Journal of Diabetes Science and Technology
2018, Vol. 12(6) 1095–1100

DOI: 10.1177/1932296818801607
journals.sagepub.com/home/dst
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A Milestone in Point of Care Capillary Blood Glucose Monitoring of Critically Ill Hospitalized Patients

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Keywords
blood glucose monitoring systems, CMS, critically ill, diabetes, FDA, ICU, point of care

During the 1990s blood glucose monitoring systems (BGMs) that were originally intended for outpatients, became adopted for use with hospital patients. They were modified, compared to outpatient systems, with the addition of quality control management software, user log-ins, docking stations, robust casing for ease of cleaning, and network integration. Point of care (POC) capillary BGM testing is a tool for enabling immediate determination of glucose levels in hospitalized patients and facilitating rapid treatment decisions. POC capillary BGM testing is currently used throughout the hospital system including in critically ill patients in intensive care units (ICUs), operating rooms, postoperative recovery rooms, and emergency department, as well as in general wards.

POC capillary blood glucose monitoring is the most frequently used tool in hospitals to allow immediate and reasonably accurate glucose measurement with a low blood volume, using a safe sampling method without risking the contamination of an intravenous or arterial line. No other method for measuring circulating glucose levels has been developed with all of these features. The alternatives to POC capillary BGM testing are all slower, more complex, require more blood, cost more, and/or are riskier for the patient.

The regulatory clearance in the US of POC BGMs for capillary blood glucose testing for critically ill hospital patients has been a difficult process. For these patients there has not been close alignment between the accuracy levels mandated by standards development organizations and regulatory agencies, the accuracy of available products, evolving standards of care for control of glycemia developed by professional societies, and the clinical practices for managing glycemia at most hospitals. But now there is good news! On July 12, 2018, the U.S. Food and Drug Administration (FDA) cleared the first POC BGM for capillary blood glucose testing in critically ill hospitalized patients. It is the Nova Biomedical StatStrip Glucose Hospital Meter System.[1] This decision is a milestone in the management of critically ill patients. It represents a coming of age of POC capillary BGM testing.

History of POC Capillary BGM in the Hospital

The optimal target for glycemic control in hospitalized critically ill patients has changed over the past two decades. Consensus standards were not established in the 1990s. In the early 2000's, tight control [80-110 mg/dl (4.4-6.1 mmol/L)] became the standard after Van den Berghe et al's important article in 2001.[2] Following a series of studies demonstrating unacceptable hypoglycemia with tight glycemic control,[3] the pendulum swung back toward a higher targeted range. In 2011, The American College of physicians recommended a target range of 140-200 mg/dl (7.8-11.1 mmol/L) in hospitalized patients.[4,5] More recently, the pendulum has swung toward what could be called "moderately tight control." The American Diabetes Association's 2018 Practice Guidelines recommends a target glucose range of 140-180 mg/dL (7.8-10.0 mmol/L) for the majority of critically ill patients and non–critically ill patients.[6] This moderate range for ICU glycemic control walks the line between the Scylla of hypoglycemia and the Charybdis of hyperglycemia.[7] A more stringent goal, such as 110-140 mg/dL (6.1-7.8 mmol/L), may be appropriate for selected patients (eg, cardiac surgery or neurosurgical patients), if this can be achieved without significant hypoglycemia. Achieving any of these target ranges and avoiding hypoglycemia requires frequent monitoring of blood glucose and for many patients, this means hourly or near-hourly blood glucose testing.

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In 2010, the FDA held a public meeting titled "Clinical Accuracy Requirements for Point of Care Blood Glucose Meters." The purpose of the public meeting was to discuss the clinical accuracy requirements of blood glucose meters and other topics related to their use in POC settings.[8] The ideas discussed there became the basis for a 2014 draft guidance on Blood Glucose Monitoring Test Systems for Prescription Point-of-Care Use.

In January 2013, Clinical Laboratory Standards Institute (CLSI) published POCT12-A3—Point-of-Care Blood Glucose Testing in Acute and Chronic Care Facilities; Approved Guideline—Third Edition. This document recommended performance goals for BGM accuracy throughout the hospital setting, including goals for critically ill patients. The recommended acceptance limits were: (1) 95% of the results must have differences from the laboratory analyzer less than 12 mg/dl below 100 mg/dl and less than 12.5% above 100 mg/dl; and (2) the sum of the number of individual results with errors that exceed 15 mg/dl below 75 mg/dl and exceed 20% at glucose concentrations at or above 75 mg/dl should not exceed 2% of all results.[9]

In 2014, an FDA draft document on BGMs for prescription POC use addressed (among other topics) the use of POC glucose meters in critically ill hospitalized patients. It stated, "Critically ill patients should not be tested with a glucose meter because results may be inaccurate. Inaccurate results may occur in severely hypotensive individuals or in dehydrated patients or patients in shock. Inaccurate results may occur for individuals experiencing a hyperglycemic-hyperosmolar state, with or without ketosis."[10] In their updated 2016 guidance, the FDA appeared to consider that some POC BGMs could be used on selected critically ill patients, by promoting the concept that the patient population studied to assess accuracy should reflect the intended use population. FDA included cautionary statements, such as the following: "Inaccurate results may occur in severely hypotensive individuals or in dehydrated patients or patients in shock," and "inaccurate results may occur for individuals experiencing a hyperglycemic hyperosmolar state, with or without ketosis."[11]

CMS Enforced FDA Policies on POC Capillary BGM

The 2014 draft guidance meant that use of POC fingerstick capillary BGMs in critically ill patients would generally be considered off-label use. The Centers for Medicare and Medicaid Services (CMS) noted FDA's position on POC BGM testing in critically ill hospitalized patients. CMS quickly accepted this position in 2014 and announced an intention to cite hospitals performing POC BGM testing in critically ill patients (unless the hospital were to meet difficult high complexity requirements for these products). This policy was decided upon, presumably to protect patients from being monitored by devices that were being used off label.[12] There was a great uproar in the diabetes professional community about the idea that a widely used tool in the treatment of hospitalized patients would be prohibited by CMS, with no viable replacement measurement technology in place.

The CMS resolution stated that a high complexity device required specific personnel and training requirements, such as in some states a mandate to be operated by a technician—not a nurse. Laboratories performing either moderate complexity or high complexity tests must comply with specific rules related to personnel education, proficiency testing, quality assurance, and quality control, with high complexity tests being more strictly regulated than moderately complex tests.

Diabetes Technology Society presented a public meeting in Arlington, Virginia, on May 13, 2014, to bring together the diabetes professional community, the FDA, and the CMS. At this meeting, clinicians called upon CMS to issue a moratorium on enforcement of this policy. The requested moratorium would allow: (1) manufacturers to collect data and specifically apply for clearance in the critically ill population; and (2) FDA to design new policies to facilitate clearance of these products for critically ill hospitalized.[13] The meeting was followed by two consensus articles reiterating the need for a moratorium on citations.[14,15] By the following year, the CMS backed off on their public pronouncements to issue citations for the use of POC capillary BGM in critically ill patients. During the following years, both FDA and industry used the moratorium time wisely and one product was approved for POC BGM in critically ill patients.

On September 23, 2014, FDA cleared the Statstrip (Nova Biomedical, Waltham, MA) for venous whole blood, arterial whole blood, neonatal heel stick, and neonatal arterial whole blood samples throughout all hospital and all professional health care settings.[16] This product was the first cleared POC device for BGM testing and was Clinical Laboratory Improvement Amendments (CLIA) waived, but it was not cleared for capillary blood. Thus, the product required (for non-neonates) blood specimens to be withdrawn from a line, which is labor intensive and risks contamination and line-associated bloodborne infection.

In 2016, FDA published its final guidance for BGM accuracy. The guideline requires that (1) 95% of all values are within $\pm 12\%$ of the comparator method for glucose concentrations > 75 mg/dL, and within ± 12 mg/dL at glucose concentrations < 75 mg/dL; and (2) 98% of values should be within $\pm 15\%$ of the comparator method for glucose concentrations >75 mg/dL, and within ± 15 mg/dL at glucose concentrations < 75 mg/dL.[11]

The 2018 FDA Advisory Panel Meeting

On March 30, 2018 the FDA Clinical Chemistry and Clinical Toxicology Devices Advisory Panel was convened to discuss the use of capillary blood samples with BGMs in patients throughout the hospital. FDA sought the panel's opinion on the benefits and risks of measuring capillary

Table 1. Accuracy for Study 1 (Meter A) for specimens with glucose ⩾75 mg/dL.

Specimen Type	Within ± 5 %	Within ± 10 %	Within ± 12 %	Within ± 15 %	Within ± 20 %	Exceeds ± 20 %
Capillary	277/567 (48.9%)	450/567 (79.4%)	484/567 (85.4%)	516/567 (91.0%)	549/567 (96.8%)	18/567 (3.2%)

Table 2. Accuracy for Study 2 (Meter A) for specimens with glucose <75 mg/dL.

Specimen Type	Within ± 5 mg/dL	Within ± 10 mg/dL	Within ± 12 mg/dL	Within ± 15 mg/dL	Exceeds ± 15 mg/dL
Capillary	907/1894 (47.9%)	1470/1894 (77.6%)	1614/1894 (85.2%)	1737/1894 (91.7%)	157/1894 (8.3%)

Table 3. Accuracy for Study 2 (Meter A) for specimens with glucose ⩾75 mg/dL.

Specimen Type	Within ± 5 %	Within ± 10 %	Within ± 12 %	Within ± 15 %	Within ± 20 %	Exceeds ± 20 %
Capillary	7473/14884 (50.2%)	11087/14884 (74.5%)	12799/14884 (86.0%)	13712/14884 (92.1%)	14350/14884 (96.4%)	534/14884 (3.6%)

blood using BGMs in patients receiving intensive medical intervention/therapy, and the considerations for CLIA waiver for this use.

The panel considered the benefits and risks of using glucose meters intended for measuring glucose in capillary blood in patients receiving intensive medical intervention/therapy. The panel felt that, "The benefits of using glucose meters for measuring blood glucose in capillary blood in patients receiving intensive medical intervention/therapy outweigh the risks."[17] However, the panel also recognized that "There are many clinical conditions (e.g., hypothermia, hypotension, shock, edema, etc) in which capillary blood testing may be problematic. Potential risk mitigation strategies included increased training of medical personnel using point-of-care testing and quality control programs."[17]

FDA typically waives tests that are over the counter (OTC). Tests that are not OTC or automatically waived may become waived if the manufacturer can show that the device is simple and accurate. For accuracy, FDA typically requires that the lower 95% two-sided confidence bound of the percentage of the samples within an appropriate "allowable total error" zone over the entire measuring interval should exceed 92%. This is equivalent to 95% with acceptable total error in a sample size of 360 test results.[17]

At the meeting, FDA presented three datasets for two different BGMS devices (with the manufacturers' permission) in intensive care setting comparing BGMS capillary test results to matched comparator method glucose measurements.

In the first study (Meter A) capillary whole blood fingerstick specimens (n = 567) were obtained within three different critical care units and meter glucose results were prospectively compared to matched (collected at the same time) arterial or venous plasma results obtained on a central laboratory system. In the second study (Meter A), over 14 000 paired critical care capillary whole blood glucose specimens were retrospectively identified in which a CLIA Waived operator used this BGM and compared the result with a plasma glucose test on the same subject. The comparator test was performed on a central laboratory system within 15 minutes. In the third study (Meter B), capillary whole blood specimens (n = 345) from patients in critical care units were tested on the meter. The results were compared with matched arterial or venous plasma results obtained at the same time and tested on a central laboratory system.

All three studies demonstrated similar performance with data points reaching: 1) the FDA 2016 Final Guidance "12 mg / 12%" target for blood glucose <75 mg/dl in 85.2 – 91.7% of datasets (with only two of the three datasets containing glucose levels below 75 mg/dl); and 2) the CLSI target for blood glucose ⩾75 mg/dl in 85.4 – 86.5% of datasets. All three studies indicated performance of Meter A or Meter B below the target of 95% of data pairs being within the acceptable limits of error (see Tables 1-5). Based on these three studies, the FDA concluded "it is probable that the performance observed in these three independent studies is representative of the performance of BGMS in capillary blood specimens in patients receiving intensive medical intervention/therapy." The FDA meeting report went on to point out that these two meters would not meet current guidelines for performance. The report concluded that "the fact that the expert community generated these standards/performance

Table 4. Accuracy for Study 3 (Meter B) for specimens with glucose <75 mg/dL.

Specimen Type	Within ± 5 mg/dL	Within ± 10 mg/dL	Within ± 12 mg/dL	Within ± 15 mg/dL	Exceeds ± 15 mg/dL
Capillary	7/12 (58.3%)	11/12 (91.7%)	11/12 (91.7%)	12/12 (100%)	0/12 (0%)

Table 5. Accuracy for Study 3 (Meter B) for specimens with glucose ⩾75 mg/dL.

Specimen Type	Within ± 5 %	Within ± 10 %	Within ± 12 %	Within ± 15 %	Within ± 20 %	Exceeds ± 20 %
Capillary	169/333 (50.8%)	272/333 (81.7%)	288/333 (86.5%)	308/333 (92.5%)	324/333 (97.3%)	9/333 (2.7%)

goals appears to demonstrate a poor understanding (likely due to the paucity of robust data) in the clinical community of the accuracy and reliability of capillary blood glucose results in certain hospital settings, including in patients receiving intensive medical intervention/therapy."[17]

Regulatory Options

It appears to us that after the meeting, the FDA had three choices for responding to the ongoing demands by clinicians to clear BGMs for capillary blood glucose testing of critically ill hospitalized patients. These were the choices.

1. Refuse to clear any current-generation products for capillary BG testing until they become more accurate in the future to where they meet current FDA guidance levels of accuracy and require clinicians to use alternate methods. Compared to current-generation POC BGMs, the other methods can be: (1) more expensive; (2) more time-consuming; (3) more difficult to manage because of a requirement for scarce technician operators of alternate POC devices in many states; and/or (4) less safe for some patients because drawing blood from a venous line or an arterial line increases the risk of a catheter related bloodstream infection and using larger blood volumes than POC BGMs require contributes to anemia. Furthermore, in some cases alternate methods have also been shown to fail to meet the accuracy levels mandated by the 2016 FDA guidance for POC blood glucose testing.[18,19] This first option would mean hospitals would have to use testing methods that have serious drawbacks.
2. Develop new guidances that are less strict and more consistent with the capabilities of current products. Current generation POC BGMs would then, by definition, be performing at the new required levels of accuracy. This second option would necessitate development of a new guidance for the accuracy of POC capillary BGM monitoring with public input, a process that could take many years.
3. Accept that for current generation products, although they do not meet current guidances, including those of FDA itself, for POC capillary BGM testing the benefits outweigh the risks. This third option would mean that failure to achieve performance specified in the FDA 2016 guidance would not be automatic grounds for FDA to not clear a BGM for critically ill.

Current Status of POC Capillary BGM

On July 12, 2018, FDA cleared the first BGM for POC capillary blood glucose monitoring for all hospital patients, specifically including those receiving intensive medical intervention therapy. It is the Nova Biomedical StatStrip Glucose Hospital Meter System.[20,21] The product was previously cleared for whole blood specimens from venous and arterial sources and heelsticks in neonates.[16] According to the FDA's 510(k) Substantial Equivalence Determination Decision Summary Assay and Instrument Combination Template for this product, two studies were performed. In the first study for BG $<$ 75 mg/dl 1 of 1 specimen (100%) was complaint and for BG $\geqslant$ 75 mg/dl 484/567 (85.4%) specimens were compliant. In the second study for BG $<$ 75 mg/dl 1614/1894 (85.2%) specimens were complaint and for BG $\geqslant$ 75 mg/dl 12799/14884 (86.0%) specimens were compliant.[21]

We commend the FDA for this action as they have chosen to use real world performance of current generation products as the basis of clearance rather than the performance mandated in their own guidance. A standard should be a blend of aspirational level performance coupled with realistically available technology. We also commend FDA for its common sense appraisal of POC capillary BG monitoring accuracy. Within the group of study patients, there was likely a wide diversity of diagnoses. The data analysis would have lost power if each diagnosis within the critically ill construct were to have been reported separately. A global data report does allow for a possibility that within the group of patients

studied there could have been a few diagnoses which comprised most of the inaccurate readings, but at this time we have no way of knowing whether this is the case. Some have argued that patients receiving vasoconstrictors should not be tested for capillary POC BG monitoring because of poor fingertip perfusion. We would like to see data published testing the use of vasopressors as a variable affecting data pair (POC capillary BGM and simultaneous laboratory analyzer venous blood) performance.

Back to the Future

Regulation of the field of POC capillary BG monitoring in critically ill patients has evolved from permitting use of outpatient BGMs in the hospital on all patients in the 1990s, to restricting POC capillary BG monitoring from critically ill patients in the 2000s, to now permitting POC capillary BG monitoring with the first cleared product for this purpose as of 2018. In the near future, we expect to see additional POC BGMs become cleared for this purpose thanks to the FDA's realistic approach to regulatory science.

Abbreviations

BGMs, blood glucose monitoring systems; CLIA, Clinical Laboratory Improvement Amendments; CLSI, Clinical Laboratory Standards Institute; CMS, Centers for Medicare and Medicaid Services; FDA, U.S. Food and Drug Administration; ICU, Intensive Care Unit; OTC, over the counter; POC, point of care.

Acknowledgment

The authors would like to thank Annamarie Sucher for her expert editorial assistance.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: DCK is a consultant for Ascensia, AstraZeneca, EOFlow, Intarcia, Lifecare, Novo, Roche Diagnostics, and Voluntis. GEU is partly supported by research grants Public Health Service Grant UL1 RR025008 from the Clinical and Translational Science Award program and 1P30DK111024-01 from the National Institutes of Health and National Center for Research Resources. GEU has received unrestricted research support for inpatient studies (to Emory University) from Merck, Novo Nordisk, AstraZeneca, Boehringer Ingelheim, and Sanofi. MJR has been a scientific advisory board member for Roche Diabetes Care, Inc and is an employee of Vanderbilt University Medical Center.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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