

Metabolic Management during Critical Illness: Glycemic Control in the ICU

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Abstract

Hyperglycemia is a commonly encountered metabolic derangement in the ICU. Important cellular pathways, such as those related to oxidant stress, immunity, and cellular homeostasis, can become deranged with prolonged and uncontrolled hyperglycemia. There is additionally a complex interplay between nutritional status, ambient glucose concentrations, and protein catabolism. While the nuances of glucose management in the ICU have been debated, results from landmark studies support the notion that for most critically ill patients moderate glycemic control is appropriate, as reflected by recent guidelines. Beyond the target population and optimal glucose range, additional factors such as hypoglycemia and glucose variability are important metrics to follow. In this regard, new technologies such as continuous glucose sensors may help alleviate the risks associated with such glucose fluctuations in the ICU. In this review, we will explore the impact of hyperglycemia upon critical cellular pathways and how nutrition provided in the ICU affects blood glucose. Additionally, important clinical trials to date will be summarized. A practical and comprehensive approach to glucose management in the ICU will be outlined, touching upon important issues such as glucose variability, target population, and hypoglycemia.

Keywords

- ▶ hyperglycemia
- ▶ hypoglycemia
- ▶ critical illness
- ▶ glycemic control
- ▶ insulin resistance

Hyperglycemia is a commonly encountered metabolic disturbance among a heterogeneous group of patients with critical illness. In a study conducted between 2012 and 2013 in an Australian medical–surgical intensive care unit (ICU), among 1,000 patients examined, the majority of patients (~80%) became hyperglycemic at some point during the first 48 hours of admission (defined as fasting blood glucose [BG] ≥ 126 mg/dL, or random BG ≥ 200 mg/dL).¹ Prevalence of critical illness–associated hyperglycemia has been reported as being even higher in other studies.² Hyperglycemia is an evolutionarily highly preserved response during periods of stress observed across many species and, *to a degree*, the old adage that it is “a compensatory mechanism to provide fuel to vital organs,” may be in part true. While many studies have highlighted the epidemiological association between

hyperglycemia and increased morbidity and mortality in numerous disease states,^{3–5} there have been, to date, somewhat discrepant results from randomized trials that have assessed whether controlling glucose intensively improves clinical outcomes.^{6–10} Added to this has been the complexity of factoring in related issues pertaining to optimal BG targets, any superimposed risks of hypoglycemia, glucose variability, questions about appropriate target populations (which might include the presence or absence of preexisting diabetes mellitus), and the method by which glucose control is attained (i.e., which insulin infusion protocol is implemented). Recent studies have also highlighted the relevance of preexisting glycemic milieu for each patient, as a higher “metabolic penalty” may be incurred by an individual with true *de novo* stress hyperglycemia.^{1,11–14} The seemingly

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simple question of what BG threshold should be used—above which stress hyperglycemia could be considered *maladaptive*—has therefore been a source of much debate and controversy in the past decade, as we have come to better appreciate the nuances of metabolic management of critically ill patients. The following brief review will highlight the physiologic consequence of uncontrolled glycemic excursions, the BG target to consider, and how to best achieve glycemic control in the ICU. Furthermore, the occurrence of hyper- as well as hypoglycemia is indirectly linked to nutritional intake during critical illness. Related concepts pertaining to ICU nutrition in the context of metabolic management will also be reviewed.

The Biology of Hyperglycemia during Critical Illness

Why Hyperglycemia Develops and How Hyperglycemia Affects Critical Cellular Pathways

While a comprehensive review of glucose and insulin dynamics during critical illness is beyond the scope of this review, there is a complex interplay between patient factors, cellular derangements, nutrition, and glycemia in the critically ill. Hyperglycemia during illness is fueled by a state of insulin resistance. Counter-regulatory hormones (such as catecholamines, cortisol, glucagon) and elevated levels of cytokines (such as interleukin-1 [IL-1], IL-6, tumor necrosis factor- α [TNF- α]) promote hyperglycemia mainly through the induction of insulin resistance, which results in impaired peripheral glucose uptake and increased endogenous glucose production (mainly through hepatic gluconeogenesis and glycogenolysis).^{15–17} In the fasting state, glycogen stores are eventually depleted, but gluconeogenesis remains unimpaired.

Hyperglycemia, in turn, has several immunomodulatory effects that are potentially deleterious in critical illness, such as increased production of anti-inflammatory cytokines like IL-10, and impairment of polymorphonuclear neutrophil function, resulting in decreased intracellular bactericidal activity, opsonic activity, and innate immunity.^{18–21} Hyperglycemia can also promote inflammation by increasing proinflammatory cytokines such as TNF- α , IL-1 β , -6, -8, and -18,²² increasing leukocyte adhesion molecules, inducing NF- κ B,²³ and promoting a procoagulant state.^{18–21} Hyperglycemia additionally exacerbates oxidative stress.^{24–26}

The Link between Oxidant Stress, Organ Dysfunction, Mitochondrial Health, and Glycemia

Increasingly recognized is the coupling between oxidant stress and mitochondrial DNA injury. Mitochondrial damage results in an inability to maintain basic cellular functions and has been associated with the onset of multiorgan dysfunction syndrome. Effective removal of damaged mitochondria through mitophagy and regeneration of healthy mitochondria is associated with better outcomes.²⁷ Interestingly, some studies suggest that this core cellular homeostatic function is worsened in the presence of hyperglycemia.²⁸

The Role of Immobility and Insulin Resistance

Exercise-stimulated glucose uptake in skeletal muscle plummets as patients become bedbound.²⁹ As a corollary, a recent study tested whether an early ICU mobilization program can increase glucose transport in contracting skeletal muscles and thereby ameliorate hyperglycemia. This concept was supported by the observation that exercise has an ability to reduce inflammation and improve insulin resistance.³⁰ For example, among healthy patients with type 2 diabetes mellitus, a single bout of 45 to 60 minutes of exercise enhanced glucose transport and insulin sensitivity by up to 20 hours after exercise.³¹ In a secondary analysis of data derived from a randomized trial studying early mobility, patients with and without ICU weakness achieved identical glycemic control (median BG 131 mg/dL in both groups, with glucose managed per standardized insulin protocol), but those randomized to early ICU mobilization (average therapy session of 25 minutes) had reduced insulin resistance as evidenced by lower daily insulin requirements.³² Additional studies are needed to validate this concept.

The Relationship between Enteral Feeding and Hyperglycemia

Normally after eating a meal, serum glucose increases and insulin is released. Together, these events trigger downregulation of glucagon release. During critical illness, this feedback loop becomes impaired. Meal ingestion normally also triggers a complex entero-hormonal response involving glucose-like peptide-1 (GLP-1), gastric inhibitory peptide (GIP), cholecystokinin (CCK), ghrelin and peptide YY. These hormones regulate intestinal motility, nutrient absorption, as well as gallbladder and pancreatic islet cell function. GIP and GLP-1 are incretin hormones secreted by the gut; they potentiate β -cell insulin secretion in a glucose-dependent fashion. GLP-1 also suppresses glucagon release, which, in turn, results in a reduction in hepatic glucose production. After a bolus meal, these hormones experience a brisk rise followed by a return to basal levels, but this pulsatile hormonal response to nutrition is dampened with continuous tube feeding (when compared with bolus, intermittent feeding) and also associated with greater insulin resistance in an experimental model in healthy piglets.^{33,34} In reality, no mammalian species eats throughout a 24-hour period, and there may be an underappreciated metabolic implication to this standard practice in the ICU.³⁵ Continuous enteral feeding may also inadvertently predispose patients to hypoglycemia due to interruptions (which are sometimes prolonged and frequent) related to procedures and tests in the ICU. Further research is needed to define the best approach to providing sufficient nutrition during critical illness.

While gastric emptying delay is recognized as a consequence of long-standing diabetes and primarily thought of as a chronic neuropathic change in the gut, there is now ample evidence that acute hyperglycemia can also slow down gastric emptying in both healthy subjects and in those with diabetes.^{36–38} Critically ill patients, already prone to ileus, may therefore be additionally disadvantaged when confronted by poorly controlled glucose concentrations. In one study, 95

consecutive feed-intolerant critically ill patients with no known history of diabetes were compared with 50 feed-tolerant critically ill patients in a medical-surgical ICU.³⁹ The groups were matched for age, gender, body mass index, APACHE score, as well as other important variables such as receipt of opioid, inotropic, and sedative medications. Feed-intolerant patients were more likely to have higher peak BG before and during feeding, demonstrated more glucose variability, and had more episodes of BG >180 mg/dL which tended to be of longer duration compared with feed-tolerant patients, despite receiving similar amounts of insulin. Prokinetic agents, such as intravenous erythromycin, are sometimes used for refractory feed intolerance in the ICU. Interestingly, some studies have suggested degree of glycemia to impact treatment responses and have demonstrated significantly muted response to prokinetic agents during hyperglycemia (vs. euglycemia) in experimental models.⁴⁰ As ileus worsens and feeding attempts get increasingly interrupted, this also likely places the patient at a higher risk for developing hypoglycemia and greater glucose variability (both concepts discussed separately later), as attempts are made to control glucose excursions without a steady provision of nutrition.

Summative Findings from Randomized Studies of Glycemic Control for ICU Patients

The first randomized control study examining the effects of stringent glucose management in the ICU was published in 2001. It demonstrated that intensive insulin therapy, with a BG goal between 80 and 110 mg/dL, improved meaningful outcomes among ventilated surgical ICU patients. The absolute reduction in ICU mortality was 3.4% (relative risk [RR], -42%) and the benefit was amplified (9.6% absolute reduction; RR -48%; number needed to treat ~10) among those requiring ICU level care for more than 5 days.¹⁰ The follow-up medical ICU study by the same group, however, showed no mortality benefit in the intention to treat analysis, although a significant mortality improvement was again demonstrated in the prespecified target population of patients who required an ICU stay of 3 days or more.⁹ From a practical perspective, however, this subset was difficult to pre-identify at the time of ICU admission. A subsequent pooled analysis of the medical ICU and the original surgical ICU cohorts from these investigations showed improvements in mortality without any observable harm.⁴¹

In comparison, the multicenter European trial Glucontrol and the German sepsis trial VISEP reported frequent protocol violations and high hypoglycemia rates, and as a result were terminated early.^{6,8,42} There were no differences in mortality observed between the conventional and the intensively treated groups in either of these studies. Finally, the most recently published NICE-SUGAR trial, the largest randomized controlled trial to date with more than 6,100 participants, seemed to favor “good but not tight” control with a BG target of 140 to 180 mg/dL.⁷ In the end, the results seen in the original Belgian study have not been replicated, and in NICE-SUGAR, extremely tight control of BG (80–108 mg/dL) was

associated with slightly *higher* 90-day mortality when compared with those patients with moderate control (144–180 mg/dL) (27.5 vs. 24.9%; odds ratio [OR] for mortality with intensive control 1.14; 95% confidence interval [CI]: 1.02–1.28; $p = 0.02$), although reasons for this observation were not clear. Summary statistics from the large multicentered studies can be found in ► **Table 1**. Follow-up evaluations from NICE-SUGAR found that severe hypoglycemia in *both* the intensive and standard care groups was associated with greater mortality. Finally, while there is significant heterogeneity between studies, the latest meta-analysis (which include results from NICE-SUGAR) concluded that very tight glucose control did not improve mortality for all-comer ICU patients.⁴³ The pooled RR for death across the 26 studies included was 0.92 (95% CI: 0.83–1.04), but when analysis was limited to surgical ICU patients, the RR was 0.63 (95% CI: 0.44–0.91, however, not adjusting for multiple testing), suggesting there still may be some benefit in selected populations (► **Fig. 1**). To reflect the cumulative evidence to date, the latest recommendations from both the American Association of Clinical Endocrinologists and the American Diabetes Association suggest a target BG range of 140 to 180 mg/dL for most ICU patients, with greater benefit derived with an average glucose at the lower end of this range.⁴⁴ The third edition of the Surviving Sepsis Campaign International guidelines from 2012 largely mirror these recommendations, suggesting treatment initiation when two or more consecutive BG measurements exceed 180 mg/dL. While setting an upper target limit of 180 mg/dL, the most recent Surviving Sepsis guidelines did not strictly predefine a target range or lower glucose threshold level given the lack of clear evidence to support one target range over another, and simply added that avoidance of hypoglycemia was paramount.⁴⁵

The Practical and Comprehensive Approach to Glycemic Management in the ICU

The Target Population

As reflected in the latest meta-analysis and expert recommendations, despite somewhat disparate results of studies, reverting back to an era of lax glucose control is unacceptable, and for *most* ICU patients moderate glucose control (140–180 mg/dL) is appropriate. One may argue, however, that, in reality, the “one-size-fits-all” approach is too imprecise, as the physiology and needs during critical illness are quite heterogeneous.

One factor to consider pertains to the presence or absence of preexisting diabetes mellitus. Indeed, not all hyperglycemia is equally associated with adverse outcomes during acute illness.^{12,14,46,47} Patients with no prior diagnosis of diabetes have worse outcomes for the same degree of hyperglycemia compared with patients with known diabetes mellitus. The mechanism to explain this phenomenon is still unknown, but confounding factors as well as the impact of the preexisting metabolic milieu are likely relevant. To support this latter possibility, at a cellular level acute fluctuations in BG levels (particularly when truly transient and unrelated to preexisting diabetes) appear to induce more ischemic injury,

Table 1 Key study characteristics and results for randomized trials of intensive insulin therapy among critically ill patients

Study	Number of patients	Patient type	Apache II score	Blood glucose target (in mg/dL)		Actual mean blood glucose achieved (in mg/dL)		Blood glucose interquartile range (25–75%)		Site of blood glucose measurement	Primary outcome	Rate of outcome		Hazard ratio
				Intensive	Control	Intensive	Control	Intensive	Control			Intensive	Control	
van den Berghe et al 2001 ¹⁰	1,548, single center	Surgical	Mean: 9 both groups	80–110	180–200 (start insulin if >215)	103	153	84–122	120–186	Arterial blood only; blood gas glucose analyzer	ICU mortality	4.6%	8.0%	Not reported; $p < 0.04$
van den Berghe et al 2006 ⁹	1,200, single center	Medical	Mean: 23 both groups	80–110	180–200 (start insulin if >215)	111	153	82–140	122–184	Arterial blood preferred with blood gas glucose analyzer; otherwise capillary via glucometer	Hospital mortality	37.3%	40.0%	0.94 (95% CI: 0.84–1.06); $p = 0.31$
Glucontrol ⁸	1,101, multi-center (21 sites)	Mixed	Mean: 15 both groups	80–110	140–180	117 median	144 median	108–130	128–162	Arterial, central venous or capillary; blood gas glucose analyzer or glucometer	ICU mortality	17.2%	15.3%	Not reported; $p = 0.41$
WISE ^{6,41}	537, multicenter (18 sites)	Mixed, limited to patients with severe sepsis or septic shock	Mean: 20 both groups	80–110	180–200 (start insulin if >200)	112	151	94–140	118–184	Capillary or arterial samples via glucometer	28-d mortality	24.7%	26.0%	0.95 (95% CI: 0.70–1.28); $p = 0.72$
NICE-SUGAR ⁷	6,104, multi-center (42 sites)	Mixed	Mean: 21.1 both groups	80–108	144–180 (start insulin if >180)	115	144	97–133	121–167	Arterial sample preferred but capillary samples accepted. (glucometer, blood gas analyzer, or central laboratory)	90-d mortality	4.6%	8.0%	1.14 (95% CI: 1.02–1.28); $p = 0.02$

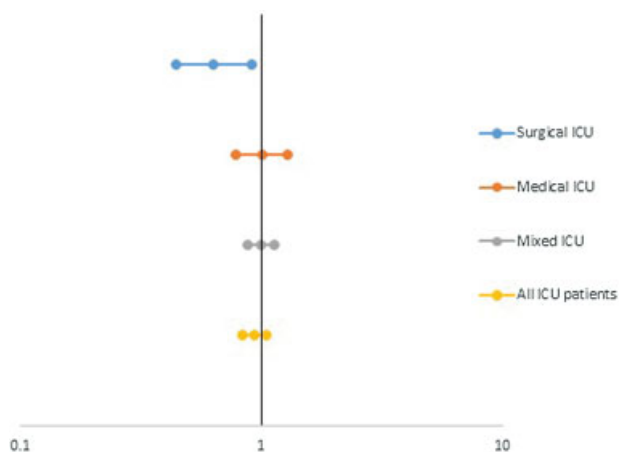


Fig. 1 Results from the post-NICE SUGAR meta-analysis: risk of 90-day mortality in clinical studies comparing conventional glycaemic control and intensive insulin therapy, stratified by ICU type. (Data adapted from Griesdale et al.⁴³)

inflammation, endothelial dysfunction, cellular apoptosis, and oxidative stress.^{48,49} Conversely, those with chronic hyperglycemia may have compensatory mechanisms in place that provide protection from acute hyperglycemia-related cellular damage. In support, recent ICU studies have shown that among hyperglycemic patients, those with higher pre-admission hemoglobin A1c (HbA1c) have significantly lower mortality compared with patients with lower HbA1c.^{11,50} Some have suggested that the greatest benefit from intensive insulin treatment may be reaped by those with newly discovered hyperglycemia or those with a low premorbid HbA1c levels,^{9,41,51} but such recommendations do not stem from properly designed clinical trials and are therefore not part of prevailing guidelines at this time.

Another example of a subset that may require special attention are neurologically injured patients. Modest hyperglycemia (in the range of 150–170 mg/dL) has been associated with morbidity and mortality in cerebral hemorrhage, ischemia, and trauma,^{52–55} and experimental animal models have shown that hyperglycemia can extend neuronal injury from ischemia.⁵⁶ Despite these observations and success seen in a limited number of neurosurgical patients in the original Leuven study,⁵⁷ other studies that have examined intensive insulin therapy among patients with cerebral injury have not shown consistent improvements in survival or functional outcome (but perhaps a modest improvement in infection rates).^{58–60} A possible reason may be related to exquisite sensitivity to even moderate hypoglycemia during acute brain injury. The balancing act between high and low BG and finding the possibly very narrow optimal range is particularly challenging in this cohort. In a small, observational study focusing on patients with acute brain injury, one group suggested that brain glucose was reduced by up to 70% among patients intensively treated with insulin (compared with 15% in the standard control group) using data obtained from cerebral microdialysis and PET imaging.⁶¹ The brain hypoglycemic threshold corresponded in this study to a BG level less than 80 mg/dL which is typically considered “safe.”

Monitoring Performance: Beyond Measuring the Average Glucose

The Role of Hypoglycemia

Tighter glucose control, no matter how well executed the protocol, will almost always lead to higher rates of hypoglycemia and some patients, such as the aforementioned brain-injured patients, may be particularly sensitive to the harmful effects of low BG concentrations. Published severe hypoglycemia rates (typically defined as the percent of patients experiencing at least one BG < 40 mg/dL) differ widely, and may be as low as 5.1% among surgical ICU patients in the original Leuven study¹⁰ to as high as nearly one in five in the medical ICU⁹ (–Table 2). There is debate about the clinical significance of these hypoglycemic events, particularly when identified quickly and appropriately addressed in a closely monitored ICU setting. Some believe that iatrogenic hypoglycemia is yet another marker of poor outcome and severity of illness and that it does not directly cause morbidity and mortality. In a large retrospective cohort study involving nearly 17,000 patients hospitalized for acute myocardial infarction, the likelihood of death in the hospital rose significantly when mean glucose levels fell below 70 mg/dL compared with those who had mean levels between 100 and 109 mg/dL (OR: 6.4; *p* = 0.01).⁶² In this study, it was *spontaneous hypoglycemia*, rather than insulin-induced hypoglycemia, that was associated with higher mortality. These data suggest that iatrogenic hypoglycemia may not carry with it significant risk. Instead, the predisposition to developing hypoglycemia in the absence of glucose-lowering therapy (as may occur in sepsis, hepatic failure, renal failure, and adrenal insufficiency) may simply identify a more vulnerable patient population.

Meanwhile, in a case–control study of a mixed medical–surgical ICU, hypoglycemia was associated with an increased risk of death after multivariate analysis (OR: 2.28 [CI: 1.41–3.7]) but on balance, the benefit reaped from glycaemic control appeared to outweigh this risk.⁶³ Others, such as Vriesendorp and colleagues, have shown no association between hypoglycemia and mortality.⁶⁴

Several commonly encountered factors have been associated with an increased risk of hypoglycemia, which may help identify patients who require closer monitoring: bicarbonate-based fluid during continuous venovenous

Table 2 Hypoglycemia rates for key randomized trials of intensive insulin therapy among critically ill patients

Study	Hypoglycemia rate (≤ 40 mg/dL)	
	Intensive (%)	Control (%)
van den Berghe et al 2001 ¹⁰	5	0.7
van den Berghe et al 2006 ⁹	18.7	3.1
Glucontrol ⁸	8.7	2.7
VISEP ^{6,41}	17.0	4.1
NICE-SUGAR ⁷	6.8	0.5

hemofiltration (CVVH), decreased rate or interruption of nutritional support, need for inotropic support, sepsis, female sex, prior diabetes, and octreotide use.⁶⁵ Septic patients may be at risk for delayed recognition of hypoglycemia when capillary finger stick measurements are used to titrate insulin during low perfusion states.^{66–68}

Despite lack of definitive data proving the dangers of hypoglycemia encountered in the ICU, it is important to remember that prolonged severe hypoglycemia can undoubtedly deplete astrocyte glycogen stores and lead to neuronal cell death and permanent brain injury. Concurrent administration of sedatives and the debilitated critically ill state may mask the usual symptoms of low BG such as anxiety, diaphoresis, tachycardia, palpitations, and perceptible change in cognitive function and may lead to delayed recognition if BG checks are not done at frequent intervals. Furthermore, one isolated hypoglycemic event may be well tolerated, but frequent and repeated episodes may deplete glycogen stores over time and place a patient at risk for neuronal injury even if each episode is of relatively short duration. The long-term neurocognitive consequences of recurrent or severe hypoglycemia are not well understood.

The Role of Glucose Variability

How we control glucose matters, and glucose variability may be as important as the mean glucoses achieved. Egi and colleagues demonstrated that glucose variability (defined as the standard deviation of glucose) was an important independent predictor of mortality—more powerful than mean glucose concentrations among a heterogeneous group of ICU patients.⁶⁹ In another study, there was a statistically significant difference in magnitude of change between two successive BG values when comparing survivors to nonsurvivors.⁷⁰ Notably, there was no difference in the conventionally reported metric of glucose control in terms of mean BG between the two groups. In a study reported by Krinsley, among patients with a mean BG level between 70 and 99 mg/dL during their ICU stay, mortality was 5.9% if this was achieved with the least amount of glucose variability⁷¹; for the same degree of “excellent” control, mortality rose to 30.1% among patients with the highest quartile of glucose variability. For patients with a mean BG ranging between 80 and 110 mg/dL, the target range utilized in the Leuven study and in subsequent trials, mortality ranged from 4.2 to 27.5% depending on the degree of glucose variability. While the incidence of severe glucose variability (defined as a BG measurement below 81 mg/dL and above 216 mg/dL occurring within 24 hours of ICU admission) appeared to be rare (occurring in only ~3% of patients) in a large retrospective cohort study examining more than 66,000 adult ICU admissions, the presence of significant BG variability was associated with higher covariate-adjusted ICU (1.5, 95% CI: 1.4–1.6) and hospital mortality (1.4, 95% CI: 1.3–1.5) when compared with the presence of hypoglycemia (BG below 81 mg/dL) only or when compared to patients without either factor (i.e., hypoglycemia and significant variability).⁷²

When patients develop hypoglycemia on intensive insulin therapy, most protocols call for administration of intravenous

dextrose. In the Leuven protocol, 10 g of dextrose was given when the BG dropped below 40 mg/dL. With BG rebounding shortly after administration of dextrose, such a protocol may therefore contribute to glucose variability. Therefore, when hypoglycemia rates are high, as was seen in the Leuven MICU study at 18.7 and at 17% in the VISEP trial, it is possible that the consequent increases in glucose variability may be negating the potential beneficial effects of glucose control.

Biologically, *in vitro* experiments have shown that fluctuating glucose levels induce apoptosis more robustly than sustained hyperglycemia, cause endothelial activation, and lead to oxidative stress.^{48,49,73} Similarly *in vivo*, rapid fluctuation in BG is associated with oxidative stress, and this relationship may be more important than the level of chronic sustained hyperglycemia among type 2 diabetics.⁷⁴ In type 1 diabetes, one interpretation of the results from the outpatient Diabetes Control and Complication Trial (DCCT) suggests that increased glucose variability is associated with higher rates of retinopathy in cohorts of patients at similar hemoglobin A1C strata.^{75,76}

Future studies need to examine and report the effect of glucose variability, as this may be an important metric to follow. With many such measures having been proposed by investigators, a standardized language and metric to describe “variability” should be established. Additionally, prospective evaluation is needed to clarify whether glucose variability is simply an epiphenomenon associated with severity of illness and the multiple interventions required in the sickest patients that lead to metabolic perturbations, including hypoglycemia, or whether it itself is a physiologic derangement in need of targeted intervention. We would add that a similar controversy has taken place for years regarding the chronic care of the diabetic patient. Yet, to date, there remains no compelling evidence that targeting glucose variability in these outpatients actually translates to improved clinical outcomes.

Monitoring Glucose

Any program of intensive glucose control necessitates accurate and precise BG concentration measurements. Currently, the “gold standard” in the inpatient setting is central laboratory measurement of plasma glucose, preferred over whole BG because it is less influenced by the prevailing hematocrit. The sample source may also affect the measured glucose value, with arterial blood, in the normal physiological range, typically registering ~10 mg/dL higher than venous blood (and ~5 mg/dL higher than capillary blood). Differences between these sites may be accentuated in the setting of significant hyperglycemia. Because of their overall convenience and rapid turnaround, capillary point-of-care (POC) (“finger stick”) meters have become inculcated into the daily work flow of hospital wards and even intensive care units. These devices use the glucose oxidase or glucose dehydrogenase reactions to estimate the BG concentration. Increased catecholamines, uric acid, and bilirubin as well as the presence of certain drugs such as acetaminophen may interfere with glucose-oxidase reactions.⁷⁷ Those that rely on the glucose dehydrogenase reaction are less subject to error

due to interfering metabolites and medications, but they may detect sugars other than glucose, such as mannose, xylose, and icodextrin, which will lead to an overestimate of the reported BG concentration.⁷⁷

Recently, the Food and Drug Administration (FDA) has challenged the appropriateness of using POC capillary meters in the hospital, as their accuracy has been validated mainly in the outpatient setting. The FDA currently endorses the standards of the International Organization for Standardization (ISO) in which 95% of glucose values measured by a device must fall within 15 mg/dL of the reference method (typically laboratory plasma glucose) for BG concentrations below 75 mg/dL and within 20% for BG concentrations above 75 mg/dL.⁷⁷ In a proposed set of guidelines, the FDA would mandate more stringent requirements for hospital-use glucose meters, for example, 99% of all values falling within 7 mg/dL for BG below 70 mg/dL and within 10% for above 75 mg/dL.⁷⁸ In addition, meter manufacturers would need to provide validation data demonstrating accuracy and precision in a variety of hospitalized patient types, including the critically ill.⁷⁹

Measuring capillary BG in the critically ill patient is indeed a challenge because commonly encountered physiologic disturbances can affect the measurements. For example, hypotension with resultant hypoperfusion and acidosis as well as severe anemia and hypothermia may introduce additional sources of error.⁸⁰ In addition to accuracy concerns, finger stick monitoring is somewhat time intensive with regard to nursing work and uncomfortable for the patient, as lancing the fingertip is necessary for each measurement. Accordingly, there has been significant recent interest in adopting “continuous glucose monitoring (CGM)” systems for inpatient use, with the hope that these new devices might help achieve smoother glycemic control and avoid the metabolic consequences of hypoglycemia and glucose variability in critically ill patients. In recent years, these devices have gained popularity in the outpatient care for patients with type 1 diabetes, particularly those on insulin pumps or other intensive management strategies. There are, however, few data on their role in intensive care unit or other hospitalized patients.

At the time of this writing, in the United States, there are two FDA-approved outpatient interstitial CGM systems (Enlite [Medtronic, Minneapolis, MN] and G4 Platinum [DexCom, San Diego, CA]) and one approved for inpatient use but only in Europe (Sentrino [Medtronic]). These devices work through a subcutaneously inserted sensor that measures the interstitial glucose concentration, which reacts with glucose oxidase to generate hydrogen peroxide in a redox reaction similar to that of many capillary glucose meters. Reciprocally, hydrogen peroxide is oxidized, releasing electrons and creating a current—the amplitude of which corresponds to the glucose concentration. This information is then transmitted continuously through radio waves to a small display device (about the size of a pager), which can present it graphically, updated every 5 minutes. Each sensor has a life of 3 to 7 days, depending on the model. Periodic calibration via capillary BG is necessary, and current devices, which remain imperfect particularly in the hypoglycemic range, require that any decisions on insulin dose changes should be made only after

the CGM glucose value (either high or low) is confirmed by a finger stick. In addition to the some of the same interferences faced by POC meters using glucose oxidase, measurement of interstitial glucose carries with it certain peculiarities. In steady state, interstitial glucose actually correlates well with ambient plasma glucose concentrations. However, it is very much influenced by the rate of change of plasma concentrations, capillary permeability, volume status, and proximate edema. Of specific importance is a lag phenomenon between the current plasma glucose reading and its interstitial counterpart amounting to approximately 15 to 30 minutes. The differences are most prominent when the BG is not in steady state, such as in the postprandial setting or after correction doses of insulin have been administered.⁸¹ Current CGM devices also provide warning alerts to the wearer regarding impending hypoglycemia and severe hyperglycemia. When worn consistently, they have been demonstrated to improve overall control and decrease hypoglycemic episodes in type 1 diabetes, in the outpatient setting.⁸²

Of note, several intravascular devices are also under investigation. These indwelling units read ambient glucose in venous blood real time.^{83–86} Other devices categorized as “intravascular” actually draw blood to and through an external sensor, subsequently either recirculated or discarded. The GlucoScout (International Biomedical Ltd., Austin, TX) is now FDA-approved for sampling arterial or venous blood every 5 minutes. Of similar design is the GlucoClear sensor (Edwards LifeSciences, Irvine, CA), now approved in Europe. Of course, any truly indwelling device carries with it the risk of infection and thrombosis, as well as possible interference from other solutions being delivered through the same vascular access channel.

Several studies have assessed the role of CGM in the hospital setting, most in the ICU.^{87–93} The majority concluded that the new technology has accuracy comparable to when used in the outpatient setting, despite circumstances of tenuous hemodynamic status or the ongoing use of pressors. For example, retrospective analysis of CGM data from 174 ICU patients being tracked via arterial BG as the reference found a practical concordance of ~99% when assessed by Clarke Error Grid analysis.⁹⁴ That is, the paired results would have each resulted in the same clinical decisions in all but 1% of results.⁹⁰ Others, however, have uncovered significant and concerning discordance specifically in the hypoglycemic range with high false-alarm rates. Rabiee and colleagues, for example, found that the CGM failed to detect up to 50% of hypoglycemic episodes in hospitalized patients as determined by finger stick BG.⁹⁵ Also, a study looking at the performance of the Sentrino, the first subcutaneous CGM device designed specifically for hospital use, while finding good overall correlation to standard BG measures, called into question the reliability of its alarms, especially in the context of hypoglycemia.⁹² The system failed to identify 6 out of 24 (25%) hypoglycemic events < 80 mg/dL as confirmed by central laboratory plasma venous values. Additionally, of 47 hypoglycemia alarms, 33 proved erroneous, resulting in a 70% false-alarm rate. As for the intravascular devices, preliminary

investigations have demonstrated them to be reasonably accurate in the ICU setting with low rates of device-related complications, although mainly in small, short-term studies.^{83–86}

Three randomized trials of CGM in the inpatient setting have been conducted to date. In two studies, by Boom et al⁹⁶ and Kopecký et al,⁹¹ no differences in glycemic control could be demonstrated with the more expensive CGM versus more conventional intermittent assessments either using arterial or capillary BG. Boom's data suggested the nursing time and costs may have been reduced, however, with CGM. In these two investigations, the standard insulin therapy protocols were being used with conventional BG monitoring. In the only such study that had adapted its insulin infusion protocol to match the more frequent and voluminous CGM data, Holzinger et al also found roughly equivalent overall glycemic control between the two groups. However, the rate of severe hypoglycemia was 1.6% in the CGM as compared with 11.5% in the control group, representing a RR reduction for these events of 86%.⁹⁷

In summary, there are no solid data yet to support the use of CGM in their current form in the ICU. However, as these devices become more accurate, especially in the hypoglycemia range, it is conceivable that they will emerge as an important method by which critical care physicians can track their patients' glucose concentrations more closely than with intermittent laboratory or POC assessments. Of course, extensive comparative effectiveness and cost-effectiveness research will need to be conducted. Additionally, more advanced glucose control algorithms will need to be developed to take advantage of the significantly more data points provided by CGM so as to more precisely titrate insulin infusions. The goal would be better and safer glucose control, with less variability. In the future, it is also possible that highly accurate CGM sensors will be able to communicate directly with insulin infusion pumps, for a truly automated system (or "artificial" or "bionic pancreas").⁹⁸ These so-called closed loop devices are being actively investigated in outpatients with type 1 diabetes. They hold significant potential to radically change current treatment paradigms across the continuum of care in patients requiring insulin therapy for their diabetes.

Considering the Influence of Nutrition on Glycemic Control

In general, energy intake should be adjusted to avoid excessive glucose intake and overfeeding to minimize the emergence of hyperglycemia. Additionally, the hormonal milieu that fuels overexuberant gluconeogenesis can also predispose to protein catabolism. Literature suggests that this catabolic state is not necessarily reversed with full caloric intake. With this in mind, some studies have shown that provision of 50% of energy needs is sufficient to maintain the same nitrogen balance as "full" feeds, and yet able to lower the incidence of overt hyperglycemia. While the optimal caloric intake during critical illness is not known, at least early on during an ICU stay, some degree of temporary underfeeding may be safe and can help control glucose excursions especially in the setting of

a severely insulin-resistant state.^{99,100} On a related note, managing glucose effectively may also ameliorate protein catabolism, as there is preliminary evidence to suggest that moderate glucose control promotes less negative nitrogen balance among medical ICU patients.¹⁰¹

While temporary mild underfeeding might be acceptable, avoidance of overt malnutrition is of obvious importance. At least among critically ill children, a prospective cohort study suggested that both hyper- and hypoglycemia were associated with worsened morbidity and mortality even after adjustment for disease severity in malnourished (but not well-fed) participants.¹⁰² A similar study in adults have not been performed, but it is conceivable that the metabolic impact of hyper- as well as hypoglycemia during critical illness may differ depending on the nutritional backdrop of the patient.

Certainly, provision of nutrition mitigates the risks associated with severe hypoglycemia, and a prolonged fasting state may in fact worsen insulin resistance. In one recent small study, a modest amount of enteral nutrition (e.g., 60% of goal rate) was demonstrated to be more effective at significantly reducing the incidence of hypoglycemic events (defined as BG < 50 mg/dL), compared with dextrose containing intravenous solutions. A relatively large volume (~150 mL/hour of 5% dextrose solution) was required to achieve similar hypoglycemia event rates.¹⁰³

Provision of lower glycemic index carbohydrates, mono-unsaturated fatty acids, and fiber may help improve glycemic control and lower insulin requirements.^{104,105} Although earlier trials suggested that glutamine and antioxidant-enriched nutritional support may improve survival with the added benefit of improved glycemic control,^{106,107} this practice is no longer recommended based on the results from the recent, large multicenter randomized trial in which early glutamine administration was associated with a trend toward worsened mortality (OR: 1.28, 95% CI: 1.00–1.64, $p = 0.05$).¹⁰⁸

Conclusion

Hyperglycemia is commonly encountered in the ICU. We now have a better understanding about critical cellular pathways that can become deranged with prolonged and uncontrolled hyperglycemia, and we are just beginning to appreciate the complex relationship between nutritional status, protein catabolism, and insulin-resistant states. For most patients, moderate glycemic control is appropriate, and new technologies such as continuous glucose sensors may help alleviate the risks associated with excessive glucose variability as well as severe hypoglycemia.

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