Devices, decisions: POC glucose in the critically ill

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January 2018—Using point-of-care glucose meters in critically ill patients can feel like tiptoeing through a regulatory minefield. Perhaps your preferred meter hasn't been cleared by the FDA for use in this population. Or maybe you're not sure which assay performance requirements should be regulating the performance of your meters. Or perhaps you're still trying to define "critically ill."

Recently published studies have aimed to clear some of those mines by evaluating the accuracy of glucose meter results in ICU and non-ICU settings and by also assessing meter performance in a clinical context rather than a strictly analytical manner.

Those studies, the four options labs have, and a look at the POC policy in place at Ohio State University Wexner Medical Center were spotlighted at last year's AACC annual meeting in a session, "The Burden of Proof for Point-of-Care Glucose Monitoring in Critically Ill Patients," presented by James H. Nichols, PhD; Alison Woodworth, PhD; and Steven Cotten, PhD.

While nursing tends to think that capillary samples are easier than phlebotomy, Dr. Nichols said, variations in operator technique mean there is ample room for error. And getting an adequate reflection of the patient's physiology isn't a given. What if the patient is cold and the fingertips are blue, is in shock, or has peripheral vascular disease and the fingertip isn't perfused well? "You're not going to get an adequate reflection of what's going on in terms of physiology," Dr. Nichols said. "And this is where the FDA's concern has been for use of glucose meters on these specific types of patients."

Roche's Accu-Chek Inform II is used at Vanderbilt University School of Medicine, where Dr. Nichols is professor of pathology, microbiology, and immunology and medical director of clinical chemistry and point-of-care testing. Among the limitations of the device, Dr. Nichols said: "If peripheral circulation is impaired, collection of capillary blood from approved sample sites is not advised as the results might not be a true reflection of the physiologic blood glucose level that's more central in that patient." That may apply in circumstances of severe dehydration as a result of diabetic ketoacidosis or due to hyperosmolar hyperglycemic non-ketotic syndrome, hypotension, shock, decompensated heart failure, or peripheral arterial occlusive disease.

Another limitation, and this is what "has been forced by the FDA on all glucose meter manufacturers," Dr. Nichols said, is that the performance of the system has not been evaluated in the critically ill. "So what does that exactly mean? Who are the critically ill? Are they just the people in our ICUs or are they elsewhere in our health system?" Each institution must define that term for itself.

When blood glucose monitoring system manufacturer instructions contain such a limitation, the use of that system on critically ill patients is considered off-label. That means, of course, it will automatically default to high complexity under CLIA—"with all the ramifications that has in terms of education of staff who can perform the testing and the documentation, the validation of the method, and the ongoing proficiency and documentation that's required," Dr. Nichols noted.

In response, experts from industry, government, and academia created a white paper, "POCT17: Use of Glucose Meters for Critically Ill Patients," released in 2016 by the Clinical and Laboratory Standards Institute. Dr. Nichols, chairholder, outlined the four options the paper presents for laboratories.

Option one: Follow the manufacturer's instructions, as Dr. Nichols and his team do at Vanderbilt. "We have already taught our staff to not use those meters on patients who have these limitations," he said. "So we're really not changing practice. We simply said: For our institution, we're defining 'critically ill' as any of the limitations in the manufacturer's package insert." This option is least disruptive for the staff, he said, "and it meets the letter of the

regulatory law."

Dr. Nichols

A poll of audience members found that 37 percent of those responding are following manufacturer limitations and, in those cases, using alternative sample types, such as venous and arterial draws instead of capillary. (The second most popular option among the audience, at 18 percent: allowing capillary samples as clinicians deem necessary.)

Option two: Switch to a meter that is cleared for use in critically ill patients. Nova Biomedical's StatStrip has such clearance but only for venous, arterial, and neonatal arterial and heel stick whole blood specimens. About 16 percent of audience members indicated they had chosen this route. "Even for that meter," Dr. Nichols emphasized, "you cannot use capillary samples" for the critically ill.

Option three: Stop using glucose meters in all critically ill patients, and instead use an alternative method such as a blood gas analyzer or send the sample to the laboratory, as about 13 percent of the audience is doing.

Option four: Use the glucose meter off-label, meaning that, as Dr. Nichols said, "you revert to CLIA high complexity, you have to do validation in critically ill patients, and you are also now limited, based on your state and based on CLIA regulations, in who can actually perform testing." About 16 percent of the audience reported using this approach.

Dr. Nichols warns labs about indirect phlebotomy, or line draws. "Many of our critically ill patients are not going to have venous or arterial samples collected individually on them," he said. "They have indwelling lines, and their samples are going to be collected off these indwelling catheters, and that's an issue because of the potential to contaminate the sample with whatever is in that line." Depending on the test, it can dilute or even elevate the results. "If you collect through a heparin lock, think about coagulation testing and use of PT or PT INRs after you have collected through that line—they will be impacted." Use of an IV line is not generally recommended, he noted, "but yet it tends to be universal practice. So be aware of that limitation."

Dr. Woodworth

Dr. Woodworth, director of clinical chemistry and point-of-care testing at the University of Kentucky Medical Center, polled the audience: "What assay performance requirements were used to evaluate your glucose meters?" Seventeen percent said the 2003 ISO 15197 requirements, while 31 percent said the CLSI 2013 point-of-care requirements (12-A3), 29 percent said the 2016 FDA guidance, and 24 percent were not aware of the performance requirements for their meters. Her reaction: "We have a real mix, and I think that's understandable. I am going to show you some data that would suggest that maybe it's not so clear-cut what we use, [and that] having really robust-type analytical requirements may not necessarily equate to clinical outcomes."

The 2003 ISO 15197 guidelines call for 95 percent of all POC glucose results to be within 15 mg/dL of the reference

method when the results are less than 75 mg/dL, or within ±20 percent with higher glucose results, 75 ng/dL or above. “These were updated in 2013 when there was more and more realization of the analytical problems with these devices,” Dr. Woodworth said. ISO 2013 says 95 percent of POC glucose results should be ±15 mg/dL and within 15 percent. “And they’ve changed the glucose concentration cutoff from 75 to 100 mg/dL,” Dr. Woodworth said.

Meanwhile, the 2013 CLSI guidance document for point-of-care testing says that 95 percent of glucose results should be within ±12.5 mg/dL or ±12.5 percent, using the cutoff of 100 mg/dL for the glucose results. More recently, in 2016, the FDA issued two sets of guidelines. One set requires that 95 percent of POC glucose results fall within ±12 mg/dL or 12 percent, using a cutoff for glucose of 75 mg/dL. The other set requires that 98 percent of results fall within 15 mg/dL for lower glucose concentrations less than 75 mg/dL and within 12 percent for glucose concentrations of 75 ng/dL or greater.

“So we have now put in place more robust requirements for the analytical performance of these glucose meters,” Dr. Woodworth said. “What does that mean for glucose testing in the real world? Fortunately, there have been several recent studies that have actually taken a look at that.”

One of those studies examined 1,815 glucose results from adults and pediatric patients with 257 different clinical conditions and complex treatment regimens; nearly 1,700 of the patients were critically ill (DuBois JA, et al. *Crit Care Med.* 2017;45[4]: 567–574).

Dr. Steven Cotten with point-of-care coordinator Sara Enders, MT(ASCP), at Ohio State University Wexner Medical Center. They and others rolled out a program two years ago, called BRAVE, that defines criteria for when a capillary specimen is appropriate. “We consider the criteria clinical decision support related to proper device use,” Dr. Cotten says.

The patients, ages two months to 99 years, were admitted to ICUs at five clinical sites in Belgium, the Netherlands, and the United States. At those sites, institution-specific IV-intensive insulin procedures for maintaining glycemic control were used as the standard of care. The authors say “the study included patients with a significant array of medical conditions with abnormal pathophysiologic factors and a vast range of medications known to interfere with the accuracy of many routinely used glucose meters and other glucose measurement methods.”

Peripheral and central arterial and venous whole blood specimens were collected in lithium heparin blood collection tubes from patients routinely tested for glucose as part of each institution’s glycemic control program. Capillary whole blood specimens were not included. Each whole blood specimen was tested with a Nova StatStrip meter.

Each specimen was then centrifuged, and the plasma was tested via the hospital's central laboratory method within 15 minutes. At four sites, that method was plasma glucose hexokinase performed on Roche's Modular P800 platform. At the remaining site, that method was glucose oxidase on Beckman Coulter's UniCel Synchron DxC.

Clinical accuracy was evaluated using the CLSI's POCT12-A3 guideline. Ninety-five percent of patient samples that were less than 100 mg/dL were within 12.5 mg/dL of the reference. And 96.5 percent of patient samples greater than 100 mg/dL fell within 12.5 percent of the reference. "Which means it passes the analytical performance requirements of the CLSI guidelines," Dr. Woodworth said. Or, as the study's authors put it, the glucose meter is "accurate and reliable for use in critically ill patients."

The authors added a caveat: "It is important to note that the study protocol and data analyses have not been applied to other whole blood, point-of-care devices and glucose methods. . . . Although this study addresses venous and arterial whole blood, an additional study is required using the same clinical accuracy algorithm to determine if capillary whole blood specimens can safely be used in critically ill patient care settings with the study BGMS [blood glucose monitoring system] and other whole blood methods."

What about the 2016 FDA guidelines? Dr. Woodworth pointed to a second study, this one from Ray Zhang, MD, PhD, and colleagues at Washington University School of Medicine, who studied three years of real-world paired meter and central laboratory results in ICU and general hospital inpatients (*Crit Care Med.* 2017;45[9]:1509–1514). This single-site study, which had the aim of examining all glucose meter tests to aid in defining "critically ill" for the purposes of glucose meter testing, came about after three hospitals in the authors' health care system were cited for violating high-complexity meter testing.

A total of 1,171,007 Roche Accu-Chek Inform II point-of-care glucose meter results and 567,687 laboratory glucose results from 14,763 general medicine/surgery inpatients and 20,970 ICU inpatients were examined to identify those with a laboratory test collection time within one hour of the meter collection time. The authors then broke down the results by ICU and non-ICU locations and by 60-, 15-, 10-, five-, and one-minute intervals.

They found that for the sample pairs collected within one minute of each other, 95 percent of ICU and 91 percent of non-ICU meter results passed the FDA 98 percent criterion, while only 89 percent of ICU and 85 percent of non-ICU sample pairs met the FDA 95 percent criterion. "So the glucose meters are not exactly meeting these robust analytical performance criteria in this particular study, but are they meeting the clinical needs of the patients?" Dr. Woodworth said.

In summing up, the authors write, "As time between meter and laboratory collection times increased, the percent of meter results passing the FDA criteria decreased but ICU meter accuracy remained higher than non-ICU throughout the 60-minute interval." They added: "Our results strongly suggest that glucose meters are just as accurate in ICU patients as in the general hospital inpatient population where they are routinely used as 'waived' tests. Here, the performance of glucose meters appeared to be better in our ICU population compared with the non-ICU population. . . . Our findings from this real-world examination in both ICU and non-ICU patient populations give us confidence that modern glucose meters can be safely used in our ICU patients."

Dr. Woodworth noted that authors of a similar 2016 study performed in the Department of Pathology at Beth Israel Deaconess Medical Center and Harvard Medical School agree that "perhaps it's better," she said, "to not look at these strict analytical criteria alone but to also look at how the glucose results might affect outcomes." She then displayed a Parkes consensus error grid that showed 97 percent of the patients in the Washington University study fell within the consensus zone, "meaning there is very little clinical risk for giving an inappropriate insulin dose in 97 percent of our patients." And the meter samples in the Washington University study were a mix of capillary, venous, or arterial/venous-line draws.

The Beth Israel Deaconess/Harvard retrospective study came to similar conclusions, Dr. Woodworth said. In that study, six months of point-of-care glucose results were matched with corresponding laboratory results, with the difference between the collection times restricted to 10 minutes (Schmolze DB, et al. *Point of Care.*

2016;15[4]:137–143). The researchers used the Clarke and Parkes consensus error grids to evaluate the clinical significance of discordances in the results. They also evaluated meter performance in the critically ill.

The point-of-care device used in the study was the Precision Xceed Pro Blood Glucose POC system from Abbott Diabetes Care, and 170,678 records from 14,395 unique patients and 76 unique hospital locations were collected. The final data set consisted of 854 POC/laboratory glucose pairs collected within 10 minutes of each other; the majority of the results were obtained from the ICU (317, 37 percent) and general medicine units (271, 32 percent).

The study found that while "method agreement was far from ideal," 98 percent of the discrepancies were clinically insignificant, and no relationship was found between severity of illness and degree of discrepancy. The authors write, "The overall agreement of POC glucose concentrations to the laboratory result is reasonable, based on the Thiel-Sen robust linear regression," which they say minimizes the effects of outliers.

They acknowledge that allowing 10 minutes to elapse between POC and lab glucose collections may capture more than just the analytical variability of the two methods. But they say it was "felt to represent a reasonable tradeoff" because decreasing the time limit to five minutes, for example, significantly reduces the number of samples to assess for accuracy.

The authors suggest that grids similar to the consensus error grids they used to analyze the data could "provide a more reasonable measure for evaluating performance of glucose meters than a set of rigorous, fixed limits such as those currently proposed by the FDA draft guidance." Such a tool, they say, could be used to evaluate differences in insulin administration outcomes and to assess the clinical suitability of POC glucose meters. At their institution, validation studies showed that 100 percent of samples across various meters and strip lots fell within 12 mg/dL or 12 percent of the laboratory method, where the validation covered glucose concentrations of 28–480 mg/dL. "Whether the meters continue to perform that well after deployment is an entirely different, but critically important, issue," they wrote. "Our data indicate that over this particular six-month period, the performance is reasonably good."
The authors were not suggesting that meters be used in situations where the manufacturer has a disclaimer. "For example," they wrote, "capillary samples should not be performed in patients who are severely dehydrated, hypotensive, or in shock; in other words, with reduced capillary perfusion."

Dr. Woodworth concluded, "So I hope today that I've shown you that glucose meters are a good, rapid assessment of blood glucose concentration, both in home and in the hospital setting, and while they don't necessarily always meet the current robust analytical performance criteria put forth by the FDA, they are meeting the clinical needs of patients."

Dr. Cotten, assistant professor of pathology and director of chemistry, immunology, toxicology, and point of care at Ohio State's Wexner Medical Center, asked the audience: "How has your hospital addressed glucose testing in critically ill patients?"

About 12 percent indicated they had removed glucose meters from their ICUs, while 15 percent had excluded the use of glucose meters based on some sort of diagnosis. Twenty-six percent had developed their own exclusion criteria, 26 percent had an alternative approach, and about 21 percent had done nothing.

So what does OSU Wexner—with its 622 meters, 6,275 users, and 65,989 monthly results—do?

"Our device has been approved for hospital use in all patient populations for venous and arterial, but again, not for capillary," Dr. Cotten said. "So the decision was made not to remove them from specific locations but instead to define criteria for when a capillary specimen is appropriate and when it's not appropriate."

The criteria are not meant to define critically ill, he tells CAP Today, but instead to take the manufacturer's package insert and create an actionable POC policy. "We consider the criteria clinical decision support related to proper device use," he said.

Those criteria had to be easy to remember, require no chart review or physician involvement, address the limitations in the device's package insert, and have no negative medical connotations (more on the latter later). Dr. Cotten and his team came up with the acronym BRAVE for the criteria: B for blood pressure (systolic blood pressure less than 80 mmHg or mean arterial pressure less than 50), R for reduced capillary refill rate (of greater than three seconds), A for acidosis (from diabetic ketoacidosis or hyperosmolar non-ketoacidosis), V for vasopressors (IV only; any dose of norepinephrine, phenylephrine, or vasopressin; epinephrine at a dose ≥0.06 mcg/kg/min; dopamine >5 mcg/kg/min), and E for edema at collection site (pitting edema, blue or purple discoloration).

The BRAVE assessment, which was rolled out in January 2016, required updating the clinical workflow so that the assessment is performed by an RN, who either then performs the glucose test or relays the information about the patient. "If the PCA is the end user, then the PCA needs to ultimately know whether or not the patient meets the criteria, and then whether or not a capillary specimen is acceptable," Dr. Cotten said.

The rollout of BRAVE "did not go very well," at least not at first, he said. Even though it had been fully vetted, the heart hospital responded that patients consistently have blood pressure less than 80— "so we added the mean arterial pressure criterion of less than 50"—and many of the patients are on vasopressors, "so we added the IV only for the vasopressors."

In the neonatal ICU, heel sticks are used exclusively, and infants can consistently have blood pressure less than 80. And in the OR, patients consistently receive vasopressors to counteract anesthesia. "So one of the criteria we added is that this policy does not apply to intraoperative management of patients. And then we also had to deal with some issues with locations that didn't have nurses available."

If the patient does not meet the BRAVE criteria, a capillary specimen should be chosen, and if the patient does meet the criteria, a venous or arterial specimen should be chosen. Early in the rollout of the criteria, however, many incorrect matches were made. "Essentially, they said the patient was critically ill but they went ahead and chose capillary as the specimen type," Dr. Cotten said. The POC manager and coordinators provided intensive education, and those numbers improved gradually.

To spread the word about the BRAVE criteria, they developed communication tools such as stickers for high-traffic areas and on docking stations and badge tags containing the criteria. They used the blank reverse side of order-of-draw cards to explain what the BRAVE letters stand for, that an RN should do the assessment, and other pertinent information. A software interface requires their answering a set of questions before a test is run.

Also important was a visual method of identifying patients in the ICU who met the criteria: small red stickers marked "BRAVE" placed on their doors, so that the PCAs performing the glucose testing are aware of that designation. "And this is where it gets back to the point of no negative medical connotations," he said. "We did not want to label patients in a public space as critically ill, so that's why this acronym works well. It's kind of a neutral word."

Through use of the BRAVE criteria, Dr. Cotten and his team found that most patients meeting the criteria were to be found in the heart hospital, rather than the ICU. "I think that's really important," he said. "If you're considering a location-based exclusion, don't just think about the ICU. You might need to think outside the box."
BRAVE is not the perfect solution, Dr. Cotten said. "When it comes to diabetic ketoacidosis patients, this is particularly challenging, and we have actually created a dilemma for nurses with this policy. They get conflicting messaging from us and from the physicians, and so it really gets back to whether or not you should use a capillary specimen." Their limitation statement says explicitly that a capillary specimen should not be used in a DKA patient due to the possibility of an incorrect result. "So that means they should default to either an arterial or venous specimen or a line or something else."

"And so based on our order sets," he continued, "they're going to get measurements every hour or every two hours," and each time they're drawn, there is a risk of infection. "These patients are notoriously difficult venipunctures. So how are you going to address that?" If a line is put in just to measure glucose, there is a risk of

bleeding and infection. Dr. Cotten's team is developing additional recommendations for DKA patients that address the difficulties related to the device limitations and the frequency of POC glucose measurement in the DKA order set. "So, with our BRAVE policy," he tells CAP TODAY, "these patients come with a unique set of challenges to balance the possibility of incorrect glucose results from a capillary specimen with recommended medical management." □n
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