortality was associated with a blood glucose target of less than 150 mg/dL.\textsuperscript{10} However, this finding was not replicated in other meta-analyses. Risk for mortality also may differ depending on patients’ baseline comorbidities. In a retrospective cohort analysis, patients without diabetes randomized to a blood glucose target of 90 to 140 mg/dL had a higher risk for mortality than those with blood glucose target of 80 to 110 mg/dL.\textsuperscript{31}

Glycemic Control in Critically Ill Patients

Hyperglycemia during critical illness initially was presumed to be an adaptive metabolic response to stress and only was treated when blood glucose concentrations were above 220 mg/dL. In 1997, Swedish authors published the results of the DIGAMI (Diabetes and Insulin-Glucose Infusion in Acute Myocardial Infarction) trial, which ushered in an era of change in the management of stress hyperglycemia.\textsuperscript{32} Patients with underlying diabetes and acute myocardial infarction, who were randomized to a blood glucose target of 126 to 196 mg/dL, demonstrated a 28% reduction in mortality. Consequently, the question of optimal glucose range in critically ill patients has come to the forefront over the past decade.

In early 2000, a blood glucose target of 80 to 110 mg/dL was used in many ICUs based on the results of Leuven 1 Surgical Trial. However, the findings of the 2009 NICE-SUGAR (Normoglycemia in Intensive Care Evaluation and Surviving Using Glucose Algorithm Regulation) trial contradicted Leuven 1. In this study, 6,104 mixed ICU patients were randomized to a blood glucose target of either 81 to 108 mg/dL or 144 to 180 mg/dL.\textsuperscript{33} The lower blood glucose target was associated with increased mortality (27.5% vs 24.9%; odds ratio [OR], 1.14; 95% confidence interval [CI], 1.02-1.28; P=0.02), as well as higher incidence of severe hypoglycemia (6.8% vs 0.5; P<0.001) when compared with the more conventional glucose target. The results of this trial called into question previous practices of targeting lower glucose in ICU patients.

Various organizations have published recommendations for blood glucose control for critically ill patients. These guidelines reflect the disparity in the literature. The American Association of Clinical Endocrinologists and American Diabetes Association’s (AACE/ADA) 2009 consensus statement recommended a blood glucose target of 140 to 180 mg/dL and against targeting blood glucose below 110 mg/dL.\textsuperscript{34} Similarly, the 2011 American College of Physicians guidelines recommend against intensive glucose control (80-110 mg/dL) and instead target blood glucose of 140 to 200 mg/dL.\textsuperscript{1} In 2012, the ADA’s position statement recommended a similar glycemic target (blood glucose 140-180 mg/dL), with a more stringent goal (110-140 mg/dL) for some critically ill patients.\textsuperscript{35} The Society of Critical Care Medicine (SCCM) developed slightly different recommendations (blood glucose target of 100-150 mg/dL) with absolute maximum blood glucose of 180 mg/dL.\textsuperscript{36} Limitations to these recommendations include a lack of high-quality evidence; many recommendations were based, in part, on single-center experiences, trials without power to detect certain outcomes, and studies with poor protocol compliance. Thus, it is important to be familiar with literature related to glycemic targets and outcomes in specific ICU populations.

**CARDIAC SURGERY**

The Leuven 1 study was one of the first to suggest tighter blood glucose for ICU patients.\textsuperscript{16} The trial included 1,548 surgical ICU patients, of which 63% were admitted for cardiac surgery. Glucose targets of 80 to 110 mg/dL and 180 to 200 mg/dL...
dl were compared and the former resulted in reduced mortality (relative risk reduction of 42%). Other advantages of the lower target included earlier extubation, decreased renal replacement therapy, and shorter ICU stays. Patients in the 80 to 110 mg/dL group also had a higher incidence of hypoglycemia (blood glucose <40 mg/dL; 5.1% vs 0.8%; relative risk, 6.65). A post hoc analysis of these patients revealed a decrease in new kidney injury, critical illness polyneuropathy, ICU mortality, and hospital mortality. Smaller studies have reported decreased mortality in cardiac surgery patients, as well as decreased morbidity, such as fewer sternal wound infections, with tighter blood glucose control (<150 mg/dL). A 2010 study by Leibowitz et al targeted a higher blood glucose range of 110 to 150 mg/dL; the groups had similar incidences of hypoglycemic episodes (2.5% moderate glucose control vs 3% conventional). Decreased rates of infection and atrial fibrillation also were demonstrated in the moderate control group. Tighter glycemic control should be considered for cardiac surgery patients, but a glucose target of 80 to 110 mg/dL should be avoided due to high rates of hypoglycemia.

**Neurosurgery/Neurology**

In a planned subanalysis of the Leuven 1 study population, patients with isolated brain injury were investigated for degree of intracranial pressure, incidence of seizures, diabetes insipidus, and long-term rehabilitation. A glucose target of 80 to 110 mg/dL was found to have a statistically significant benefit on intracranial pressure and seizure incidence in 63 patients with isolated brain injury. However, a recent meta-analysis demonstrated that glucose control after a neurologic event such as ischemic stroke, aneurysmal subarachnoid hemorrhage, intraparenchymal hemorrhage, or traumatic brain injury does not yield a mortality benefit (OR, 0.97; 95% CI, 0.81-1.16). Other trials found similar results related to mortality as well as significantly increased episodes of hypoglycemia with a blood glucose target of 80 to 110 mg/dL. In this population, hypoglycemic episodes also are associated with increased mortality.

**Surgical/Medical**

In 2006, the authors of Leuven 1 published the results of insulin therapy in medical ICU (MICU) patients (Leuven 2). A glucose target of 80 to 110 mg/dL was associated with reduced mortality only in a subset of patients admitted to the MICU for more than 3 days. Patients in the MICU for fewer than 3 days had higher mortality. Morbidity was reduced for new renal injury, length of mechanical ventilation, and hospital and ICU stay for the 80 to 110 mg/dL group, regardless of length of stay. The difference in overall rates of hypoglycemia was statistically significant between groups: 18.7% for those with a blood glucose target of 80 to 110 mg/dL, versus 3.1% for those with a target of 180 to 200 mg/dL. Furthermore, 25.1% of patients in the 80 to 110 mg/dL group admitted to the ICU for more than 3 days experienced a hypoglycemic episode compared with 3.9% of those with the higher target.

Subsequent studies have not replicated the mortality and morbidity benefits seen in Leuven 1. A recent meta-analysis that included NICE-SUGAR data found mortality to vary by ICU, with surgical ICU (SICU) patients appearing to benefit from tighter blood glucose control. Other meta-analyses have shown an inconsistent association in SICU patients. Overall, a blood glucose target of 80 to 110 mg/dL should be avoided in MICU and SICU patients. Additional studies are needed to determine the optimal blood glucose target for noncardiac surgery patients.

**Severe Sepsis and Septic Shock**

SCCM’s Surviving Sepsis Campaign (SSC) provides specific recommendations on blood glucose goals for patients with severe sepsis or septic shock. Following the results of Leuven 1 and 2, SSC guidelines recommended the use of a blood glucose target of 80 to 110 mg/dL. However, in a randomized controlled trial of septic patients treated with hydrocortisone and a blood glucose target of 80 to 110 mg/dL or 150 mg/dL or less, there was no difference in mortality. Similarly, in patients with severe sepsis, a target of 80 to 110 mg/dL was not associated with a mortality benefit, but it was associated with more adverse events such as hypoglycemia. The 2012 SSC guidelines now recommend a blood glucose of ≤180 mg/dL.

**Management of Stress Hyperglycemia**

Stress hyperglycemia in critically ill patients can be challenging to manage. Treatment consists of targeting a blood glucose range that avoids the adverse effects of hyperglycemia while preventing hypoglycemia. Limiting fluctuations in blood glucose and maintaining a specified goal is essential to success and minimization of adverse patient outcomes. In a large retrospective cohort of septic patients, glucose variability was independently associated with hospital mortality. Similar studies have shown a greater predictive ability of glycemic variability on patient outcomes compared with targeting...
a specific glucose range.56,57 These studies imply that a more important management goal may be to decrease glucose variability. Recently, MacKenzie et al revealed that central tendency (mean or median serum glucose), glycemic variability, and minimum glucose value all were associated with patient outcomes.58 Further research is needed to determine glycemic variability goals; nevertheless, specifying blood glucose targets and minimizing glycemic variability are important components of critical illness management.

Treatment of hyperglycemia in critically ill patients in the ICU should occur when blood glucose concentrations are persistently elevated (Figure 2, page 54). Two blood glucose measurements higher than 180 mg/dL should trigger the initiation of insulin.50,53,54 Insulin can be administered either subcutaneously or via continuous infusion. Patient-specific factors should be taken into consideration when selecting a formulation. Insulin infusions are the most physiologic method for achieving glycemic goals, with a very short half-life (5–9 minutes) that allows for easy titration as clinical status changes. Ideal candidates for insulin infusions include patients who are hemodynamically unstable, undergoing targeted temperature management, edematous, receiving vasopressors or high-dose corticosteroids, or have type 1 diabetes or unpredictable nutrition.13,14 Subcutaneous insulin administration during critical illness can be complicated by the aforementioned factors. It may be considered first-line therapy in specific situations, such as in patients with low insulin requirements or in clinically stable patients.74 In critically ill patients, initial treatment of stress hyperglycemia typically is accomplished with IV insulin therapy. An insulin infusion ideally is administered via a protocol. The ideal protocol should quickly reach and maintain target blood glucose, account for the current blood glucose and rate of change in blood glucose values, balance stability and responsiveness, result in minimal rates of hypoglycemia, and clearly communicate titration instructions and frequency of blood glucose monitoring based on blood glucose stability to nurses.59–61 The Yale Insulin Drip Protocol encompasses all of these elements. The initial blood glucose value is used to determine whether a bolus is needed and the initial infusion rate, both of which are based on a formula. Subsequent adjustments to the infusion incorporate both the current blood glucose and rate of change.62 Additionally, this protocol is associated with a low incidence of both severe and moderate hypoglycemia.61 Similarly, in the North Carolina Protocol developed by Braithwaite et al, columns are selected to maintain blood glucose within target range. Patients begin in column 2 and switch columns on the basis of response, which accounts for rate of change.54 The column method was further modified by the University of Washington. This protocol uses 4 columns based on insulin sensitivity, with column 1 for insulin-sensitive patients and column 4 for insulin-resistant patients, whereas the infusion rate for the protocol developed by Bode et al is based on the degree of insulin resistance calculated with an insulin sensitivity factor.55,56 Initially, blood glucose monitoring should occur hourly until blood glucose reaches the target range and remains within range for 2 to 3 hours; then blood glucose monitoring can occur every 2 hours. Ultimately, there is no preferred insulin infusion protocol. Protocol selection should be a multidisciplinary decision that takes into account institution-specific factors that may affect implementation, adherence, and patient safety and outcomes.

Sensitivity to insulin can change rapidly with improvement in illness, resulting in reduced insulin requirements. In some instances, patients may not require insulin once acute illness has resolved. For other patients, insulin maintenance therapy may be required. In this situation, when blood glucose is consistently within target, transition from IV to subcutaneous therapy may be considered. Patient-specific factors should be taken into account before such a transition. These include ensuring that patients are receiving consistent nutrition, are hemodynamically stable, are off vasopressors, are receiving a stable dose of corticosteroids, have minimal peripheral edema, and that any infection they might have is resolving.9,50 Transition should be delayed if there is disruption in nutrition.9,50 Overall, patients with type 1 or 2 diabetes or who need more than 1 unit per hour of IV insulin will likely require transition to subcutaneous insulin. Once a patient is transitioned to subcutaneous insulin, blood glucose monitoring should occur 4 to 6 times daily (at least before meals and at bedtime).

A basal-bolus strategy is preferred for conversion from IV to subcutaneous insulin.9,50,53 The basal-bolus strategy should be considered for patients with resolving acute illness who are receiving oral nutrition. This strategy consists of administration of basal insulin in the form of long-acting (glargine) or intermediate-acting (isophane) with bolus insulin in the form of rapid-acting (aspart) or short-acting (regular) with meals. Eighty percent of the total insulin infusion dose from the previous 24 hours is divided equally between basal and bolus insulin.33,59 Conversely, for patients receiving enteral nutrition, basal insulin with corrective doses of short-acting insulin is recommended. In a prospective study, ICU and ward patients were randomized to receive 40%, 60%, or 80% of their total insulin infusion dose as insulin glargine. A conversion of 80% was associated with the highest percentage of blood glucose values within target range.67 Similarly, in a retrospective study of neurosurgical ICU patients, a 60% to 70% conversion to NPH insulin resulted in a higher percentage of glucose values within the desired range compared with ≤50% conversion.58 Based on these data, a conversion of approximately 60% to 80% may be appropriate for most patients. Overlapping subcutaneous insulin with IV insulin therapy is important to ensure adequate time for absorption and prevent rebound hyperglycemia. For short- and rapid-acting insulin, therapy should be initiated 1 to 2 hours before discontinuation of IV insulin, whereas a 2- to 4-hour overlap should be allotted for intermediate- and long-acting insulin.

Hyperglycemia is a potential complication of insulin therapy. It is defined as either moderate (blood glucose ≤70 mg/dL) or severe (blood glucose ≤40 mg/dL) and is associated with adverse outcomes.51 Subtle signs of hyperglycemia such as headache, fatigue, and confusion may be confounded in critically ill by the underlying disease or use of medications such as sedatives. Seizures, cardiac arrhythmias, neurocognitive impairment, and coma typically manifest with severe or prolonged hyperglycemia.20,69,70

Hyperglycemia, irrespective of severity, is associated with increased mortality. In a post hoc analysis conducted by the NICE-SUGAR investigators, both moderate and severe hyperglycemia were associated with increased mortality.71 Interestingly, in a study with a more conservative definition of hyperglycemia (blood glucose ≤81 mg/dL), higher mortality also was observed.70 Some patients may be predisposed to hyperglycemia. In a retrospective study, several factors were associated with an increased risk for severe hyperglycemia (blood glucose ≤45 mg/dL): continuous renal replacement therapy with bicarbonate-based replacement fluid, discontinuation of nutrition without adjustment in insulin, and a history of diabetes, sepsis, or vasopressor therapy.72 Mechanical ventilation and severity of illness also have been identified as potential risk factors.

Prevention is crucial to abating the consequences of hypoglycemia. Interruptions in nutrition should be anticipated and insulin should be held preemptively or dextrose infusion should be administered. In patients with renal or hepatic dysfunction, careful insulin monitoring and titration should be performed. During corticosteroid tapers, empiric insulin dose reductions should be considered. Early recognition and treatment of moderate hypoglycemia averts progression to severe hypoglycemia.

Conclusions

Stress hyperglycemia commonly occurs in the ICU and is associated with adverse patient outcomes such as increased mortality and morbidity. Consequently, diligent monitoring and management are essential parts of care. This consists of identification of glycemic targets including blood glucose goal, reduction of glycemic variability, and prevention of hypoglycemia. Understanding of these targets and stress hyperglycemia continues to evolve. In particular, blood glucose goals have shifted from one extreme to the other over the past 2 decades. Based on the results of recent studies, conventional glucose control (blood glucose ≤180 mg/dL) is preferred as opposed to intensive control (blood glucose ≤110 mg/dL), which is likely more harmful than beneficial. Data suggest that stricter blood glucose control (≤150 mg/dL) may be warranted for cardiac surgery and possibly surgical ICU patients, but further studies are needed before definitive recommendations can be made.

Hyperglycemia in the ICU is best managed with insulin therapy. Insulin infusions are preferred because they can be easily adjusted based on changes in patients’ clinical status and converted to subcutaneous insulin, if needed, when acute illness has resolved. Development of institution-specific insulin protocols is essential for safe management. These should emerge from a multidisciplinary committee that determines blood glucose targets, evaluates the capability of the protocol to achieve the targets, and analyzes the protocol for areas of quality improvement.