Ghaith Alhatemi, MD
Department of Internal Medicine, Saint Mary Mercy Hospital, Livonia, MI; Department of Internal Medicine, Wayne State University/Detroit Medical Center, Detroit, MI

Haider Aldiwani, MD
Department of Internal Medicine, Palomar Medical Center, Escondido, CA

Rafal Alhatemi, MD
Department of Internal Medicine, Wayne State University/Detroit Medical Center, Detroit, MI

Marwah Hussein, MD
Department of Internal Medicine, Division of Endocrinology, Wayne State University/Detroit Medical Center, Detroit, MI

Suzan Mahdai, MD
Department of Internal Medicine, Scripps Mercy Hospital Chula Vista, San Diego, CA

Berhane Seyoum, MD
Department of Internal Medicine, Division of Endocrinology, Wayne State University/Detroit Medical Center, Detroit, MI

Glycemic control in the critically ill: Less is more

ABSTRACT

Hyperglycemia is associated with poor clinical outcomes in critically ill patients. Initial clinical trials of intensive insulin therapy targeting blood glucose levels of 80 to 110 mg/dL showed improved outcomes, but subsequent trials found no benefits and even increased harm with this approach. Emerging literature has evaluated other glycemic indices including time-in-target blood glucose range, glycemic variability, and stress hyperglycemia ratio. These indices, while well described in observational studies, have not been addressed in the initial trials. Additionally, the patient's preexisting diabetes status and preadmission diabetic control may modulate the outcomes of stringent glycemic control, with worse outcomes of hyperglycemia being observed in patients without diabetes and in those with well-controlled diabetes. Most medical societies recommend less stringent glucose control in the range of 140 to 180 mg/dL for critically ill patients.

KEY POINTS

- Hyperglycemia is associated with increased morbidity and mortality in critically ill patients and should be treated.
- Enhancing the amount of time glucose levels are in the target range and minimizing glycemic variability have been associated with improved outcomes in critically ill patients.
- Hypoglycemia has been independently associated with an increased risk of death in critically ill patients.
- Although the optimal blood glucose target for patients in the intensive care unit is not known, a target of 140 to 180 mg/dL is the most acceptable.

doi:10.3949/ccjm.89a.20171

Hyperglycemia has been associated with adverse clinical outcomes in critically ill patients, regardless of diabetes status.[1–7] Proposed causes of stress hyperglycemia include excessive counterregulatory hormones (corticosteroid, glucagon, growth hormone, catecholamines) and release of cytokines tumor necrosis factor (TNF)-alpha and interleukin (IL)-1. These factors can promote a transient state of insulin resistance that can lead to decreased insulin action on suppressing gluconeogenesis and also to decreased uptake of insulin-mediated skeletal muscle glucose.[8] Factors contributing to hyperglycemia in hospitalized patients include medications (steroids, catecholamines), parenteral nutrition, and intravenous medications diluted in dextrose.[9]

See related editorial page 189

Further, hyperglycemia itself induces production of inflammatory cytokines (IL-6, IL-8, and TNF-alpha) and reactive oxygen species.[10] It also impairs the neutrophil functions of chemotaxis and bactericidal activity.[11] Additionally, hyperglycemia and hyperinsulinemia have been shown to increase tissue procoagulant activity that may add to the procoagulant state.[12] These mechanisms may explain the poor outcomes observed with hyperglycemia.

Initial single-center randomized clinical trials (RCTs) of intensive insulin therapy targeting blood glucose levels in the fasting range (80–110 mg/dL) (referred to as the Leuven trials) found significant mortality and morbidity benefit,[13,14] and this strategy gained popularity. However, subsequent multicenter RCTs[15–17] failed to replicate these findings, and the larg-

est RCT, the Normoglycemia in Intensive Care Evaluation–Survival Using Glucose Algorithm Regulation (NICE-SUGAR) trial,[17] reported evidence of harm with this intervention.

Other glycemic indices have shown independent impacts on outcomes in the intensive care unit (ICU). In fact, the time-in-range (TIR, the amount of time the glucose level is in the target range), glycemic variability, and the modulation effect of preexisting diabetes status, although thoroughly evaluated by observational studies, were not examined in the early RCTs. This may explain potential differences in outcomes between these trials.

This review will discuss findings from the major RCTs, metrics of glycemic control, and recommendations of professional medical societies for target blood glucose ranges in critically ill patients.

METRICS OF GLYCEMIC CONTROL

Hyperglycemia

In observational study results published from 2003 to 2009, hyperglycemia was generally associated with adverse clinical outcomes in critically ill patients in various settings (medical, surgical, trauma, and neurologic).[1–7] For example, in one retrospective analysis,[4] hyperglycemia had a graded effect on hospital mortality. In other trials,[1,5–7] trauma patients with hyperglycemia had increased mortality rates, hospital length of stay, ICU length of stay, and incidences of nosocomial infection. Moreover, hyperglycemia was associated with worse neurologic outcomes and elevated intracranial pressure in patients with severe traumatic brain injury, and early hyperglycemia was an independent predictor of worse scores on the Glasgow Coma Scale.[3]

The relationship between hyperglycemia and mortality in ICU patients is modulated by diabetes status

The relationship between hyperglycemia and mortality in ICU patients is modulated by their diabetes status. Observational studies[2,18–20] have shown that the greatest reduction in mortality associated with intensive insulin therapy (target goal 80–110 mg/dL) was seen in patients without diabetes. In Egi et al,[18] multivariate logistic regression analysis showed greater reduction in odds of mortality (odds ratio 0.45) when 80–110 mg/dL was used in patients without diabetes compared with other blood glucose targets. In contrast, for patients with diabetes, the mortality benefit had a poor correlation. The cohorts of critically ill patients with diabetes were not identical. Thus, preadmission diabetic control as evidenced by hemoglobin A1c (HbA1c) levels might have a differential impact on the hyperglycemia-mortality relationship. For instance, in a retrospective observational study of patients with HbA1c levels obtained at admission,[21] for patients with a low HbA1c level (< 7%), increases in mean blood glucose values were associated with increased mortality risk; the risk was decreased when the HbA1c was above 7%.[21] This may signify that patients with poorly controlled diabetes may benefit from a less stringent glucose target.

In addition to mortality outcomes, early hyperglycemia (defined as elevated blood glucose on hospital day 1 or 2),[5] hyperglycemia at admission,[6,7] and worsening or highly variable hyperglycemia[1] were associated with higher rates of infectious complications in critically ill patients. After correction for severity of illness and other variables including age, elevated glucose was an independent predictor of increased infectious morbidity in these studies.[1,5–7]

To study the complex interplay between acute and chronic hyperglycemia on mortality in hospitalized patients, Roberts et al[22] developed the stress hyperglycemia ratio, calculated as the blood glucose level at admission divided by the estimated average glucose, which was inferred from the HbA1c as follows: the estimated average glucose equals HbA1c × 1.59, minus 2.59.[23] In Roberts et al,[22] the stress hyperglycemia ratio but not admission hyperglycemia was associated with adverse outcomes. These findings were corroborated by other cohort studies,[24,25] demonstrating that the stress hyperglycemia ratio was independently associated with increased risk of death and additional complications.

Time in the target glucose range

The TIR had been proposed as a "unifying" metric of glycemic control because it is affected by hyperglycemia, hypoglycemia, and glycemic variability. The Glucontrol study[16] was the only RCT that explicitly reported TIR. A subsequent post hoc analysis of data from this study showed that a TIR greater than 50% for

a glucose target of 140 to 180 mg/dL was independently associated with increased rate of survival.[26] A series of single-center studies using the SPRINT (Specialized Relative Insulin Nutrition Tables) protocol, a tight glycemic control intervention, examined the effect of TIR (termed "cumulative time in band") on organ failure and mortality in critically ill patients receiving intensive insulin therapy.[27–29] Reduced organ failure, as evidenced by a reduction in the SOFA (Sequential Organ Failure Assessment) score, was associated with a TIR greater than 50%,[27] while a TIR greater than 70% was independently associated with improved survival.[29]

A subsequent prospective study of patients after cardiac surgery showed improved outcomes in decreased duration of both mechanical ventilation and ICU length of stay in those with a TIR greater than 80%, regardless of diabetes status. The incidence of sternal wound infections was significantly higher in patients with a TIR below 80% vs patients with a TIR above 80%.[30]

The effect of diabetes status on TIR outcomes has been studied by Krinsley and Preiser.[31] In their retrospective analysis of the prospectively collected data, and independent of severity of illness and ICU length of stay, a TIR greater than 80% for a blood glucose of 70 to 140 mg/dL was strongly associated with increased survival in critically ill patients without diabetes but not in patients with diabetes. One could argue that the design of the study did not include data on baseline glycemic control before ICU admission, and so it questions whether poorly controlled diabetes has any impact on the benefits of a high TIR.

A more recent landmark retrospective multicenter study by Lanspa et al[32] published in 2019 sought to examine this effect and found that a TIR greater than 80% for a blood glucose target of 70 to 139 mg/dL was independently associated with reduced mortality in patients with or without diabetes. However, when diabetes status was stratified into well-controlled and poorly controlled disease (based on HbA1c), the TIR effect was not significant in patients with poorly controlled diabetes.[32] This finding suggests that antecedent poor glucose control may potentially confound the effects of tight glycemic control if not taken into consideration.

Glycemic variability

Glycemic variability is defined as the fluctuation of blood glucose or other parameters of glucose homeostasis over a given time. The most frequently used metrics for assessing short-term within-day glycemic variability are the following:

- Standard deviation of glucose
- Coefficient of variation for glucose
- Mean amplitude of glycemic excursions.[33]

Ryan et al[34] proposed another metric for glycemic variability in type 1 diabetes, termed the glycemic lability index, based on the change in glucose level over a 4-week period. A discussion of the interpretation and reference values of these indices is beyond the scope of this review.

There is strong evidence that high glycemic variability is associated with increased short-term and long-term mortality and hospital length of stay in heterogeneous cohorts of critically ill patients,[35–39] with 1 study[36] showing a higher mortality rate with increasing glycemic variability in patients with sepsis when the glycemic lability index was divided into deciles. Increased rates of bacteremia,[40] nosocomial infections,[41] and surgical site infections[42] have also been linked to increased glycemic variability. For example, Atamna et al[40] found that increased glycemic variability (expressed as coefficient of variation for glucose) increased the risk of bacteremia in non-ICU patients hospitalized for acute infectious illnesses. Donati et al[41] found that in critically ill patients, increased glycemic variability in all 3 indices noted above were significantly associated with infectious morbidity and mortality, with the highest quartile of the glycemic lability index having the strongest association with ICU-acquired infection. Subramaniam et al[42] reported that postoperative glycemic variability in the first 24 hours after cardiac surgery carried the highest rate of a composite of postoperative adverse events, including superficial and deep sternal wound infections.

There is strong evidence that high glycemic variability is associated with increased short-term and long-term mortality rates and hospital length of stay in critically ill patients

Several studies have evaluated the effects of antecedent diabetes status as well as hypoglycemia.[20,43,44] Interestingly, when Krinsley et al[20,43] stratified patients based on their prior diagnosis of diabetes, a high glycemic variability (using the coefficient of variation for glucose) was associated with increased mortality and

shortened survival in acutely ill patients without diabetes but not in patients with diabetes. The landmark study by Lanspa et al[44] used a standardized electronic insulin protocol to minimize interphysician variability in insulin titration. They found that even though the coefficient of variation was independently associated with 30-day mortality, this association was higher for patients without diabetes than for those with diabetes. Although these studies were adequately powered and their populations were stratified for diabetes state, their potential weakness is that the stratification was made based on either chart review[20,43] or the International Classification of Diseases (ICD)-9 codes[44] without including the HbA1c. Thus, diabetes diagnoses could have been missed. In addition, the effect of glycemic variability was not studied in patients with well-controlled vs poorly controlled diabetes, based on HbA1c values, as was done for the TIR.

The effect of glycemic variability on mortality outcomes, though potentially confounded by hypoglycemia, was also proven to be a strong independent predictor of mortality when adjusting for hypoglycemia and disease severity.[44,45] In fact, in 1 study,[46] the risk of hypoglycemia was 3.2 times higher in patients with increased glycemic variability.

Glycemic variability, though potentially confounded by hypoglycemia, is a strong independent predictor of mortality

HYPOGLYCEMIA: A COMPLICATING FACTOR

The American Diabetes Association defines hypoglycemia as a blood glucose level below 70 mg/dL and classifies it as follows:

- Level 1: 70 to ≥ 54 mg/dL
- Level 2: < 54 mg/dL
- Level 3: a clinical event characterized by altered mental or physical status requiring assistance for treatment of hypoglycemia.[47]

In observational studies, hypoglycemia has been independently associated with increased risk of death in critically ill patients.[48–52] In RCTs, a pooled analysis of the NICE-SUGAR study[53] and the study by Meyfroidt et al[54] showed that hypoglycemia increased the odds of mortality. In one study,[52] mild hypoglycemia (defined as < 70 mg/dL) was associated with increased mortality regardless of diabetes status and diagnosis of conditions (medical, surgical, or trauma). In a retrospective study, Bagshaw et al[48] found that early hypoglycemia (defined as within 24 hours of ICU admission) and its severity were associated with increasing mortality in a dose-dependent fashion. Interestingly, mortality was higher in patients with 2 episodes of hypoglycemia than in those with only 1 episode.[48] Saliba et al[55] examined outcomes based on whether hypoglycemia was induced by medication (iatrogenic) or was spontaneous during the course of critical illness. When results were stratified based on the cause of hypoglycemia, they found that the effects on mortality rates were equally harmful and that the cause did not have a significant impact.[55]

GLYCEMIC TARGETS IN CLINICAL STUDIES

Single-center trials

In 2010, Meyfroidt et al[54] published results of a retrospective analysis of data first published in 2001 by Van den Berghe et al.[13] In that trial, 1,548 patients (mainly with cardiac disease) admitted to the surgical ICU were randomized to receive either intensive insulin therapy (glucose goal of 80–110 mg/dL) or hyperglycemia treatment only when it reached the renal threshold (180–220 mg/dL). Reductions in mortality, critical illness polyneuropathy, acute renal failure, transfusion requirement, and bloodstream infections were more significant in the intensive insulin therapy group than in the "tolerating-hyperglycemia" group. However, hypoglycemia was more frequent in the intensive treatment cohort.[13]

In 2006, Van den Berghe et al[14] published results from a similar trial in 1,200 exclusively medical ICU patients. The insulin infusion protocols and nutritional strategies were the same as in the study of surgical patients. Results showed that intensive insulin therapy did not decrease hospital mortality rates. However, the group had significant reductions in length of ICU and hospital stay, mechanical ventilation duration, and acute renal failure. As in the first trial, hypoglycemia was significantly more prevalent in the intensive insulin treatment group.[14]

Multicenter trials

Subsequent multicenter RCTs failed to confirm the mortality benefits of intensive insulin

therapy reported by Van den Berghe et al[13,14] and Meyfroidt et al.[54] The Efficacy of Volume Substitution and Insulin Therapy in Severe Sepsis study (VISEP)[15] was conducted in medical and surgical ICU patients with sepsis, with results published in 2008. One year later, results were published from the Glucontrol study,[16] conducted in a similar population. However, both studies were terminated prematurely due to increased hypoglycemia in the intensive therapy arm in VISEP[15] and a high rate of unintended protocol violations in Glucontrol.[16]

Enthusiasm for strict glycemic control was further reduced by the 2009 publication of results from the international multicenter NICE-SUGAR study,[17] which randomized 6,104 patients. In NICE-SUGAR, the intensive insulin therapy cohort (glucose target 81–108 mg/dL) had higher 90-day mortality rates and a higher incidence of severe hypoglycemia (< 40 mg/dL) than the conventional therapy group (glucose target 144–180 mg/dL). Moreover, there was no reported difference between the groups in ICU or hospital length of stay, duration of mechanical ventilation, or need for renal replacement therapy. In a 24-month follow-up study of NICE-SUGAR,[56] no differences were detected in favorable neurologic outcomes or mortality in patients with traumatic brain injury.

EXPLAINING DISCREPANCIES IN STUDY RESULTS

Difference in blood glucose targets

The Leuven studies[13,14] and VISEP[15] used target glucose levels of 80 to 110 mg/dL (stringent) in the intervention groups and 180 to 200 mg/dL (loose) in the control groups. In contrast, the Glucontrol study used 80 to 110 mg/dL for the intervention group (stringent) and 140 to 180 mg/dL (intermediate) for the controls,[16] and the NICE-SUGAR study[17] used 81 to 108 mg/dL (stringent) for the interventional arm and 144 to 180 mg/dL (intermediate) for the controls. Thus, comparisons between stringent and intermediate glucose targets have not been addressed by adequately powered RCTs.

In attempts to find an optimal blood glucose target, Yamada et al[57] and Yatabe et al[58] performed network meta-analyses of published RCTs comparing insulin regimens in critically ill adults with hyperglycemia. Unlike the standard pairwise meta-analysis, a network meta-analysis has the advantage of comparing the efficacy of more than 2 interventions, using direct and indirect or mixed comparisons for the intervention groups.[59] Using a common comparator, indirect comparisons can examine intervention arms that had no prior direct head-to-head comparisons in clinical trials. The 2 meta-analyses[57,58] divided study groups into 4 interventions based on different blood glucose targets: tight (80–100 mg/dL), moderate (110–140 mg/dL, 110–144 mg/dL), mild (140–180 mg/dL, 144–180 mg/dL), and loose (> 180 mg/dL). Results revealed no significant difference relevant to the mortality risk for any comparison. However, these findings should be interpreted with caution, as the validity of indirect and mixed comparisons is built on the assumption that there are no differences between trials other than the intervention or treatment (in this case, a target blood glucose value), which is clearly a limitation given the methodologic differences of the key trials.

Differences in other glycemic control metrics and diabetes status

The TIR, glycemic variability, preexisting diabetes status, and preadmission glycemic control play important modifying roles on the benefits of stringent insulin therapy on mortality outcomes, as discussed above. Apart from the Glucontrol trial that reported TIR and glycemic variability,[16] earlier RCTs based comparisons solely on the blood glucose target, which can potentially confound the results.

Enthusiasm for strict glycemic control was diminished by results from the NICE-SUGAR study

Differences in methods of glucose measurement

Inaccurate glucose measurement can lead to insulin dosing errors that can cause hypoglycemia. A review article by Inoue et al[60] found that the first Leuven trial[13] used precise blood-gas analyzers, which are more accurate than traditional point-of-care capillary glucose meters. Subsequent trials—medical Leuven,[14] VISEP,[15] Glucontrol,[16] and NICE-SUGAR[17]—used both arterial and capillary analyzers. The point-of-care glucose meters, while having the advantage of ease of use and rapidity, can be affected by anemia,[61] arterial oxygen tension,[62]

TABLE 1

Recommendations for blood glucose targets for insulin therapy

Professional society	Year	Recommendations
American Diabetes Association[70]	2021	Insulin therapy should be initiated for treatment of persistent hyperglycemia at a threshold 180 mg/dL. Once insulin therapy is started, a target blood glucose range of 140–180 mg/dL is recommended for most critically ill patients. More stringent goals, such as 110–140 mg/dL, may be appropriate for selected patients if they can be achieved without significant hypoglycemia.
American College of Physicians[71]	2014	Best practice advice 1: Clinicians should target a blood glucose level of 140–200 mg/dL if insulin therapy is used in surgical or medical patients in the intensive care unit. Best practice advice 2: Clinicians should avoid targets < 140 mg/dL because harms are likely to increase with lower glood glucose targets.
Society of Critical Care Medicine[72]	2012	A blood glucose level ≥ 150 mg/dL should trigger initiation of insulin therapy, titrated to keep the level < 150 mg/dL for most adult intensive care unit patients, and to maintain blood glucose values absolutely < 180 mg/dL using a protocol that achieves a low rate of hypoglycemia (blood glucose ≤ 70 mg/dL) despite limited impact on patient mortality.

We hypothesize that a standardized computer-based insulin protocol can minimize interclinician variability and enhance compliance of the treating team

and the patient's medications,[63] especially given the outdated glucose monitors used in these studies.

Continuous glucose monitoring was not available at the time of the initial RCTs. This technology can offer a significant benefit in improving glycemic control,[64,65] using a wide range of metrics such as TIR, time above range, and time below range, which can provide more precise data on glycemic control than conventional intermittent glucose monitoring.[66] Clinical trials evaluating continuous glucose monitoring in hospitalized patients have been mainly confined to the intravascular route,[67,68] and thus, minimally invasive devices have not been thoroughly studied. We believe that use of continuous glucose monitoring can probably provide more objective information on optimal blood glucose targets for future trials, especially when combined with validated computerized insulin protocols.

Differences in insulin administration protocols

The Leuven trials[13,14] and VISEP[15] used a strict algorithm for insulin titration. In contrast, the NICE-SUGAR[17] trial protocol was less standardized, allowing physicians to use their discretion and thus introducing interclinician variability in insulin administration, which can jeopardize TIR and increase glycemic variability.

In a multicenter international RCT published in 2017,[69] a clinically validated computer algorithm for insulin infusion was compared with a nurse-driven protocol. Results showed that the computerized protocol achieved higher quality of blood glucose control as evidenced by lower hypoglycemia rates, high TIR, and low glycemic variability than the nurse-driven protocol. We hypothesize that a standardized computer-based insulin protocol can minimize interclinician variability and enhance compliance of the treating team.

WHAT DO MEDICAL SOCIETIES RECOMMEND?

Several medical societies have guidelines on blood glucose targets for insulin therapy (**Table 1**).[70–72]

The American Diabetes Association,[70] citing the NICE-SUGAR trial results,[17] recommends that insulin therapy be started for persistent hyperglycemia (> 180 mg/dL) with a target glucose range of 140 to 180 mg/dL in most critically ill patients, and notes that more aggressive goals (110–140 mg/dL) may be more appropriate for specific groups of patients (eg, postsurgical patients or patients with cardiac surgery) if these targets can be achieved without significant hypoglycemia. On the other hand, glucose concentrations above 180 mg/dL may be acceptable in terminally ill patients, in patients with severe comorbid conditions, and in inpatient care settings where frequent glucose monitoring or close nursing supervision is not feasible.[70]

The American College of Physicians[71] recommends targeting a blood glucose range of 140 to 200 mg/dL in surgical and medical ICU patients, avoiding targets below 140 mg/dL due to likely increased harm.

Guidelines of the Society of Critical Care Medicine[72] suggest a blood glucose value of 150 mg/dL or greater to trigger the use of insulin therapy, with the goal of maintaining a glucose level below 150 mg/dL for most critically ill patients and maintaining the glucose level absolutely below 180 mg/dL.

TAKE-HOME MESSAGE

The optimal blood glucose target for patients in the ICU remains unknown, but a target of 140 to 180 mg/dL is the most acceptable for critically ill patients. We believe that future studies investigating the optimal target for ICU patients should do the following:

- Include other glycemic metrics
- Take into account preadmission diabetes diagnosis and premorbid glycemic control (based on the HbA1c)
- Use accurate blood glucose monitoring methods combined with a standardized validated insulin algorithm.

This will enable studies to shed light on appropriate glycemic targets and may lead to a more individualized approach for the critically ill patient rather than a universal approach.

DISCLOSURES

The authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

REFERENCES

1. **Bochicchio GV, Sung J, Joshi M, et al**. Persistent hyperglycemia is predictive of outcome in critically ill trauma patients. J Trauma 2005; 58(5):921–924. doi:10.1097/01.ta.0000162141.26392.07
2. **Falciglia M, Freyberg RW, Almenoff PL, D'Alessio DA, Render ML**. Hyperglycemia-related mortality in critically ill patients varies with admission diagnosis. Crit Care Med 2009; 37(12):3001–3009. doi:10.1097/CCM.0b013e3181b083f7
3. **Jeremitsky E, Omert LA, Dunham CM, Wilberger J, Rodriguez A**. The impact of hyperglycemia on patients with severe brain injury. J Trauma 2005; 58(1):47–50. doi:10.1097/01.ta.0000135158.42242.b1
4. **Krinsley JS**. Association between hyperglycemia and inreased hospital mortality in a heterogeneous population of critically ill patients. Mayo Clin Proc 2003; 78(12):1471–1478. doi:10.4065/78.12.1471
5. **Laird AM, Miller PR, Kilgo PD, Meredith JW, Chang MC**. Relationship of early hyperglycemia to mortality in trauma patients. J Trauma 2004; 56(5):1058–1062. doi:10.1097/01.ta.0000123267.39011.9f
6. **Sung J, Bochicchio GV, Joshi M, Bochicchio K, Tracy K, Scalea TM**. Admission hyperglycemia is predictive of outcome in critically ill trauma patients. J Trauma 2005; 59(1):80–83. doi:10.1097/01.ta.0000171452.96585.84
7. **Yendamuri S, Fulda GJ, Tinkoff GH**. Admission hyperglycemia as a prognostic indicator in trauma. J Trauma 2003; 55(1):33–38. doi:10.1097/01.TA.0000074434.39928.72
8. **McCowen KC, Malhotra A, Bistrian BR**. Stress-induced hyperglycemia. Crit Care Clin 2001; 17(1):107–124. doi:10.1016/s0749-0704(05)70154-8
9. **Corathers SD, Falciglia M**. The role of hyperglycemia in acute illness: supporting evidence and its limitations. Nutrition 2011; 27(3): 276–281. doi:10.1016/j.nut.2010.07.013
10. **Stentz FB, Umpierrez GE, Cuervo R, Kitabchi AE**. Proinflammatory cytokines, markers of cardiovascular risks, oxidative stress, and lipid peroxidation in patients with hyperglycemic crises. Diabetes 2004; 53(8):2079–2086. doi:10.2337/diabetes.53.8.2079
11. **Delamaire M, Maugendre D, Moreno M, Le Goff MC, Allannic H, Genetet B**. Impaired leucocyte functions in diabetic patients. Diabet Med 1997; 14(1):29–34. doi:10.1002/(SICI)1096-9136(199701)14:1<29::AID-DIA300>3.0.CO;2-V
12. **Boden G, Rao AK**. Effects of hyperglycemia and hyperinsulinemia on the tissue factor pathway of blood coagulation. Curr Diab Rep 2007; 7(3):223–227. doi:10.1007/s11892-007-0035-1
13. **Van den Berghe G, Wouters P, Weekers F, et al**. Intensive insulin therapy in critically ill patients. N Engl J Med 2001; 345(19): 1359–1367. doi:10.1056/NEJMoa011300
14. **Van den Berghe G, Wilmer A, Hermans G, et al**. Intensive insulin therapy in the medical ICU. N Engl J Med 2006; 354(5):449–461. doi:10.1056/NEJMoa052521
15. **Brunkhorst FM, Engel C, Bloos F, et al**. Intensive insulin therapy and pentastarch resuscitation in severe sepsis. N Engl J Med 2008; 358(2):125–139. doi:10.1056/NEJMoa070716
16. **Preiser JC, Devos P, Ruiz-Santana S, et al**. A prospective randomised multi-centre controlled trial on tight glucose control by intensive insulin therapy in adult intensive care units: the Glucontrol study. Intensive Care Med 2009; 35(10):1738–1748. doi:10.1007/s00134-009-1585-2
17. **NICE-SUGAR Study Investigators, Finfer S, Chittock DR, Li Y, et al**.

Intensive versus conventional glucose control in critically ill patients. N Engl J Med 2009; 360(13):1283–1297. doi:10.1056/NEJMoa0810625
18. **Egi M, Bellomo R, Stachowski E, et al**. Blood glucose concentration and outcome of critical illness: the impact of diabetes. Crit Care Med 2008; 36(8):2249–2255. doi:10.1097/CCM.0b013e318181039a
19. **Krinsley JS**. Glycemic control, diabetic status, and mortality in a heterogeneous population of critically ill patients before and during the era of intensive glycemic management: six and one-half years' experience at a university-affiliated community hospital. Semin Thorac Cardiovasc Surg 2006; 18(4):317–325. doi:10.1053/j.semtcvs.2006.12.003
20. **Krinsley JS, Egi M, Kiss A, et al**. Diabetic status and the relation of the three domains of glycemic control to mortality in critically ill patients: an international multicenter cohort study. Crit Care 2013; 17(2):R37. doi:10.1186/cc12547
21. **Egi M, Bellomo R, Stachowski E, et al**. The interaction of chronic and acute glycemia with mortality in critically ill patients with diabetes. Crit Care Med 2011; 39(1):105–111. doi:10.1097/CCM.0b013e3181feb5ea
22. **Roberts GW, Quinn SJ, Valentine N, et al**. Relative hyperglycemia, a marker of critical illness: introducing the stress hyperglycemia ratio. J Clin Endocrinol Metab 2015; 100(12):4490-4497. doi:10.1210/jc.2015-2660
23. **Nathan DM, Kuenen J, Borg R, et al**. Translating the A1C assay into estimated average glucose values. Diabetes Care 2008; 31(8): 1473–1478. doi:10.2337/dc08-0545
24. **Preiser JC, Lheureux O, Prevedello D**. A step toward personalized glycemic control. Crit Care Med 2018; 46(6):1019–1020. doi:10.1097/CCM.0000000000003107
25. **Yang Y, Kim TH, Yoon KH, et al**. The stress hyperglycemia ratio, an index of relative hyperglycemia, as a predictor of clinical outcomes after percutaneous coronary intervention. Int J Cardiol 2017; 241:57–63. doi:10.1016/j.ijcard.2017.02.065
26. **Penning S, Chase JG, Preiser JC, et al**. Does the achievement of an intermediate glycemic target reduce organ failure and mortality? A post hoc analysis of the Glucontrol trial. J Crit Care 2014; 29(3): 374–379. doi:10.1016/j.jcrc.2014.01.013
27. **Chase JG, Pretty CG, Pfeifer L, et al**. Organ failure and tight glycemic control in the SPRINT study. Crit Care 2010; 14(4):R154. doi:10.1186/cc9224
28. **Chase JG, Shaw G, Le Compte A, et al**. Implementation and evaluation of the SPRINT protocol for tight glycemic control in critically ill patients: a clinical practice change. Crit Care 2008; 12(2):R49. doi:10.1186/cc6868
29. **Signal M, Le Compte A, Shaw GM, Chase JG**. Glycemic levels in critically ill patients: are normoglycemia and low variability associated with improved outcomes? J Diabetes Sci Technol 2012; 6(5): 1030–1037. doi:10.1177/193229681200600506
30. **Omar AS, Salama A, Allam M, et al**. Association of time in blood glucose range with outcomes following cardiac surgery. BMC Anesthesiol 2015; 15(1):14. doi:10.1186/1471-2253-15-14
31. **Krinsley JS, Preiser JC**. Time in blood glucose range 70 to 140 mg/dl > 80% is strongly associated with increased survival in non-diabetic critically ill adults. Crit Care 2015; 19(1):179. doi:10.1186/s13054-015-0908-7
32. **Lanspa MJ, Krinsley JS, Hersh AM, et al**. Percentage of time in range 70 to 139 mg/dl is associated with reduced mortality among critically ill patients receiving IV insulin infusion. Chest 2019; 156(5):878–886. doi:10.1016/j.chest.2019.05.016
33. **Monnier L, Colette C, Owens D**. Glucose variability: do we have to revisit the profusion of definitions to avoid confusion? Diabetes Metab 2018; 44(2):97–100. doi:10.1016/j.diabet.2017.10.005
34. **Ryan EA, Shandro T, Green K, et al**. Assessment of the severity of hypoglycemia and glycemic lability in type 1 diabetic subjects undergoing islet transplantation. Diabetes 2004; 53(4):955–962. doi:10.2337/diabetes.53.4.955
35. **Akirov A, Diker-Cohen T, Masri-Iraqi H, Shimon I**. High glucose variability increases mortality risk in hospitalized patients. J Clin Endocrinol Metab 2017; 102(7):2230–2241. doi:10.1210/jc.2017-00450
36. **Ali NA, O'Brien JM Jr, Dungan K, et al**. Glucose variability and mortality in patients with sepsis. Crit Care Med 2008; 36(8):2316–2321. doi:10.1097/CCM.0b013e3181810378
37. **Egi M, Bellomo R, Stachowski E, French CJ, Hart G**. Variability of blood glucose concentration and short-term mortality in critically ill patients. Anesthesiology 2006; 105(2):244–252. doi:10.1097/00000542-200608000-00006
38. **Hermanides J, Vriesendorp TM, Bosman RJ, Zandstra DF, Hoekstra JB, Devries JH**. Glucose variability is associated with intensive care unit mortality. Crit Care Med 2010; 38(3):838–842. doi:10.1097/CCM.0b013e3181cc4be9
39. **Todi S, Bhattacharya M**. Glycemic variability and outcome in critically ill. Indian J Crit Care Med 2014; 18(5):285–290. doi:10.4103/0972-5229.132484
40. **Atamna A, Ayada G, Akirov A, Shochat T, Bishara J, Elis A**. High blood glucose variability is associated with bacteremia and mortality in patients hospitalized with acute infection. QJM 2019; 112(2): 101–106. doi:10.1093/qjmed/hcy235
41. **Donati A, Damiani E, Domizi R, et al**. Glycaemic variability, infections and mortality in a medical-surgical intensive care unit. Crit Care Resusc 2014; 16(1):13–23. pmid:24588431
42. **Subramaniam B, Lerner A, Novack V, et al**. Increased glycemic variability in patients with elevated preoperative HbA1C predicts adverse outcomes following coronary artery bypass grafting surgery. Anesth Analg 2014; 118(2):277–287. doi:10.1213/ANE.0000000000000100
43. **Krinsley JS**. Glycemic variability and mortality in critically ill patients: the impact of diabetes. J Diabetes Sci Technol 2009; 3(6):1292–1301. doi:10.1177/193229680900300609
44. **Lanspa MJ, Dickerson J, Morris AH, Orme JF, Holmen J, Hirshberg EL**. Coefficient of glucose variation is independently associated with mortality in critically ill patients receiving intravenous insulin. Crit Care 2014; 18(2):R86. doi:10.1186/cc13851
45. **Krinsley JS**. Glycemic variability: a strong independent predictor of mortality in critically ill patients. Crit Care Med 2008; 36(11): 3008–3013. doi:10.1097/CCM.0b013e31818b38d2
46. **Kauffmann RM, Hayes RM, Buske BD, et al**. Increasing blood glucose variability heralds hypoglycemia in the critically ill. J Surg Res 2011; 170(2):257–264. doi:10.1016/j.jss.2011.03.008
47. **American Diabetes Association**. 6. Glycemic targets: standards of medical care in diabetes-2021. Diabetes Care 2021; 44(suppl 1): S73–S84. doi:10.2337/dc21-S006
48. **Bagshaw SM, Bellomo R, Jacka MJ, et al**. The impact of early hypoglycemia and blood glucose variability on outcome in critical illness. Crit Care 2009; 13(3):R91. doi:10.1186/cc7921
49. **Egi M, Bellomo R, Stachowski E, et al**. Hypoglycemia and outcome in critically ill patients. Mayo Clin Proc 2010; 85(3):217–224. doi:10.4065/mcp.2009.0394
50. **Hermanides J, Bosman RJ, Vriesendorp TM, et al**. Hypoglycemia is associated with intensive care unit mortality. Crit Care Med 2010; 38(6):1430–1434. doi:10.1097/CCM.0b013e3181de562c
51. **Krinsley JS, Grover A**. Severe hypoglycemia in critically ill patients: risk factors and outcomes. Crit Care Med 2007; 35(10):2262–2267. doi:10.1097/01.CCM.0000282073.98414.4B
52. **Krinsley JS, Schultz MJ, Spronk PE, et al**. Mild hypoglycemia is independently associated with increased mortality in the critically ill. Crit Care 2011; 15(4):R173. doi:10.1186/cc10322
53. **NICE-SUGAR Study Investigators, Finfer S, Liu B, et al**. Hypoglycemia and risk of death in critically ill patients. N Engl J Med 2012; 367(12):1108–1118. doi:10.1056/NEJMoa1204942
54. **Meyfroidt G, Keenan DM, Wang X, Wouters PJ, Veldhuis JD, Van den Berghe G**. Dynamic characteristics of blood glucose time series during the course of critical illness: effects of intensive insulin therapy and relative association with mortality. Crit Care Med 2010; 38(4):1021–1029. doi:10.1097/CCM.0b013e3181cf710e
55. **Saliba L, Cook CH, Dungan KM, Porter K, Murphy CV**. Medication-induced and spontaneous hypoglycemia carry the same risk for hospital mortality in critically ill patients. J Crit Care 2016; 36:13–17. doi:10.1016/j.jcrc.2016.06.010

56. **NICE-SUGAR Study Investigators for the Australian and New Zealand Intensive Care Society Clinical Trials Group and the Canadian Critical Care Trials Group, Finfer S, Chittock D, Li Y, et al**. Intensive versus conventional glucose control in critically ill patients with traumatic brain injury: long-term follow-up of a subgroup of patients from the NICE-SUGAR study. Intensive Care Med 2015; 41(6):1037–1047. doi:10.1007/s00134-015-3757-6
57. **Yamada T, Shojima N, Noma H, Yamauchi T, Kadowaki T**. Glycemic control, mortality, and hypoglycemia in critically ill patients: a systematic review and network meta-analysis of randomized controlled trials. Intensive Care Med 2017; 43(1):1–15. doi:10.1007/s00134-016-4523-0
58. **Yatabe T, Inoue S, Sakaguchi M, Egi M**. The optimal target for acute glycemic control in critically ill patients: a network meta-analysis. Intensive Care Med 2017;43(1):16–28. doi:10.1007/s00134-016-4558-2
59. **Cipriani A, Higgins JP, Geddes JR, Salanti G**. Conceptual and technical challenges in network meta-analysis. Ann Intern Med 2013; 159(2):130–137. doi:10.7326/0003-4819-159-2-201307160-00008
60. **Inoue S, Egi M, Kotani J, Morita K**. Accuracy of blood-glucose measurements using glucose meters and arterial blood gas analyzers in critically ill adult patients: systematic review. Crit Care 2013; 17(2):R48. doi:10.1186/cc12567
61. **Mann EA, Salinas J, Pidcoke HF, Wolf SE, Holcomb JB, Wade CE**. Error rates resulting from anemia can be corrected in multiple commonly used point-of-care glucometers. J Trauma 2008; 64(1):15–21. doi:10.1097/TA.0b013e318160b9e4
62. **Tang Z, Louie RF, Payes M, Chang KC, Kost GJ**. Oxygen effects on glucose measurements with a reference analyzer and three handheld meters. Diabetes Technol Ther 2000; 2(3):349–362. doi:10.1089/15209150050194215
63. **Tang Z, Du X, Louie RF, Kost GJ**. Effects of drugs on glucose measurements with handheld glucose meters and a portable glucose analyzer. Am J Clin Pathol 2000; 113(1):75–86. doi:10.1309/QAW1-X5XW-BVRQ-5LKQ
64. **Beck RW, Riddlesworth T, Ruedy K, et al**. Effect of continuous glucose monitoring on glycemic control in adults with type 1 diabetes using insulin injections: the DIAMOND randomized clinical trial. JAMA 2017; 317(4):371–378. doi:10.1001/jama.2016.19975
65. **Beck RW, Riddlesworth TD, Ruedy K, et al**. Continuous glucose monitoring versus usual care in patients with type 2 diabetes receiving multiple daily insulin injections: a randomized trial. Ann Intern Med 2017; 167(6):365–374. doi:10.7326/M16-2855
66. **Danne T, Nimri R, Battelino T, et al**. International consensus on use of continuous glucose monitoring. Diabetes Care 2017; 40(12): 1631–1640. doi:10.2337/dc17-1600
67. **Bochicchio GV, Nasraway S, Moore L, Furnary A, Nohra E, Bochicchio K**. Results of a multicenter prospective pivotal trial of the first inline continuous glucose monitor in critically ill patients. J Trauma Acute Care Surg 2017; 82(6):1049–1054. doi:10.1097/TA.0000000000001444
68. **Righy Shinotsuka C, Brasseur A, Fagnoul D, So T, Vincent JL, Preiser JC**. Manual versus Automated moNitoring Accuracy of GlucosE II (MANAGE II). Crit Care 2016; 20(1):380. doi:10.1186/s13054-016-1547-3
69. **Dubois J, Van Herpe T, van Hooijdonk RT, et al**. Software-guided versus nurse-directed blood glucose control in critically ill patients: the LOGIC-2 multicenter randomized controlled clinical trial. Crit Care 2017; 21(1):212. doi:10.1186/s13054-017-1799-6
70. **American Diabetes Association**. 15. Diabetes care in the hospital: standards of medical care in diabetes-2021. Diabetes Care 2021; 44(suppl 1):S211–S220. doi:10.2337/dc21-S015
71. **Qaseem A, Chou R, Humphrey LL, Shekelle P; Clinical Guidelines Committee of the American College of Physicians**. Inpatient glycemic control: best practice advice from the Clinical Guidelines Committee of the American College of Physicians. Am J Med Qual 2014; 29(2):95–98. doi:10.1177/1062860613489339
72. **Jacobi J, Bircher N, Krinsley J, et al**. Guidelines for the use of an insulin infusion for the management of hyperglycemia in critically ill patients. Crit Care Med 2012; 40(12):3251–3276. doi:10.1097/CCM.0b013e3182653269

***Address**: Ghaith Alhatemi, MD, Department of Internal Medicine, Wayne State University/Detroit Medical Center, 4201 St Antoine, 3R, Detroit, MI 48201; galhatem@med.wayne.edu*