Continuous Glucose Monitoring Devices for Use in the ICU

R. T. M. van Hooijdonk, J. H. Leopold, and M. J. Schultz

Introduction

Many critically ill patients are treated with insulin for shorter or longer periods during their stay in the intensive care unit (ICU) [1]. Intensive monitoring of the blood glucose level is a prerequisite for efficient and safe insulin titration in these patients [2]. Glucose levels are currently monitored manually in the ICU by intermittent measurements of the blood glucose level in central laboratories or using laboratory-based blood gas analyzers and/or glucose strips at the bedside [3]. Intermittent manual glucose monitoring, however, is impractical and expensive, time and blood consuming [4], and could even cause dangerous insulin titration errors in critically ill patients [5].

Glucose monitoring through so-called continuous glucose monitoring (CGM) could overcome some of the shortcomings and drawbacks of intermittent manual glucose monitoring. Specifically, CGM could allow for smoother insulin adjustments based on trends of the glucose level visualized on a monitor [3]. Several CGM devices for use in the ICU are being developed. These all require thorough accuracy testing in diverse cohorts of critically ill patient before they can be implemented in daily ICU practice.

This chapter provides an overview of the diverse CGM techniques and CGM devices intended for use in the ICU. This chapter also deals with how point and trend accuracy of CGM systems could be studied in critically ill patients and how accuracy results could be reported.

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Search Strategy

We searched MEDLINE (1966–2013) using the following search terms: ('intensive care'[MeSH Terms] OR 'intensive care'[tiab]) OR 'critical care'[MeSH Terms] OR 'critical care'[tiab] OR ('critical illness'[MeSH Terms] OR 'critical illness'[tiab]) AND 'glucose'[tiab] AND ('continuous glucose monitoring'[tiab] OR 'continuous glucose measurement'[tiab] OR 'CGM'[tiab]). Retrieved articles, and cross-referenced studies from those articles, were screened for pertinent information. Articles were selected if they evaluated a CGM device intended for use in ICU patients. Articles reporting on studies in animals were excluded, as were articles reporting on studies of CGM in populations other than ICU patients. Revisions and articles that did not report outcomes of interest were also excluded, and if duplicate articles of the same study were found in abstract form or other articles, we considered the most complete data set.

We then performed an internet search, using similar search terms in Google™. We visited commercial websites identified by this search and looked for pertinent information. We also visited websites of medical congresses for information and abstracts of studies that had not yet been published.

In August 2013, the two searches identified several CGM devices that were already available for use, as well as devices that were in a developmental phase (Table 1). Studies concerning CGM accuracy in critically ill patients were very limited, and the results of most studies were only available on commercial websites or in abstracts presented at medical congresses.

CGM Devices

Common to all CGM devices is that they measure glucose levels continuously, or intermittently but frequently, but in different body fluids (i. e., whole blood, plasma, dialysate, or interstitial fluid) using dissimilar procedures (e. g., automated blood draws, or no blood draws at all) and distinctive measurement techniques (i. e., based on a chemical reaction, or using fluorescence or spectroscopy) (Table 1).

Measurement in plasma is considered the 'gold standard' for intermittent glucose measurements in the ICU setting, but of all the CGM devices only one device is reported to measure glucose levels in automated bedside-prepared plasma (OptiScanner). Other devices measure glucose levels in whole blood (GlySure, GluCath, and GlucoClear), dialysate from blood (Eirus and Diramo) or interstitial body fluids (Sentrino, Symphony, and GlucoDay).

CGM devices are reported to measure the glucose level in venous blood via a sensor inserted through a peripheral venous catheter (GluCath) or a central venous catheter (GlySure). Other CGM devices automatically draw venous blood via a central venous catheter (OptiScanner) or via a peripheral venous catheter (GlucoClear). For measurements of the glucose level in subcutaneous tissue, one single sensor or a set of sensors is used (Symphony, Sentrino). Systems that measure glucose levels in dialysate, prepare dialysate in a catheter designed for this pur-

Table 1 Overview of continuous glucose monitoring (CGM) devices intended for use in intensive care unit (ICU) patients

Device Name	Manufacturer	Glucose is measured in:	Sampling technique	Measurement technique	Frequency of measurements
OptiScanner	OptiScan Biomedical Corporation	plasma created from central venous whole blood	blood drawn via a central venous catheter	mid-infrared	15 minutes
GlySure	GlySure Limited	central venous whole blood	blood sensor-based	fluorescence	not reported
Eirus	Maquet	central venous whole blood	dialysate	glucose oxidase	1 minute
Diramo	Flowsion AS	central venous or peripheral arterial whole blood	dialysate	glucose oxidase	1 second
GluCath	GluMetrics Incorporated	peripheral venous or arterial whole blood	blood sensor-based	fluorescence	10 seconds
GlucoClear	Edwards Lifesciences	peripheral venous whole blood	blood sensor-based	glucose oxidase	5 minutes
Symphony	Echo Therapeutics	interstitial fluid	transdermal biosensor	glucose oxidase through hydrogel	1 minute
Sentrino	Medtronic Incorporated	interstitial fluid	fluid sensor-based	glucose oxidase	not reported
GlucoDay	A. Menarini Diagnostics	interstitial fluid	dialysate	glucose oxidase	3 minutes

pose and inserted into a central vein (Eirus, Diramo) or into the subcutis (GlucoDay).

CGM devices measure glucose levels by using the glucose oxidase test (Eirus, Diramo, GlucoClear, Symphony, Sentrino and GlucoDay), fluorescence (GlySure and GluCath) or spectroscopy (OptiScanner). The glucose oxidase test is based on an enzymatic reaction, which uses glucose oxidase as a catalyst to bind glucose to water and oxygen to form gluconic acid and hydrogen peroxide. When there is more glucose, more hydrogen peroxide will be released, which can subsequently be measured [6]. The fluorescence technique is based on emission of light by a substance after absorbing light. Fluorescent chemistry is sensitive to glucose. When the glucose level increases, the fluorescent signal increases, which is detected with an optical fiber [7]. The spectroscopy technique is based on the characteristic absorption of vibrational nodes of different molecules, including glucose. Mid-infrared spectroscopy can be used because the glucose spectral peaks are in the mid-infrared region [8].

Potential Drawbacks

Glucose levels in plasma are higher than in whole blood, demanding a conversion factor that depends on the hematocrit level [9]. Furthermore, arterial blood glucose levels are higher compared to peripheral venous glucose levels (difference of ~0.2 mmol/l) and central venous glucose levels (difference of ~0.3 to 0.4 mmol/l) [10]. Glucose levels in dialysate tend to be slightly lower compared to glucose levels in surrounding fluids from which the dialysate is created [11]. Glucose levels in subcutaneous tissues are dependent on the speed by which glucose diffuses from the blood compartment to the interstitial spaces, as well as the rate at which glucose is taken up by cells in the subcutaneous compartment [12]. Users may take these drawbacks into account when using GCM devices in daily practice, but researchers certainly will need to correct for this when determining GCM accuracy.

A potential disadvantage of any biosensor is the buildup of body fluid deposits on sensor surfaces, for which repeated calibrations and eventually sensor replacements are needed [13]. Need for repeated replacements of (parts of the) system is not limited to sensor-based devices, though, because all CGM devices need replacement of other parts of the system, such as cartridges, and/or dialysate-membranes. Furthermore, with the exception of CGM using a transdermal sensor (Symphony), all CGM devices must be considered ‘invasive’, and as such could cause infections and/or bleeding. Additionally, all CGM devices that measure the blood glucose level in a vein are at risk of presenting erroneous glucose levels when glucose, or other substances that interfere with the measuring technique, are infused through the same catheter or close to that catheter.

Finally, the oxygen level and the pH could affect measurements by both the glucose oxidase test and the fluorescence technique [6, 7]. Drugs can interfere with the glucose oxidation reaction through molecules oxidizing with hydrogen perox-

ide [6] and mid-infrared spectroscopy by producing spectrums of molecules other than glucose [8]. Users need to be aware of these drawbacks when using GCM devices in their practice.

Point and/or Trend Accuracy

All CGM devices need accuracy testing in cohorts of patients in which they will be used. Two different types of accuracy can be tested: 'point accuracy' and 'trend accuracy'. Point accuracy is the accuracy of intermittent measurements at a static point. Trend accuracy is the accuracy to detect changes in glucose levels.

Several point accuracy metrics have been used to report accuracy, including correlation coefficients, mean absolute difference (MAD) or mean absolute relative difference (MARD), and Bland-Altman plots [14, 15]. A high correlation coefficient (close to 1 or −1) means that paired glucose measurements (measurement by the device versus measurement by a reference test) lie along any straight line – but this line may not lie along the line of equality where differences between paired measurements are zero. Both MAD and MARD summarize all paired glucose measurements in a single number, but unfortunately this process causes loss of important information. Another frequently used metric to demonstrate point accuracy is presenting all collected paired glucose measurements, with bias (the mean overall difference between the paired measurements) and limits of agreement (mean difference ± 1.96 * standard deviation) in Bland-Altman plots [16].

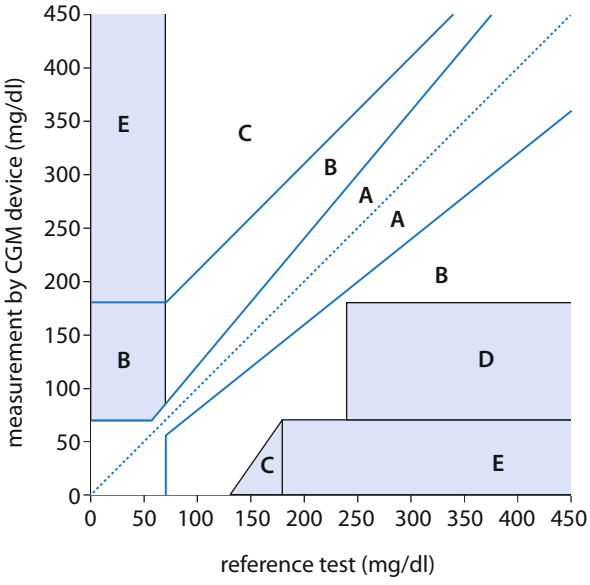


Fig. 1 The Clarke error grid. Paired measurements are plotted; measurements are most accurate in zones A and least accurate in zone E, where measurements are erroneous. See text for more details

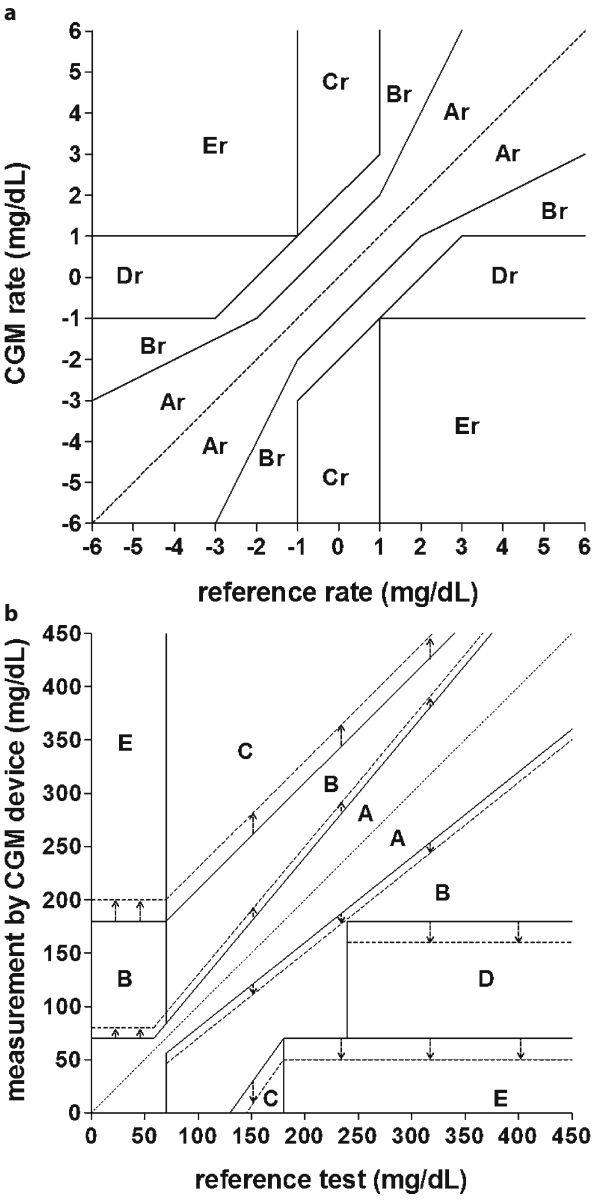
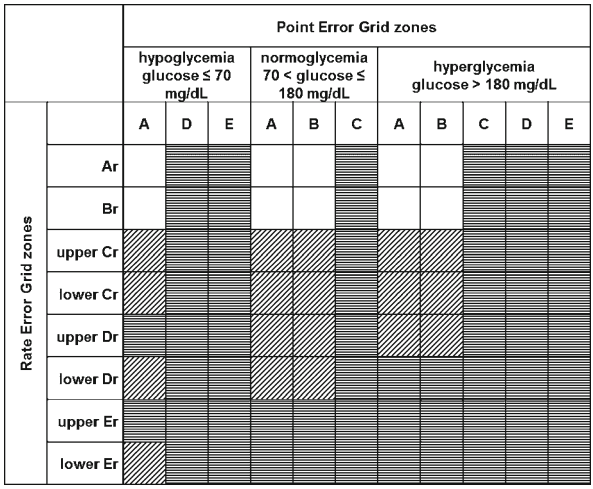


Fig. 2 The continuous glucose error grid with the 'rate error grid' (panel **a**), the 'point error grid' (panel **b**) and the 'error matrix' (panel **c**). The rate error grid is divided into zone Ar-Er, with Ar being the most accurate zone and Er being the least accurate (erroneous) zone; the point error grid has similar zones to the Clark error gird (CEG, Fig. 1), but the limits are dependent on rates of change: When there is no significant glucose change, zones are similar to the original CEG; with declining reference glucose levels upper limits change; with increasing reference glucose levels the lower limits change (see *arrows* in panel **b**); the results of the point error grid and rate error grid are put into an error matrix (panel **c**) with 3 zones; accurate readings (☐), benign errors (///) and erroneous readings (=). See text for details

Fig. 2 *Continued*

c



Reports on studies testing the accuracy of home glucose meter commonly use so-called Clark error grids (CEG) (Fig. 1). A CEG visualizes information by presenting all collected paired glucose measurements and 'scoring' clinical accuracy [17]. For this, a CEG is divided into five paired 'zones': Zones A (measurement within 20 % of the reference or glucose levels < 70 mg/dl); zones B (measurement more than 20 % different from the reference but still clinically acceptable as it would not cause change in the rate of insulin infusion); zones C (measurement that would lead to unnecessary changes in insulin infusion, i. e., overcorrecting acceptable glucose levels); zones D (potentially dangerous hypo- or hyperglycemic events are missed); and zones E (levels that would lead to a decision opposite to that required, i. e., treatment for hypoglycemia instead of hyperglycemia). General consensus is that 95 % of the values should be in zones A and 5 % in zones B [14].

It must be noted that the CEG was originally designed for testing accuracy of home glucose meters, not ICU meters. At the moment, it is uncertain whether the CEG zones are useful in the ICU setting. As an alternative to the CEG, an insulin titration-error grid has been proposed [18]. In this grid, very much like the original CEG, accuracy zones are based on a specific guideline for insulin titration. As guidelines for insulin titration differ (extensively) between ICUs worldwide, it could be difficult to compare results of accuracy testing of CGM devices using these grids.

R-deviation (RD) and absolute R deviation (ARD) have been proposed as rate accuracy metrics [15]. RD is defined as the difference between rates of change of measurements by the device and the reference test, divided by the time interval [15]. The ARD is the absolute value of RD [15]. Unfortunately, as for MAD and MARD, reporting only RD or ARD causes loss of important information.

More recently, the 'continuous glucose-error grid analysis' (CG-EGA) has been proposed for testing rate accuracy of CGM devices (Fig. 2) [19]. The CG-EGA

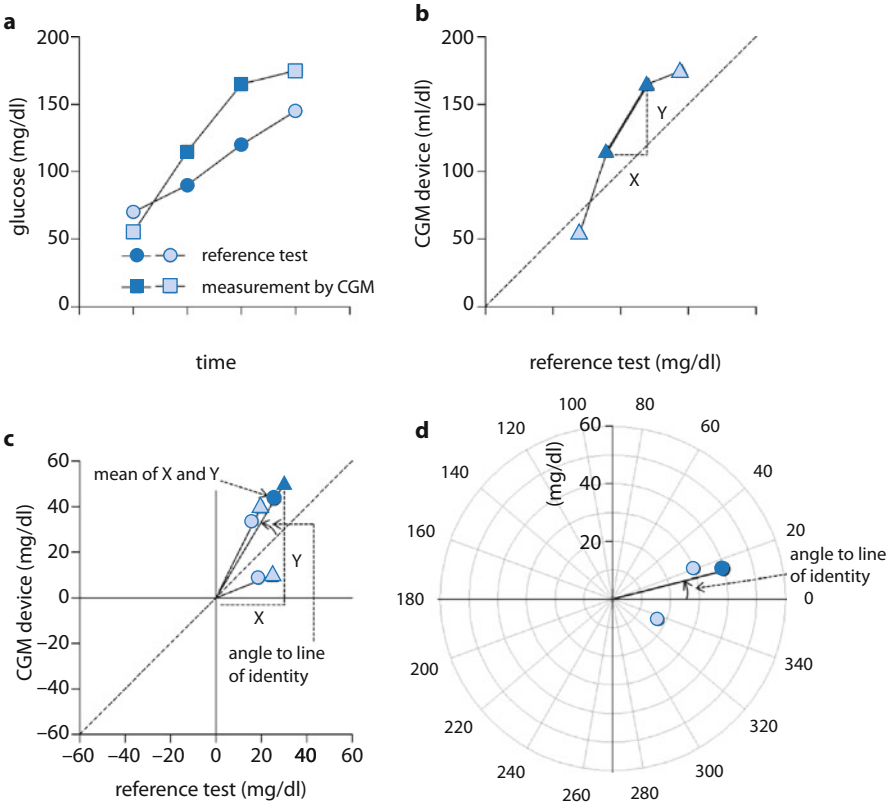


Fig. 3 A polar plot. The 4 panels indicate how a polar plot is constructed. Panel **a** shows four paired glucose measurements. Panel **b** visualizes the same measurements with continuous glucose monitoring (CGM) measurements on the *Y*-axis and reference test measurements on the *X*-axis (note that the solid dots and squares in panel **a** represent the same measurements as solid triangles in panel **b**); a line is drawn between the consecutive measurements. In panel **c**, the difference between two consecutive readings (or the rate of change) by the CGM device is plotted on the Y-axis against the difference (or the rate of change) between two readings by the reference test on the *x*-axis (note how the rates of change make a particular angle with the line of identity, which is the line where the rate of change detected by the CGM device and by the reference test is the same). The radius is calculated as the mean of the rates measured by the CGM device and the reference test (dots in panel **c**). The angle with the line of identity is one coordinate in the polar plot with the radius being the other coordinate. The transformation to the polar plot is made in panel **d**, with the dark blue dot representing the same dark blue dot in panel **c**. Measurements with a large angle, i. e., a large difference between the rate of change measured with CGM and the reference test, are less accurate. Criteria for defining good and poor trend accuracy for the polar plot are uncertain

combines point accuracy with rate accuracy though a rate error grid, a point error grid, and an error matrix. The rate error grid plots the rate of change of the glucose level measured by the CGM device and the reference test. A bit similar to the original CEG, the rate error grid is divided into 5 paired 'zones': Zones

Ar (rate, the accurate zone) and Br (the benign error zone) – in these zones errors do not cause inaccurate adjustments; zones Cr (over- or underestimation of the rate of change); zones Dr (reference test detects a change, which is undetected by the CGM device); and zones Er (reference test detects a change, but an opposite change is detected by the CGM device). The point error grid looks like the original CEG, but also takes glucose changes into account. Indeed, in this adjusted grid, zones are defined depending on the speed of change of glucose levels. When there is no significant glucose change, zones are similar to the original CEG, but when reference glucose levels are decreasing, the upper limits change, and when reference glucose levels are increasing, the lower limits change. Finally, results from the point and error grids are put into an error matrix with three regions, one for hypoglycemic range, one for normoglycemic range and one for hyperglycemic range. The CG-EGA is a complex tool and creation of a CG-EGA requires (very) frequent sampling to come to meaningful conclusions. However, one should keep in mind that the rate of sampling has an important effect on the results [20].

An alternative for the CG-EGA could be the polar plot, originally developed for testing trend accuracy of cardiac output monitors (Fig. 3) [21]. A polar plot shows the agreement between measurements by a device and measurements by a reference test as the angle made with the line of identity (where the difference between the measurements is zero) and the magnitude of change as the radian [21]. This method of accuracy testing has, however, not yet been used for testing accuracy of CGM devices.

Reported Accuracies of CGM Devices

Studies on point accuracy of CGM devices for use in the ICU are very scarce (Table 2). The search in Medline identified only two point accuracy studies in ICU patients (Eirus [11] and GlucoDay [22]). The internet search identified several point accuracy studies presented as abstracts (Glysure [23], GluCath [24], Symphony [25] and Sentrino [26]) or on commercial websites (OptiScanner [27], Diramo [28] and GlucoClear [29]). Most studies were rather small in terms of the number of patients as well as the number of paired measurements. Notably, accuracy was sometimes only tested in 'less severely ill' patient populations, e. g., patients in the ICU after (cardiac) surgery [11, 25, 26, 28, 29].

Two studies tested trend accuracy (GlucoDay [22], Symphony [25]). In the study on GlucoDay, a paired sample was obtained in five medical ICU patients every 15 minutes. The error matrix of the CG-EGA showed that all samples in the hypoglycemic range were in zone A, in the hyperglycemic range 88 % were in zone A and B and in the normoglycemic range 94 % were in zone A and B [22]. In the study of Symphony in post-cardiac surgery patients, paired samples were obtained only every 30–60 minutes. Although not specified for the range of glucose levels, 100 % of the samples were in the A and B zones [25].

Table 2 Overview of studies of continuous glucose monitoring (CGM) devices in intensive care unit (ICU) patients

Device	Patients studied	Number of paired samples	Point accuracy	Trend accuracy
OptiScanner [27]	63 medical or surgical ICU patients	Not reported	CEG analysis: 100 % in zones A+B	–
GlySure [23]	16 medical or surgical ICU patients	296	CEG analysis: 99.6 % in zones A+B	–
Eirus [11]	30 perioperative cardiac surgery patients	607	CEG analysis: 100 % in zones A+B; MARD 5.6 %	–
Diramo [28]	10 postoperative cardiac surgery patients	359	CEG analysis: 100 % in zones A+B; MARD 4.1 %	–
GluCath [24]	5 postoperative cardiac surgery	202	MARD 5.5 %	–
GlucoClear [29]	10 postoperative surgical ICU patients	1393	CEG analysis: 100 % in zones A+B; MARD 5.0 %	–
Symphony [25]	15 perioperative cardiac surgery	> 600	MARD 12.3 %	CG-EGA: 99.6 % in zones A+B of the error matrix (not specified for which range)
Sentrino [26]	21 postoperative cardiac surgery patients	864	MARD 12.2	–
GlucoDay [22]	50 medical ICU patients (5 patients were included for trend accuracy)	N = 820 (for 2-point calibration) N = 555 (for 6-point calibration)	CEG analysis: 95 % in zones A+B for 2 point calibration; 97 % in zones A+B for 6 point calibration	CG-EGA: 100 % in zones A of hypoglycemic range, 88.1 % in zones A+B of hyperglycemic range, 93.8 % in zones A+B of normoglycemic range

CEG: Clark error grid; MARD: mean absolute relative difference; CG-EGA: continuous glucose error grid analysis; –: no data

Discussion

The most frequently suggested potential benefit of CGM in ICU patients is a reduction in time spent by nurses measuring glucose levels [30]. Whether CGM truly reduces time spent on glucose monitoring has, however, not yet been demonstrated. CGM devices could indeed reduce the number of manual measurements. However, initiation, repeated manual calibrations and replacement of (parts of) the system could also use up nursing time. Whether time spent with using CGM weighs against the burden of intermittent manual measurement in central laboratories or using laboratory-based blood gas analyzers and/or strips at the bedside could be the subject of future studies.

Intermittent manual glucose monitoring is usually seen as expensive [4]. It is questionable, however, whether use of CGM will reduce costs associated with glucose monitoring. Indeed, CGM devices will come at a price, as do the disposables used with these devices. Costs for glucose monitoring should never be considered in isolation, but together with potential financial benefits and other healthcare costs (e. g., cost prevented by reducing the incidence of dysglycemia). Therefore, health-economy analyses could accompany future studies of CGM in critically ill patients.

It has been suggested that CGM could prevent dangerous insulin titration errors in critically ill patients [5]. One trial of glucose control confirmed that CGM prevented hypoglycemia, but overall glucose control did not improve [31]. One trial of closed-loop CGM-insulin titration did show improved glucose control [32]. Of note, these two trials used a home CGM device and frequent intermittent manual glucose measurements were still necessary.

The number of studies assessing the accuracy of CGM devices is surprisingly small. In addition, the numbers of patients studied in each investigation are low and most studies have been performed only in a highly selected ICU population (e. g., patients after cardiac surgery). It could be questioned whether accuracy is also good in 'more severely ill' patients, such as patients with severe sepsis or septic shock.

Point accuracy of some CGM devices is low. The question is whether such CGM devices are useless in the ICU setting. One advantage of CGM is that there will be many more glucose readings than with manual intermittent glucose monitoring. Thus, the user could detect trends, and trend accuracy may be more important than point accuracy. An analogy that supports use of CGM devices with poor point accuracy is the comparison between camcorders versus still cameras, as previously pointed out by Kovatchev et al. [19], "Still cameras produce highly accurate snapshots at random sparse points in time, and camcorders generally offer lower resolution of each separate image but capture the dynamics of the action. Thus, it would be inappropriate to gauge the accuracy of still cameras and camcorders using the same static measure of the number of pixels in a single image. Similarly, it is inappropriate to gauge the precision of [. . .] devices using the same measures and to ignore the temporal characteristics of the observed process."

Conclusions

Implementation of CGM devices in daily ICU practice is at hand. Several CGM devices, using different body fluids and diverse sample and measuring techniques, have been or are being developed. These devices all need accuracy testing. The number of studies assessing the accuracy of CGM devices is still limited, and most studies have included only low numbers of highly selected ICU patients.

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