An uneasy dance with POC glucose in the ICU

Anne Paxton

October 2013—Too much of a good thing can be wonderful," Mae West famously said. And some feel our culture of excess reflects that value. Perhaps as a reaction there has been a surge of interest recently in the embrace of "enough" as a worthwhile goal. But when it comes to precise measurement of glucose values in the intensive care unit, the often-warring needs for speed and accuracy make the issue a critical matter of patient care. For point-of-care glucose testing in the ICU, how much precision is "enough"?

That's the question at the heart of a simmering debate in clinical chemistry. In January, the Clinical and Laboratory Standards Institute released new guidelines for the appropriate uses of POC blood glucose testing in the hospital, including performance standards for the glucose testing devices (Point-of-Care Blood Glucose Testing in Acute and Chronic Care Facilities; Approved Guideline—Third Edition, POCT12-A3). The International Organization for Standardization has also issued new performance standards for home testing.

At the same time, the Food and Drug Administration has expressed reservations about use of the POC devices in treating critical care patients, with new FDA guidelines reportedly in the works. Particularly controversial has been the whole area of point-of-care glucose testing in the ICU because of one of its major uses: tight glycemic control.

"There have been questions about the impact of tight glycemic control on patients probably since the protocol took hold a decade ago," says Timothy R. Hamill, MD, vice chair of the CAP Point-of-Care Testing Committee and director of clinical laboratories at the University of California, San Francisco. "Initially, the idea was that if you keep glucose levels tightly controlled—below 100 mg/dL and even down to the 70s—there will be fewer infections, decreased morbidity, and lower length of stay."
But about five years ago, a growing number of questions were raised about whether the glucose meters were sufficiently accurate to make the protocol work. "Around 72 mg/dL, if you were off by 10 or 20 points, that could be a real problem. Then more recently, some papers have appeared suggesting that really tight glycemic control, less than 100, has been associated with improved outcomes in a lot of patients but a higher incidence of hypoglycemia."

So a rethinking process has been underway, Dr. Hamill says. In June 2012, the American College of Physicians recommended a more modest protocol with glucose kept at 140 to 200 mg/dL. At that level, he points out, there will be less trouble with a result that is off by 10 mg/dL.

But amid that shift in approach, fresh alarm was sparked last year when the FDA told Roche Diagnostics that its new glucose meter had to include a packet insert saying it was not approved for use with critically ill patients. While the FDA backed off after receiving a flood of comments, the agency still requires a notice that the devices have not been evaluated on critically ill patients, and it is reportedly working on tighter guidelines in that regard.

The accuracy of the meters has been improving. The devices are exhibiting less cross-reactivity with other sugars, and less variability of results, and are typically about plus or minus 10 percent, Dr. Hamill notes. But there has been continuing worry about the meters' not being sufficiently accurate for use with critically ill patients. "The FDA and the Centers for Medicare and Medicaid Services said we haven't evaluated these in critically ill populations, and I think they were saying we haven't evaluated these specifically for managing TGC in a critically ill population."

At UCSF, when the meters were brought on board, "we did the validation and compared them to in-lab testing to make sure the accuracy was acceptable. We did not go out and specifically identify a group of critically ill patients to test in parallel and see if the meters showed the same accuracy."

"The main issue is what your definition is of critically ill patients, and why you are using the tests," Dr. Hamill says. "There hasn't been any guidance on that. It's the ICU setting where TGC is really being practiced, but there are

critically ill patients throughout the hospital—in the ER, in the OR, and even out in the acute care ward where a patient might be fine and then become critically ill."

When you talk to people in the OR or ED setting or even on the wards, he adds, "they say 'I'm not using it for TGC. I just want to know if the patient's glucose level is less than 100 mg/dL or greater than 500 mg/dL; I'm not trying to titrate them.' In their minds, the accuracy of the instrument isn't even an issue."

Dr. Hamill believes the FDA's broad statement that the meters should not be used in critically ill patients "really missed the mark." But since the FDA softened its stance about the meters, it's left everything in a gray area, he says. "It hasn't been resolved. It's really been left up to lab directors to determine what they want to do."

In discussions among members of the CAP Point-of-Care Testing Committee, he says, "we've been saying maybe we should try to provide some guidance about how to try to determine the accuracy and precision of your glucose meters in your institution in the population of critically ill patients. But even within the committee we struggled to come up with any kind of guidance," and no guidelines have yet been produced.

At the same time, there has been anything but a reduction in the volume of POC glucose testing. "We're seeing a significant increase at our institution," Dr. Hamill says. "We were doing between 500 and 600 POC glucose tests a day and we're now seeing up to 900 and sometimes over 1,000 a day. So we try to make the ICU doctors aware that the meters are not as robust as what we have in the clinical lab, and let them know that before making significant changes in treatment they should send a sample to us."

Dr. Hamill agrees that the FDA should be concerned. "I fully understand where the FDA is coming from, and there is a need to achieve as accurate a device as we possibly can get, although I think it's going to be a struggle for the vendors to get down to the sub-five percent precision rate."
The bigger issue, he believes, is that clinicians need to understand the limitations of the devices. "What we don't want to do is not use the devices at all. I think that would be a huge step backward for medicine, because they are very valuable in patient care, and in many settings I'm not so worried about the accuracy and even sub-20 percent would be okay."

One of the problems with the POC glucose meters has to do with the specimen of choice: a fingerstick specimen, says Peter Howanitz, MD, vice chair and clinical laboratory director of the Department of Pathology, SUNY Downstate Medical Center. "It's not an ideal specimen. It's easy to get, it's convenient, and it doesn't take much education to teach a person how to obtain one, but biologically there are a lot of other problems. If a patient is hypoglycemic, for example—and that's a good number of the patients who come into the ER—the glucose values can become artifactually low in a variety of tissues." Similarly, glucose values measured with a fingerstick will be markedly elevated if a patient has just eaten.

In the influential van den Berghe study (Intensive insulin therapy in critically ill patients. N Engl J Med. 2001;345:1359–1367), the 2001 Belgian study that was a major impetus to the widespread adoption of TGC protocols, whole blood measurements were made on blood gas analyzers, Dr. Howanitz points out. An advantage of that choice is that potassium and glucose can be measured at the same time. "But one problem we have with whole blood instruments like this is that there's hemolysis, and a small amount of hemolysis can lead to major increases in potassium levels."

When using the glucose meters, on the other hand, clinicians don't fully understand that glucose values are artificially low in patients who are in shock, in Dr. Howanitz's experience. "And that's a very, very important point. Despite our having this in our procedure manual and on exams for individuals in our institution who do glucose testing, it's something that's frequently overlooked."

The development of standards over the years for just how precise glucose should be and how precise these meters are, or should be, has been useful, he says. "But most of them are just based on individuals' judgment. They're highly variable. So the CLSI has recommendations, the FDA has them, the ADA has them, and they're all different."

“My overall take on this is we desperately need more information about where the ‘sweet spot’ is for glucose testing by these meters and where we should use other kinds of testing modalities,” says Dr. Howanitz. “I don’t think we should abandon POC glucose meters, but we do need more information.”

David Sacks, MBChB, chief of the clinical chemistry service and senior investigator at the National Institutes of Health Clinical Center, characterizes the use of glucose meters in the ICU as analogous to off-label uses. “Patients in the ICU are really sick. So it’s not the same as somebody with diabetes who sticks their finger, because the patient has lots of other things going on that affect their peripheral circulation.”

“When you have low blood pressure, hypotensive shock, the first way the body adapts to that is by shutting down peripheral circulation so there is less blood to the extremities. When you do a fingerstick, there is reduced oxygenation of the blood, so it’s not as accurate, period.”

Dr. Sacks, who is lead author of the new CLSI performance standards, believes they haven’t come a moment too soon—but he doesn’t see them as the last word. Until recently, different organizations have thought it made sense that POC glucose meter results were acceptable if they were within 20 percent of the target value 95 percent of the time. “I can’t believe people accepted that,” Dr. Sacks says. The new CLSI target of plus or minus 12.5 percent is better, in his view, though many feel it is still an inadequate standard.

Much of the problem with POC use of glucose meters stems from the burgeoning market for home use meters, he says. “Most of the meters are designed for patients to use to do self-monitoring, and so manufacturers have spent a lot of time and effort trying to make the meters faster, to give results in five seconds instead of one minute as the old meters used to do, to reduce sample volumes, and to make the meters small and portable so patients can carry them around and they can withstand being dropped.” But, he notes, “The technology in this small handheld device is not going to be the same as in a big central laboratory instrument.”

Almost every hospital institution has tight glycemic control protocols in the ICUs, Dr. Sacks notes. “But what was overlooked in evaluating the initial paper [the van den Berghe study]—or perhaps they didn’t look as carefully as they might have in retrospect—is the fact that glucose meters were not used. The sites in the study used arterial blood gas instruments, which is quite different from fingerstick samples measured on a glucose meter in the ICU,” he says.

After the NICE SUGAR study (Intensive versus conventional glucose control in critically ill patients. N Engl J Med. 2009;360:1283–1297) was conducted in Australia, New Zealand, and Canada and produced the finding that TGC protocol patients had increased mortality, clinicians started seeing TGC in a different light. “Everybody took a step back and said, ‘Oops, thank you, we shouldn’t be doing this,’ and they sort of loosened the criteria for TGC. It became more moderate,” Dr. Sacks says. “But one of the big issues there was that glucose was measured in different sites by different methods, unlike the Belgian study where they used the exact same test for everybody.”

More recently, moderate TGC has come under a cloud because other studies have found that it increased mortality in patients without diabetes compared with tight glycemic control. “There are probably more than 500 papers on TGC in ICUs published in 2012. Some say TGC is good, others say it’s not so good, and others say we need to be more cautious. So I think nobody really knows what to do,” Dr. Sacks says. The American Diabetes Association and the American College of Endocrinology, he notes, have called for a less aggressive approach to TGG, at least outside the ICU.

What really stoked the controversy over glucose meters in the ICU was an FDA hearing in 2010, says Frederick Kiechle, MD, PhD, medical director of clinical pathology, Memorial Healthcare System, and a member of Pathology Consultants of South Broward, Hollywood, Fla. “A representative from Belgium said if you were not measuring arterial blood gases using a Radiometer-type device, ‘you were not providing the best care for the patient, and we’d never use a handheld glucose device in Europe.’”

“In America, we’ve said the handheld glucose devices are all basically the same and we believe their accuracy is just fine. But the FDA was asking whether there shouldn’t be two types of meters: one for inpatients with a tighter coefficient of variation and therefore more accuracy and precision, another for use by patients at home. And therein lies the crux of the argument,” says Dr. Kiechle, a member of the CAP Chemistry Resource Committee.

It was something of a coincidence that Roche happened to be the first manufacturer to submit a new device application shortly after that hearing, he notes. “There was a lot of confusion about what they wanted to accomplish in terms of meters, and I think Roche got caught in the middle. I do know the company has the data to support its findings about use of the meters in critically ill patients.”

“It has been a problem from day one what these meters are really intended to do,” says James H. Nichols, PhD, professor of pathology, microbiology, and immunology and medical director, clinical chemistry, Vanderbilt University School of Medicine. While data-management features and storage of QC and patient results, and more recently wireless data transmission, have made the devices more sophisticated, “basically the technology inside the meter hasn’t much changed” since they were approved for home use, he says.

Dr. Nichols, who was consensus committee vice chairholder for the CLSI POCT12 guideline, points out that physicians have seen glucose meters as an easy way to get a quick result but didn’t realize all the challenges. What has brought the issue to the fore? “I think it’s because we’ve had a lot of bad outcomes in patients, and they’ve become public. If you look at the historical complaints the FDA has received from people who have been mistreated based on a glucose value, and even deaths because they got a wrong glucose at home, it’s reached a head with the FDA.”

But he doesn’t agree with the FDA’s reaction targeting Roche’s new device. “Clearly the Roche meter was validated on an inpatient population in multiple areas of the hospital. That was part of the data that was submitted. So why did the FDA choose to kind of ignore that? I have to raise my hands and say I don’t know.”
The new CLSI standard for precision is a little tighter than the accepted ISO standard of 15 percent. But the CLSI document was held up for a number of months by debate among committee members over the standard and getting everyone in the industry to strive toward the new goal, Dr. Nichols says.

“Everybody should be developing a technology that gives better performance or tighter agreement, and that is in fact what is happening. But out in the field, people are still using the old meters. You’re not going to see changes to the standard until you see the next generation of devices. So I think it’s just a question that consumers need to be asking manufacturers: What is your performance and how does it compare to the old standard?”

With use of the meters for tight glycemic control, the argument may be made that if users of the meters get a 150 one time and 190 the next, “it’s just the noise of the meter. I may be dosing with insulin a little too much on one measurement and too little on the next, but it will all average itself out. But does it lead to the same outcomes? That’s where the jury is still out.”

Nevertheless, Dr. Nichols notes, hospitals are still doing more and more TGC on patients in the belief that it is going to lead to improved outcomes. “There’s been kind of a ‘creep’ of this protocol from cardiac patients to all critical care patients, and as you start to expand you get all different types of complexities, because critical care patients don’t have just one thing wrong; they have multiple organ problems.”

Even though hospitals don’t have strong statistics to support the practice of TGC, he says, “Since everyone is doing it you would be odd man out and at risk if you didn’t offer it.” But this creates a special responsibility for laboratorians: “We just have to be aware of the conditions when instruments might fail and make sure physicians understand those, and we have to prevent use of devices under conditions we know will get poor results.”

Despite the fact that many standard-setting issues remain unresolved, tight glycemic control protocols are not going away anytime soon, Dr. Sacks says. “But they should be adopted with considerable caution,” he adds, and those who make the decisions should be aware of the limitations of POC glucose meters and the potential pitfalls of their use.

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