

Glucose Measurement: Confounding Issues in Setting Targets for Inpatient Management

KATHLEEN DUNGAN, MD¹
JOHN CHAPMAN, PhD²

SUSAN S. BRAITHWAITE, MD³
JOHN BUSE, MD, PhD³

Van den Berghe et al. (1) reported a significant reduction in mortality with normoglycemia (target value 80–110 mg/dl) in patients whose medical intensive care unit (ICU) stay was >72 h and reduced morbidity in all patients, regardless of the duration of ICU stay. Although severe hypoglycemia did not occur in the Van den Berghe et al. study, 18.7% of patients in the intensive treatment group compared with 3.1% of those who received conventional therapy did experience hypoglycemia (defined as glucose <40 mg/dl), albeit with no adverse consequences reported. However, altered consciousness is common in the ICU, and even severe hypoglycemia may be unrecognized. Other studies (2,3) examining intensive insulin protocols in various inpatient settings have suggested benefits in clinical outcomes associated with improved glycemic control. In a mixed ICU population, Van den Berghe et al. (2) previously demonstrated reduced morbidity and mortality with three- to fourfold less hypoglycemia than the medical ICU population (2). Thus, careful assessment of glucose measurement and how it may impact the targets selected in the hospital are critical safety issues in intensive management of hyperglycemia. As a result of increasing evidence that tight glycemic control is beneficial in the management of inpatients with diabetes, the American Diabetes Association (ADA) currently recommends a glucose target “as close to 110 mg/dl as possible and generally

<180 mg/dl” for critically ill patients (4). The American Association of Clinical Endocrinologists recommends the “upper limits for glycemic targets” of 110 mg/dl in critically ill patients (5).

In practice, it may be difficult to obtain the level of glycemic control (average glucose 111 mg/dl in the intensively managed group) achieved by Van den Berghe et al. Though a wider range of glucose values has been targeted, rarely have mean glucose values between 80 and 110 mg/dl been achieved, particularly in those studies involving patients with diabetes (6). In many hospitals, samples for laboratory glucose determination are obtained from either venous or arterial sites to determine serum or plasma glucose. These laboratory values are generally obtained less frequently than bedside capillary glucose values using point-of-care (POC) systems that report whole-blood glucose or plasma glucose values. In the Van den Berghe et al. study, a HemoCue B glucose analyzer was used to report the values of arterial whole-blood glucose.

Variability is introduced into the reporting of glucose values because of patient variables and also because of differences between assays (Table 1). Patient variables may include issues of physiology and interfering substances. These variables may be of importance when there are unexpected laboratory results. Among institutional variables, there are differences between assay characteristics, performance of commercial products, the

source of the sample, and specimen matrix (i.e., plasma versus whole blood). This study will review assay principles, patient variables, and systematic variables and then encourage clinicians to carefully consider how standard recommendations regarding glycemic targets, particularly in the ICU, should be implemented in their individual health care facilities.

ASSAY PRINCIPLES — In this review, we will signify reference laboratory methods with the term “central laboratory method.” “POC” refers to hand-held devices or portable ward-based analyzers. We recognize that some of these devices are also used in the ambulatory setting. “Plasma correlated” refers to glucose concentrations measured in samples of whole blood but are converted to values that would be expected of plasma measurements.

Table 1—Confounding variables in glucose measurement

Variable	Methodology affected*	
	GO	GD
Whole blood	↓	↓
Arterial	↑	↑
Capillary	↑	↑
Postprandial state	↑	↑
Hematocrit		
Anemia	↑	↑
Polycythemia	↓	↓
Oxygen concentration		
Hypoxia	↑	—
Oxygen therapy	↓	—
pH (6.8–7.55)	—	—
Low pH	−/↓	—
High pH	−/↑	—
Hypothermia	↑	↓/↑
Hypotension	↑	↑/↓
Drugs		
Ascorbic acid	↓	↑/−
Acetaminophen	↓	↑
Dopamine	—	↓
Icodextrin	—	↑
Mannitol	↑	—

*Change relative to venous plasma measured at central laboratory. GO, glucose oxidase.

From the ¹Division of Endocrinology, Ohio State University School of Medicine, Columbus, Ohio; the ²Department of Pathology and Laboratory Medicine, University of North Carolina School of Medicine, Chapel Hill, North Carolina; and the ³Division of Endocrinology, University of North Carolina School of Medicine, Chapel Hill, North Carolina.

Address correspondence and reprint requests to John Buse, MD, PhD, CB# 7110, Old Clinic 5039, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599-7110. E-mail: jrbuse@med.unc.edu.

Received for publication 8 August 2006 and accepted in revised form 2 November 2006.

J.B. has received research support from BD Research Laboratories and Dexcom and has been a paid consultant for Johnson & Johnson.

Abbreviations: ADA, American Diabetes Association; CAP, College of American Pathologists; GD, glucose-1-dehydrogenase; ICU, intensive care unit; POC, point of care.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

DOI: 10.2337/dc06-1679

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Enzymatic reaction

Glucose measurements are based on one of three enzymes: glucose oxidase, glucose-1-dehydrogenase (GD), or hexokinase (7). For POC devices, glucose oxidase is the classic methodology. Glucose oxidase requires oxygen and water and is therefore susceptible to extremes of hydration or oxygenation. Glucose oxidase-catalyzed reactions result in the production of gluconic acid and hydrogen peroxide, the latter of which is detected by various means. GD, like glucose oxidase, is specific for β -D-glucose but may have less interference than glucose oxidase-based techniques. Hexokinase, the basis for many central laboratory methods, phosphorylates D-glucose to form glucose-6-phosphate, which is then oxidized with concurrent reduction of NAD to NADH.

Detection method

The enzymatic reaction is either colorimetrically or amperometrically detected. Colorimetric detection is available for techniques using glucose oxidase, in which H_2O_2 reacts with various hydrogen donors to produce a color change that is proportional to the glucose concentration. Most POC colorimetric reactions are measured using a reflectance photometer that converts the reflected light to an electronic signal for digital display. Amperometric detection is available for either glucose oxidase- or GD-based POC devices, in which the electrical current produced from the reaction is directly measured. In the case of hexokinase, NADH reacts with the dye to produce the color change.

POC techniques

POC devices typically use test strips (biosensors) with a porous layer that separates blood cells from the enzyme-impregnated reagent layer (7). In general, biosensor technology is less precise and less accurate than the wet chemistry methods used in most central laboratory methods. Blood gas analyzers are often used at the bedside and generally use wet chemistry techniques that more closely approximate central laboratory methods (8).

A notable exception to this biosensor technology is the HemoCue B analyzer used in the Van den Berghe et al. studies, a POC method that measures glucose via GD using a disposable microcuvette instead of a traditional biosensor (9). The HemoCue B Glucose Analyzer (HemoCue AB, Angelholm, Sweden) measures glu-

cose via absorbance of reaction products at unique wavelengths. The method allows colorimetric measurement from a whole-blood sample.

Interstitial fluid glucose monitoring

Other investigators have focused on continuous interstitial fluid glucose measurements in order to simplify the need for frequent capillary sampling (10). However, the measurement of glucose in interstitial fluid is complex and affected by tissue perfusion, temperature, and local humoral factors (11). A detailed discussion of this technology is beyond the scope of this review.

PATIENT VARIABLES WITHIN A POPULATION

Patient factors

Hypotension. In the ICU, multiple variables that may affect bedside glucose measurements may be present all at once. In particular, hypotension may result in a reduction of perfusion and an increase in glucose utilization, potentially obscuring the true result for capillary whole-blood samples. A GD-based POC device demonstrated that in 31 hypotensive patients (systolic blood pressure <90 mmHg), capillary whole-blood values differed from the central laboratory venous plasma glucose to a greater extent than those of normal control subjects (-61.7 ± 12.4 vs. -14.1 ± 2.0 mg/dl, $P < 0.001$) (12). Sixty-four percent of values fell outside the acceptable range of 20% compared with 10% of the control group. On the other hand, venous samples measured with the POC meter correlated well with the central laboratory method. A glucose oxidase methodology fared no better in 38 patients with shock (13). Capillary whole-blood glucose was significantly higher than the venous plasma glucose determined by the central laboratory method (mean difference 77 mg/dl, $P = 0.04$), but venous whole-blood glucose on the POC device was no different (13). In addition, 31.6% of the capillary glucose measurements were outside of the allowable 20% variance. Other studies (8,14) that did not show an effect were limited by sample size. More recently, Kulkarni et al. (15) reported that in cases of hypoperfusion, the accuracy of agreement between an arterial blood gas POC method and GD-based POC capillary glucose readings may still result in undetected hypoglycemia when a lower limit of 80 mg/dl is targeted. This occurs despite what would

otherwise be considered low bias (4.0 mg/dl) and imprecision (16.2 mg/dl).

Hematocrit. In general, increases in hematocrit are known to decrease glucose measurements and vice versa. Although manufacturers set acceptable testing limits for hematocrit, POC devices do not exclude samples by hematocrit, and hematocrit is not always known at the time of testing. Proposed mechanisms include mechanical impedance of plasma diffusion into the reagent layer of the strip at higher hematocrit and increased relative plasma volume at higher viscosity, resulting in slower diffusion of glucose (16). The net result would potentially mask hypoglycemia in patients with anemia and underestimate glucose in patients with polycythemia. A POC glucose meter that measures and automatically corrects for hematocrit was recently described and had less error than other devices (17).

An in vitro study examined the effects of hematocrit on six different POC glucose meters (18). At low hematocrit, most POC systems yielded a higher glucose result (5–15%) relative to venous plasma, and the opposite was true at higher hematocrit (–10 to 30%), with the exception of amperometric glucose oxidase methods, which yielded lower values at all three hematocrit levels.

Differences have been observed in clinical studies as well (19). Surgical patients may be most at risk for errors in glucose measurement as a result of fluctuations in hematocrit (20–22).

The HemoCue system, which determines glucose concentration on lysed whole blood instead of measurement based on membrane separation of plasma from red cells, does not show significant hematocrit dependence (23). However, this GD-based POC system has been shown to falsely produce decreased glucose values in patients with methemoglobin values >10% (24).

Oxygenation. High oxygen tension, i.e., $pO_2 > 100$ mmHg, can falsely lower glucose readings on some glucose oxidase-based POC instruments, particularly in patients on oxygen therapy. Oxygen levels as high as 400 mmHg may be seen with surgical patients, particularly those undergoing cardiopulmonary bypass (25). Conversely, higher altitudes overestimate glucose readings by 15% with glucose oxidase methods (26). As might be expected, the effect is largest in arterial blood and smallest in venous blood, but there is little data on the effect of pO_2 on capillary whole blood (27).

Tang et al. (28) evaluated six POC glucose meter systems with respect to effects of oxygenation using venous whole blood and venous plasma. Measurements at $pO_2 > 100$ mmHg were outside of error tolerances (15 mg/dl for glucose < 100 mg/dl or 15% for glucose > 100 mg/dl) 14.3–31.6% of the time. Overall, lower oxygen tension (40 mmHg) had a negligible effect. An older study reported errors at lower pO_2 (29).

Kurahashi et al. (30) found that arterial whole blood from surgical patients using an amperometric glucose oxidase-based POC meter underestimated glucose by 39 mg/dl. Similar results were reported elsewhere with some glucose oxidase—but not GD-based POC devices in mixed hospital patients (19,31).

pH. As with any enzymatic reaction, changes in pH may affect the performance of the POC meter. This has not been shown to be a major source of error at a pH range of 6.97–7.84 (32) or at lower pH (6.8–7.55) (31). However, Kilpatrick et al. (29) found significant deviation in glucose measurement at pH < 6.95 and > 7.85 , with $> 15\%$ from the central laboratory whole-blood method using an older POC method. Nonetheless, this may be cause for concern in cases of severe acidosis (e.g., diabetic ketoacidosis), or where other factors may contribute, leading to clinically significant interpretation errors.

Temperature. Some data suggest that cold temperatures may produce discrepant results (26,33). Active warming may improve measurements; conversely, the effects of fever are unknown.

Interfering substances

The majority of substances that interfere with glucose oxidase-based POC devices do so at the peroxide reduction detection step and not at the level of the enzyme itself (which is very specific for β -D-glucose). Table 1 lists some examples. In the case of the photometric strips, reducing agents such as acetaminophen and ascorbic acid may consume peroxide and diminish its reaction with the dye, thus resulting in lower readings (34). Newer amperometric POC devices have attempted to compensate for this by introducing a third electrode that reduces background current (34). Devices that use GD as the catalyst tend to have less interference but may occasionally falsely increase POC readings through direct oxidation at the electrode (34). Blood gas analyzers may also give more accurate

POC results in patients with possible drug interferences (35).

Drugs. Tang et al. (34) examined the effects of therapeutic and toxic concentrations of 30 different drugs on glucose readings from six different POC glucose meters. In this study, a comparatively low error threshold of ± 6 mg/dl was used. Interferences were found for ascorbic acid, acetaminophen, dopamine, and mannitol. At high doses, ascorbic acid increased GD-based POC readings but decreased those that used glucose oxidase (34). False low glucose readings were reported with other glucose oxidase-based POC devices (36,37) but not with testing based on hexokinase or other GD-based methods (36).

Acetaminophen increased POC glucose readings with GD meters but decreased readings with some, but not all, glucose oxidase-based meters at therapeutic drug levels (34). This may be particularly problematic in overdose patients, in whom hypoglycemia may develop in the presence of hepatic failure. Other reports (36,38) had similar findings, and there may be a reduction in glucose measurements in patients given only 1.5–2 g acetaminophen (39).

Dopamine increased glucose values on GD-based POC systems, primarily at high drug concentrations (34,40). Mannitol increased glucose oxidase-based POC readings, possibly through detection by the analyzer or by a nonspecific osmotic effect (34,35). Finally, interferences with salicylates (36) and nitroprusside (41) have been described in past literature but not more recently (34).

Other substances. Most GD-based POC devices display large overestimations of glucose in patients undergoing peritoneal dialysis using icodextrin as an osmotic agent (42–44). Icodextrin is metabolized to maltose and is indistinguishable from glucose on GD-based POC devices. A similar mechanism of interference prompted U.S. Food and Drug Administration warnings for intravenous immunoglobulin solutions (45). Skin preparations have been reported to interfere (46). Other patient factors, such as bilirubin (9,47), triglycerides (9,47), and paraproteinemias (48–51), may also cause “pseudohypoglycemia.”

SOURCES OF SYSTEMATIC DIFFERENCE BETWEEN INSTITUTIONS

When the method of measurement of circulating glucose differs between institutions, the absolute

values and variability of glucose measurements will systematically differ. These systematic differences have implications for the appropriate glucose targets and algorithms of care developed on the basis of demonstrated risks and benefits of interventions in published studies; appropriate targets in one site with one methodology may not be generalizable.

Standards for comparison

Much of the difficulty with assessing the performance of POC glucose measuring devices lies in the lack of consensus among professional and regulatory groups regarding allowable error (52–55). As a result, published studies are often difficult to directly compare. Of these, the ADA guidelines established in 1996 are the most stringent, calling for total error (bias plus imprecision) of $< 10\%$ for current devices and $< 5\%$ for future devices (55). Error grids have been used in an attempt to predict clinically important errors; however, they are comparatively inaccurate (56).

Standards do not specify differences for POC devices that are intended for hospital use versus those meters intended for home use. Despite a strong correlation between capillary whole-blood glucose and central laboratory methods in an ICU population as a whole, bedside POC devices may be unreliable for use in the individual patient in the ICU (15). A simulation modeling study showed that for glucose meters that achieve both coefficient of variation (CV) and bias ≤ 5 –6% (total $< 14\%$), major errors in insulin dosing are rare, but up to 23% of measurements would result in small errors (57). Therefore, it would seem that the ADA guidelines should serve as the minimum proficiency standard in the hospital.

Performance of POC devices

Over the past decade, POC devices for measuring glucose have become more user friendly, resulting in greater accuracy (58). In hospital patients, recent studies report 91–100% accuracy of various POC devices (30,31). Although the accuracy may have significantly improved in published studies under controlled conditions, this may not be true in the typical clinical setting, particularly among hospitalized patients. The latest College of American Pathologists (CAP) proficiency results demonstrate large CVs for mean glucose values obtained from all POC instruments at all institutions combined (59). At glucose levels of 120–170 mg/dl

(mean 143.8 mg/dl), the overall interlaboratory CV is 15.1%; in the hypoglycemic range, the CV is 31.9% (26.3–66.6 mg/dl, mean 45.7 mg/dl). This variability is at least in part due to differences between instruments because CVs for individual instruments are lower, ranging from 3.9 to 10.9% in the mid-100 range and 6.2 to 13.3% in the hypoglycemic range. Depending on the type of device used, the mean glucose measurement for a particular unknown test sample reported by an institution varies by >30% at glucose levels >150 mg/dl and by 60% in the hypoglycemic range. In comparison, interlaboratory CVs for various central laboratory methods are uniformly <5%. The variability among POC devices may be due to analytical differences in instruments or due to user interfaces that are more susceptible to operator error. For an institution to be considered proficient, results should deviate by no more than 12 mg/dl or 20% from the peer group mean, but this may be inadequate as institutions aim to establish tighter glycemic control using recent standardized guidelines of inpatient management.

Operator error

Unfortunately, operator error is incompletely captured with CAP data, as well as with studies that evaluate POC devices based on aqueous controls, venous samples, or prepared blood samples (60,61). However, the potential for operator error still exists and remains the largest source of error (up to 91–97%) overall (46,62–64). Sources of error such as differences between lots of test strips (up to 14.5 mg/dl) in some (28,65) but not all (19,31) studies may be unrecognized. It is advisable to regularly test split-sample controls referenced to the central laboratory method to detect both performer error and instrument accuracy (62). Quality control may be particularly challenging in ICU and surgical patients (62,63). Programs that use training, quality control procedures combined with national interhospital proficiency surveys, and newer technology have produced significant improvements in precision (62,66,67).

Source of sample

Differences in measurements among blood sources (i.e., arterial, capillary, or venous) may be attributable to variations in glucose extraction by tissues, perfusion, oxygenation, pH, feeding, and temperature (see PATIENT FACTORS above), as well as theoretically neurovascular func-

tion (68). It has been suggested that on average, arterial glucose concentrations at normal pO_2 are 5 mg/dl higher than capillary blood and ~10 mg/dl greater than venous concentrations (69). In recent studies, assessments are limited due to a lack of data comparing all sources of blood, particularly arterial versus venous blood.

Arterial samples compared with capillary samples. Some ICU studies using arterial samples measured with the POC device show acceptable agreement with capillary blood (70,71). A recent abstract found that with newer POC devices in ICU patients, arterial samples had greater accuracy than capillary whole-blood compared with the central whole-blood method (72). However, an older GD-based POC device reported no greater accuracy with arterial whole blood than with capillary whole blood in 50 postcardiothoracic surgery patients, resulting in potential errors of insulin dosing in 31 of 50 patients (20). Using a plasma-correlated glucose oxidase method in 30 critically ill patients, arterial measurements were $8.8 \pm 17.8\%$ higher, and capillary measurements were $3.6 \pm 15\%$ higher on the POC meter than on the arterial plasma central laboratory method (14). On error grid analysis, only 88% of arterial and 73% of capillary readings fell within target range using the POC meter. Arterial blood gas analysis performed better than the POC device (14).

Venous samples compared with capillary samples. A POC GD device in 31 patients with diabetes reported venous whole-blood measurements exceeding capillary whole blood by 9.6% (72). In mixed hospital patients (31) and hypotensive patients (12,13), venous whole blood measured on POC devices was found to be superior to capillary whole blood on the same device, with the exception of one study (73). However, in a recent study (74) using a POC GD-based method, glucose measured from the same site showed better agreement with the central laboratory (POC venous whole blood vs. central laboratory venous plasma, $R^2 = 0.83$) than glucose measured from different sites (POC capillary whole blood vs. central laboratory venous plasma, $R^2 = 0.55$). The authors argue that anatomical site is more important in determining glucose values than specimen matrix.

Postprandial state. Differences between sources of blood may be amplified in the postprandial state (72,75–77). During

periods of fasting, capillary glucose may be only slightly (2–5 mg/dl) higher than venous plasma glucose. After a glucose load, however, capillary glucose values may be 20–25% higher than venous plasma values (75). Conversely, hyperglycemia may be misdiagnosed in blood samples drawn from intravenous lines carrying dextrose.

Differences between plasma and whole blood (specimen matrix)

The difference between plasma and whole blood is the most important variable that clinicians must consider when setting targets for inpatient glucose measurement. These differences are a consequence of variables in specimen matrix, including water content, lipid and protein concentrations, and cellular elements (see PATIENT FACTORS). Although the glucose concentration in the water that makes up plasma is equal to that of erythrocytes, plasma has greater water content than erythrocytes and therefore exhibits higher glucose levels than whole blood (78). The World Health Organization uses a conversion factor of 1.12 that has been mathematically derived assuming a hematocrit of 45% and a red cell-to-plasma water ratio of ~0.80 (79). The conversion factor is less appropriate in patients with severe perturbations in hydration, osmolality, or hemoglobin. In general, manufacturer specifications describe limitations in methodologies under these conditions, but the clinician must be aware that POC devices are not capable of excluding such samples. Furthermore, based on simple regression analyses, the conversion between plasma and whole blood is dependent on the glucose level itself and may vary considerably at extremes of glucose measurement (76,80). Whole blood may be tested with the POC meter but converted to equivalent plasma glucose values obtained from donor blood samples supplemented with glucose; therefore, measurements of plasma samples are inaccurate on such devices (81). On the other hand, meters may attempt to approximate plasma glucose directly via ultrafiltration of erythrocytes from samples with the use of a specialized porous membrane (74). Finally, some POC devices have the capability of reporting values as whole-blood or plasma equivalents, and this is not always specified in studies (82).

Arterial whole blood compared with arterial plasma. Limited data exists for this important comparison. The conversion of arterial whole-blood glucose to

plasma-correlated results may not be valid using POC measurements in cardiothoracic surgery patients (20). A glucose oxidase-based device in 10 ICU patients found only a small difference (0.76 mg/dl) between POC arterial whole-blood values compared with the arterial plasma central laboratory method, but wide CIs negate this finding (14).

Venous whole blood compared with venous plasma. Using four amperometric and two colorimetric glucose oxidase-based devices in 31 patients with diabetes, Kuwa et al. (72) found that venous whole blood measured with the central laboratory method was 11.3% less than venous plasma measured with the central laboratory method. A 13% difference was reported in 126 healthy volunteers (81).

Capillary whole blood compared with venous plasma. In recent studies, variable results from POC devices are in part attributable to manufacturers' efforts to convert results of measurements made on samples of whole blood to plasma-correlated values (72). In the Kuwa et al. (72) study, the mean capillary whole-blood glucose measurements from several POC devices combined was actually 3.2% higher than venous plasma glucose determined by the central laboratory method (contrary to the expected relationship that would be created by the difference in matrix but consistent with the difference that would be created by site of sampling). Other studies using plasma-correlated POC devices in ICU (83) and mixed hospital (80) patients also showed similar results. Therefore, the site of sampling may outweigh the importance of matrix in determining systematic differences. Conversely, the HemoCue B glucose meter (which reports whole-blood glucose) produced results that were contrary to expectation based on site of sampling but were consistent with expectation based on the matrix (77).

Ramifications for the clinician

Unfortunately, studies that directly compare plasma and whole-blood glucose measurements from all sources (arterial, capillary, and venous) are lacking. However, it should be assumed that under physiologic conditions, glucose measurement determined from arterial sites generally exceeds that of capillary sites, which, in turn, is greater than venous sites. Glucose from plasma generally exceeds that of whole blood. In 2001, the International Federation of Clinical Chemistry recommended that glucose

meters be calibrated to plasma glucose, using a constant factor of 1.11 (78). In fact, most, but not all, meters today are calibrated to report plasma glucose values. A notable exception is the HemoCue B glucose analyzer used in the Van den Berghe et al. studies, which reports whole-blood values. Based on CAP data, most hospitals do use plasma-correlated methods. Therefore, it is imperative that hospitals using these devices set targets that reflect plasma glucose rather than whole-blood glucose. Failure to do so may result in more significant hypoglycemia than was reported in the Van den Berghe et al. data.

CONCLUSIONS — Manufacturers have improved the accuracy of glucose measurement with many (84) but not all (85) newer generation devices, mainly through improvements in user interfaces that reduce operator error. However, for individuals in the hospital, variables that are unique to the patient must be considered, particularly in situations where discrepancies arise between the bedside measurement and the clinical scenario. Nowhere else is there greater potential for multiple confounding factors to be present at once than in the hospital setting. Furthermore, the accuracy of POC devices may not be sufficient to achieve tight glycemic control in hospital patients, and studies are not standardized in methods of glucose measurement, despite well-characterized differences in specimen source and matrix. Unfortunately, the unacceptable time delay imposed by central reference laboratory measurements mandates the use of POC in the ICU. Accurate, well-validated blood sensors, particularly those that provide continuous readings, are sorely needed. In the meantime, providers should use caution when selecting patients for monitoring glucose with the use of bedside monitors. If the whole-blood glucose targets of the Van den Berghe et al. study (80–110 mg/dl) are to be applied to venous plasma-correlated values used in many hospitals, a more appropriate target range might be 90–120 mg/dl. Targets should be individualized in each institution and in each setting based on the methodology of glucose testing and the needs of a given patient population to reflect, at a minimum, the 1.11 whole blood-to-plasma glucose conversion factor recommended by the International Federation of Clinical Chemistry.

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