Continuous glucose control in the ICU: Report of a 2013 Round Table meeting

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Abstract

Achieving adequate glucose control in critically ill patients is complex but an important part of optimal patient management. Until relatively recently, intermittent measurements of blood glucose have been the only means of monitoring blood glucose levels. With growing interest in the possible beneficial effects of continuous over intermittent monitoring and the development of several continuous glucose monitoring (CGM) systems, a Round Table conference was convened to discuss and where possible reach consensus on the various aspects related to glucose monitoring and management using these systems. In this report, we discuss the advantages and limitations of the different types of devices available, the potential advantages of continuous over intermittent testing, the relative importance of trend and point accuracy, the standards necessary for reporting results in clinical trials and for recognition by official bodies, and the changes that may be needed in current glucose management protocols as a result of a move towards increased use of CGM. We close with a list of the research priorities in this field, which will be necessary if CGM is to become a routine part of daily practice in the management of critically ill patients.

Introduction

Achieving adequate glucose control in intensive care unit (ICU) patients is complex and difficult to perform optimally. Until relatively recently, intermittent blood-gas analyzer and central laboratory measurements of blood glucose from arterial blood samples have been the only means of monitoring blood glucose levels [1]. However, intermittent measurements are limited by the workload associated with the sampling process and the potential that between-measurement events may be missed. With growing interest in the possible beneficial effects of continuous over intermittent monitoring and the development of several continuous glucose monitoring (CGM) systems, a Round Table conference was convened in March 2013 to further discuss and where possible reach consensus on various aspects related to glucose monitoring and management. A board of leading experts in the field of glucose control in ICU patients and invited members of interested industry companies joined for presentation and discussion. After the meeting, a draft report was circulated to all participants by email for critical review. Representatives of the invited Industry companies were asked to include a brief summary of their devices in the appendix of this report, but other than participation in the open discussion periods of the meeting, had no influence on content.

Continuous glucose monitoring

Definitions

Continuous glucose monitoring has been proposed as a means to improve management of dysglycemia. Although termed "continuous", current systems still sample intermittently, with a measurement interval of a few milliseconds up to 15 minutes. Some systems average the frequent intermittent measurements and display them as a single reading, possibly as a moving average, updated regularly. Nevertheless, such measurements can be considered as having "real-time" value especially when compared to their intermittent counterparts, although physiological or data processing lag time may be present depending on the sampled body fluid. Two factors can be considered when defining "continuous": the frequency of actual glucose measurements and the immediacy of the data display. Clearly, measurements need to be frequent enough to capture all glucose dynamics. Based on current knowledge of the physiology of glucose and insulin metabolism in non-critically ill patients [2], an interval of 10-15 minutes between measurements is the likely maximum interval that would detect most glycemic dynamics, although faster dynamics may be observed when parenteral nutrition is modified and particularly when an intravenous glucose bolus is administered. The Clinical and Laboratory Standards Institute (CLSI) guidelines use 15 minutes as the cut-off for their definition of continuous monitoring [3], but which cut-off should be used to separate

"continuous" from "frequent intermittent" sampling is debatable. More data on glucose trends in the critically ill are needed before clinically relevant sampling frequencies can be defined. The real-time output of CGM devices should be as instantaneous as possible although there will generally be a lag period, the duration of which will depend on the site and frequency of sampling and data processing. The continuous display enables trends to be identified and visualized.

Importantly, the purposes of any such device are to improve clinically relevant outcomes and to reduce associated nursing workload and ideally costs. Although the overall accuracy of many CGM systems is less than that of intermittent systems using central laboratory testing [4], this limitation is to some degree mitigated by the ability to follow the direction of change in glucose levels, theoretically allowing earlier intervention to maintain blood glucose concentrations within acceptable ranges. A less-often cited advantage is the decreased need for multiple finger-pricks or blood pulls with a continuous system, which may reduce patient discomfort and nurse workload [5, 6].

Several CGM systems are now available for clinical use and early results from clinical trials in critically ill adults [7-14] and children [15, 16] have been published. However, no studies have assessed clinical outcomes using the continuous approach compared to an intermittent system; furthermore the different sensors used, the different comparators, and the lack of standardized performance metrics make it difficult to compare results.

B. Overview of techniques for glucose measurement

The three predominant techniques currently used for continuously measuring glucose levels in the ICU involve glucose oxidase, mid-infrared spectroscopy and fluorescence.

1. The glucose oxidase technique, perhaps the most widely used and best known of the three methods, is based on the sensing of hydrogen peroxide (H_2O_2) released when glucose is converted to glucolactone: the greater the concentration of glucose, the more hydrogen peroxide will be released and the stronger the signal. Results can be influenced by interference from molecules other than glucose, e.g., uric acid, acetaminophen and salicylic acid, which oxidize the H_2O_2.
2. Mid-infrared spectroscopy detects an absorption spectrum for glucose in plasma using different wavelength filters.
3. Fluorescence techniques rely on quenched chemical fluorescence to measure glucose concentration [17]. An optical sensor is positioned in a blood vessel on the end of an optical fiber. In the presence of glucose, the bond between the quencher and the fluorophore is weakened, resulting in an increase in fluorescence that is proportional to the blood glucose concentration. Fluorescence glucose-sensing methods may offer greater sensitivity in the hypoglycemic range if binding proteins

with disassociation constants in this range are used [17]. However, fluorescence glucose sensors are associated with a foreign body response, are sensitive to local pH and/or oxygen, and require a light source.

Monitoring sites: Clinical experience

Various monitoring sites have been proposed and are used by the different CGM devices currently available or in development. Glucose can be measured in whole blood, plasma, interstitial fluid, and microdialysis fluid and values will vary according to which fluid is being used: as stated by Cengiz and Tamborlane, "not all blood glucose is created equal" [18]. Generally, plasma glucose is considered the "gold standard". Glucose dissolves in water and because plasma (~93%) has a higher water concentration than do red blood cells (~71%), plasma will have a higher glucose concentration than will whole blood. The difference in laboratory-measured glucose concentration between whole blood and plasma will also vary with the hematocrit. Because some glucose diffuses from the plasma to interstitial fluid and tissues as blood circulates through the capillary system, arterial blood glucose is usually higher than venous glucose. Arterial blood glucose and capillary blood glucose are generally similar, although when blood glucose levels change rapidly, there may be a delay before similar changes are seen in capillary blood. Microdialysis fluid measurements use a probe with a membrane impermeable to macromolecules but permeable to low molecular weight compounds, such as glucose and lactate. Flow of isotonic fluid within the membrane enables a degree of equilibrium to be reached between the surrounding fluid and the dialysate fluid although microdialysis concentrations tend to be slightly lower than those actually present in the surrounding tissue or blood.

The degree of invasiveness of a CGM technique varies from highly invasive, e.g., intravascular devices, through the minimally invasive subcutaneous techniques, to non-invasive transdermal devices. Although studies comparing the accuracy and performance of more vs. less invasive CGM systems have not yet been performed, preliminary data suggest that moving through the spectrum from invasive to non-invasive, accuracy generally decreases as does the risk of complications, including infections. The type of monitor selected should be adjusted to patient characteristics, including the severity of illness of the patient and the type of access available. For example, a severely ill, unstable ICU patient will likely already have arterial and/or central venous lines *in situ* allowing invasive intravascular monitoring, whereas a stable patient ready for ward transfer can be monitored using a less- or non-invasive device. Moreover, severely ill patients are more likely to be receiving mechanical ventilation and/or sedative agents making clinical symptoms of hypoglycemia more difficult to detect and perhaps arguing in favor of the more accurate invasive devices. When

comparing devices it is essential to state which reference measurement technique is used so that results can be easily compared. Whenever possible, arterial glucose measurements with a blood gas analyzer or by a central laboratory should be used as the comparator as these are the most accurate and reproducible [1]; when this is not possible, or when the device under study uses venous sampling, venous blood glucose should be used as the comparator. When venous sampling is used, the specific vessel should be defined.

Intravascular CGM devices can be divided into three groups: (1) those that have an intravascular sensor actually inserted into the lumen of an artery or peripheral/central vein and directly measure the blood glucose concentration without consuming blood in the process; (2) those in which a small blood sample is taken from the intravascular catheter and passed over an external sensor; and (3) those in which a blood sample is re-circulated after passing through an external sensor without blood loss. The accuracy of intravascular microdialysis probes will vary according to their position – for example, if integrated into the central venous catheter, a much larger membrane will be possible than if positioned in a smaller peripheral vein catheter, allowing a greater area for equilibration and a more rapid and reliable result [19]. Recent studies using a central venous catheter with a microdialysis membrane have demonstrated good agreement between microdialysis glucose measurements and reference venous and arterial blood gas values in patients undergoing major abdominal surgery or cardiac surgery [20, 21].

Interstitial fluid glucose is generally measured with subcutaneous probes, often inserted on the abdominal wall or upper arm. Because subcutaneous devices have been used for some years in the non-critically ill diabetic population, more data are available for these devices than for others. Interstitial fluid glucose levels depend on the rate of glucose diffusion from plasma to the interstitial fluid and the rate of uptake by subcutaneous tissue cells; hence, they are influenced by blood flow, the metabolic rate of adjacent cells, capillary permeability, degree of hydration or edema, etc, all of which may be altered in critically ill patients making such measurement potentially less reliable [18]. However, several subcutaneous devices have been tested in critically ill patients and have been shown to have good agreement with reference arterial and venous samples [12, 22-24]. Moreover, similar accuracy has been reported in critically ill patients with and without shock requiring norepinephrine therapy [22], and in cardiac surgery versus non-critically ill patients [25, 26]. Nevertheless, the accuracy of interstitial fluid monitoring needs to be further investigated, in particular in unstable patients. One concern with subcutaneous interstitial fluid probes is the tissue trauma created during insertion, such that measurements may be less accurate for several hours after insertion. There is a time lag between change in blood glucose and that measured in the interstitial fluid, which is, however, unlikely to result in ineffective treatment in case of an emerging

hypo- or hyper-glycemic event [27-30]. The clinical relevance of this time-lag needs to be contrasted against current practice with a typical delay of 5 to 10 minutes to take the sample and to measure glucose on an analyzer.

Transcutaneous devices are also being developed. One such device uses a biosensor that can measure transdermal glucose flux, which is proportional to the blood glucose concentration. The skin is prepared by microabrasion to remove the dead surface cells and the biosensor then applied, using the glucose oxidase reaction to create a measureable signal for interstitial glucose. In pilot studies of cardiac surgery patients, good agreement with peripheral blood was demonstrated [31, 32].

All techniques have limitations related in part to the sampling site used (venous, arterial or capillary blood, plasma, and interstitial fluid) [18], but also to the need for anticoagulation with some intravascular devices, problems of local inflammation, and need for recalibration. Rice and Cousins [33] recently proposed a list of attributes for the "ideal" CGM system (Box 1).

For all CGM systems, the following performance characteristics related to the clinical utility of the system need to be clearly defined:

- Frequency of sampling
- Delay to display
- Lag time
- Biofilm development
- Measurement accuracy
- Reliability (time to sensor failure, frequency and duration of data gaps)
- Need for and frequency of calibration
- Ability to recognize and correct for interference
- Automation
- Need for anti-coagulation
- Safety
- Site of access
- Handling of outlier values
- Alarms
- Clinical effectiveness (i.e. impact on glucose control and prevention of hypoglycemia)
- Cost-effectiveness
- Possibility of combining glucose monitoring with other measurements

Trend accuracy vs point accuracy

One of the key advantages of CGM systems is their ability to identify and display trends in blood glucose measurement. Hence, when considering the performance of these devices, additional metrics may need to be developed to complement current assessment of accuracy in terms of individual blood glucose values compared to a standard laboratory-based control. Point accuracy is defined as the difference between the current displayed blood glucose value and the current true blood glucose value. Trend accuracy is defined as the degree to which an estimate of the rate of change in blood glucose concentration over a given time interval approximates the true rate of change. Further research is required to establish the duration over which trend accuracy should be calculated and the relative importance of point accuracy vs. trend accuracy in terms of clinical outcomes.

In theory, the use of trending could have several potential advantages over individual values (figure 1), including:

- that it is less sensitive to random noise, because, if present, noise will be filtered out by the trend line, at least when the period used to calculate the trend is long enough;
- there is little effect of bias – the presence of a constant over- or under-shoot of the value will not affect the trend;

However, there are also several disadvantages:

- There is a lag time when calculating the trend which will be dependent on the frequency of sampling and the number of measurements and time-lapse over which those measures are used. With longer time intervals between measurements, trending will reflect real changes less accurately, certainly when changes are rapid and intervals are long.
- If there is a lag time or a bias, extrapolation of the trend line can amplify the error.
- Most current glycemic control protocols rely on PID (proportional, integral, derivative) control with insulin rates determined as a function of the current blood glucose (P), accumulation of historical blood glucose values (I), and the trend (rate of change) in blood glucose (D). Hence for current protocols, all three aspects need to be accurate – it is not sufficient just to have accurate trend accuracy, point accuracy also needs to be good.

Thus, at the present time, both good point accuracy and good trend accuracy are required to achieve optimal glycemic control. However, the more continuous the measurement, the clearer and more reliable the trend will become. In the future, use of algorithms designed specifically for CGM may also reduce the need for highly accurate point measurements. The period of time over which trend should be assessed will depend on lag time and may also depend on the type of patient.

Standards for reporting performance

Standards for reporting of clinical trials of CGM systems need to be developed so that results can be easily compared. When considering clinical trial result reporting, we can consider factors related to the patients and the device per se and those related to the impact of the device on clinical outcomes. In terms of the device itself, several aspects need to be reported regarding demographics (age, gender, comorbidities, including diabetes, disease severity), use of vasoactive drugs, design (single-center vs. multicenter, type of center, number of samples, comparator), glucose targets (target range, definition of hypoglycemia and hyperglycemia, time in range, accuracy analytical and clinical, number of patients unable to monitor and reasons, down-time and display time [(time needed for calibration when no signal/reading available]), and safety (bleeding events, infections, outliers, alarm performance).

In terms of characterization of accuracy of the system being tested versus the comparator, the Bland-Altman plot remains an indispensable technique, showing the difference between the two measurements either as a function of the average of the two measurements or, when there is a "gold standard", as a function of the comparator [34]. The 95% confidence interval (1.96 x standard deviation) of a tested blood glucose meter against a gold standard can be deduced from these plots. Various grid systems have also been proposed, of which the Clarke error grid [35] is currently the most widely used. However, this grid was not designed for CGM systems and does not reflect rapid changes in the blood glucose level or account for potential errors in insulin dosing. As such, the so-called continuous glucose error grid analysis (cEGA) has been proposed, which is designed to capture errors in the rate and direction of change in glucose between measurement methods [36]. This technique, initially developed for outpatient care, is an interesting approach but relatively complex, requiring specific software and frequent sampling [37]. The R-deviation is another potential metric to assess the accuracy of CGM systems [38]. This value is a numerical metric of rate of change accuracy, based on the deviation between the rates of change in reference and test sensor glucose fluctuations.

How to report on the impact of a device in combination with a treatment protocol on clinically relevant outcomes is perhaps less clear. For this purpose, three domains of glycemic control can be considered: hyperglycemia, hypoglycemia, and glycemic variability [39]. Glucose complexity has been suggested as a possible fourth domain [40]. The three domains are all associated with increased mortality in critically ill patients [39] and, as such, the number and duration of hypo- and hyper-glycemic episodes (using prespecified parameters), the time in target, the degree of glucose variability (and possibly complexity) should all be reported when assessing the clinical impact of a new device, in addition to clinical outcomes, including mortality and morbidity measures. Further

study is needed to determine how best to define trend and hypoglycemia (including sensitivity and specificity) for regulatory approval (see below).

Alarms, warning signals

Alarms on CGM systems generally concern the three domains of glycemic control: hypoglycemia, hyperglycemia, and glycemic variability or rate of change. Each domain is associated with specific detrimental effects. Hyperglycemia is associated, among others, with increased glucose oxidation with release of superoxide, increased risk of infections, and decreased gut function. Hypoglycemia is associated with multiple cardiovascular and neuropsychological effects and with prolonged ICU stay [41-44]. Both hypo- and hyper-glycemia are associated with increased mortality rates in critically ill patients as is increased variability [39]. However, the risks associated with hypoglycemia may be different in conjunction with tight glucose control [45]. Determining at which value alarms should be set for each domain remains difficult. The clinical impact of hypo/hyperglycemia will vary according to the degree and time away from normal values (figure 2), with considerable overlap among individuals. Several studies have suggested that patients with acute coronary syndromes and severe brain injury may be more sensitive to low blood glucose levels [46, 47], at least in the absence of tight glucose control [48]. Therefore, in some groups of critically ill patients, target glucose ranges may need to be set higher than in other groups. Generally, a blood glucose $\leq$ 40 mg/dl is considered as representing severe hypoglycemia [1, 49] and a level 41-70 mg/dl as moderate hypoglycemia [1], but studies have used different definitions. Hyperglycemia is variably considered as values > 140 or 180 mg/dl. Glycemic variability is even more difficult to define; a relatively high value of the coefficient of variation of > 20% has been suggested to define high variability, because it is associated with a worse outcome than values < 20%. Variability is also related to ongoing therapy. Glycemic targets will also vary according to individual patient characteristics including age; comorbidities, notably diabetes; type of patient, e.g. surgical versus medical, etc. Alarm settings therefore need to be adjustable for individual patients. Further study is needed to define optimal target ranges for different groups of patients and to clarify the impact of alarms on clinical practice and patient outcomes. With the development of better validated CGM systems and better knowledge of glucose trends in the critically ill, alarms for trend changes will be developed and have the potential to prevent hyper- and hypoglycemia. Predictive alerts are already in use on some devices inserted subcutaneously.

Criteria for approval by the official bodies

In terms of safety and effectiveness, it is unclear which metrics should be used to indicate sufficient accuracy and reliability. The CLSI has produced new standards for point-of-care (POC) testing [50] stating that 95% of results must be within ±12 mg/dL of the reference method for laboratory concentrations <100 mg/dL or within ±12.5% for laboratory concentrations ≥ 100 mg/dl; 98% of results should be within 15 mg/dL of the reference method for values < 75 mg/dL (or within±20% for values ≥ 75 mg/dL). However, these standards may not be applicable to CGM systems. In our 2013 Consensus document, we suggested that the minimum standard for glucose meters to be used in critically ill patients should be that 98% of readings are within 12.5% of a reference standard (or within ±10 mg/dl for readings < 100 mg/dl); the remaining 2% of readings should be within 20% of a reference standard [1]. The mean absolute relative difference (MARD) should be cited and values will need to be <14%. Values >18% are considered to represent poor accuracy. For trend accuracy there is not yet an accepted metric. The R-deviation may be useful, but further study is needed [38]. Other concerns that need to be addressed include signal stability, drift, variability, and drop-out; potential interferences, e.g., acidosis, hematocrit, bilirubin, hemoglobin, medications and intravenous fluids; edema and nutritional status; number and characterization of outliers. As yet, there are no clearly defined metrics for reporting what is sufficient in terms of accuracy and reliability. A major advantage of CGM systems is the frequency of measurement and the ability to follow trends. One could argue that more frequent measurements may offset lower point accuracy and that concomitant development of new glucose protocols using CGM may be required. CGM systems could be used to improve the efficacy of glucose control but also to reduce the number of hypoglycemic episodes [9] and the relative importance of CGM in achieving these objectives is yet to be determined.

Insulin Algorithms

An algorithm can be defined as “a formalized sequence of instructions for solving a complex problem in finite processing steps” [51]. Algorithms in the field of tight glucose control are used to standardize care, for quality assurance and to avoid intuitive decision making. An optimal system should be accurate, safe, efficacious, simple to use, reliable, flexible for different patient populations, assessable in real-time, fit into workflow, require a low number of glucose measurements (if not based on CGM), take into account inter-and intra-patient variability and carbohydrate intake. Algorithms should incorporate dynamic scale protocols, instead of static sliding-scale protocols [52]. Although early algorithms were paper-based [53, 54], increasingly, glucose control algorithms are computer-based, enabling more complex protocols to be developed. Several studies have demonstrated improved glucose control with computer-based compared to paper-based algorithms

[55-57]. Nevertheless, better standardization of algorithm development is needed [58]. A common type of algorithm is the PID algorithm in which deviation of the blood glucose value from the target range is corrected by adjusting the dose of insulin using a linear combination of absolute deviation, trend, and the sum of past deviations [59]. Another main type of glucose algorithm used in critical care is the model-based or model-predictive control algorithm, which adjusts insulin dose according to a mathematical model of the relationship between blood glucose and insulin. This type of algorithm is much more sophisticated than previous algorithms [60, 61].

Many algorithms for glucose control have been developed and all differ in their assessment of insulin needs. Wilson et al. [62] identified 12 different algorithms and, using blood glucose records from an actual hyperglycemic patient, calculated the insulin doses that would have been recommended by each protocol. There was considerable variability among protocols in patterns and ranges of recommended insulin dose (range 27–115 units), and adjustments to dose when nearing target glucose. Protocols therefore behave differently and may have greater influence on outcomes than the glucose measurement error. Different algorithms may be better suited to various patient populations or clinical settings.

The development of many local algorithms is haphazard and not supported by evidence. However, clinical testing and comparison of algorithms is resource intensive in terms of patients, staff, time, and costs. Moreover, the majority of algorithms for glycemic control in the ICU use the current technology of intermittent glucose measurements and new algorithms will need to be designed if CGM systems become more widely used. When comparing algorithms, standard glucose-centric outcomes need to be reported, including numbers of hypo- and hyper-glycemic episodes. One useful parameter that has been suggested is the cumulative time-in-band, which calculates the percentage of blood glucose values within a specified range of blood glucose values. This measure is independent of sampling frequency, can be applied to all algorithms and is simple to calculate. However, this metric is only useful when comparing algorithms that target the same blood glucose band.

In silico simulation models using “virtual” ICU patients have been suggested to reduce some of the burden of clinical algorithm comparisons and to accelerate the assessment process. These systems can be used to optimize design parameters and safety features, test effects of changes in nutrition or other medications and interventions, and assess effects of measurements errors or delays. However, in silico testing can never replace real-life validation in clinical studies. Moreover, the value of simulation is highly related to the prediction performance of the virtual patient model. At least four currently available ICU simulators are known: the Cambridge [63], Virginia [64], Leuven [65], and Christchurch [66] models and simulation models are beginning to be used in the critical care

setting of glycemic control. Wilinska et al. [67] used simulation to compare the effects of different algorithms used in randomized clinical trials; the study results were reproduced in the simulated population. The same authors also used simulation to evaluate the performance of a newly proposed "I, Pancreas" algorithm, noting that in their 10 "virtual" patients, tight glucose control was achieved 38% of the time [68]. Signal et al. used in silico modeling to assess the effects of using a specific insulin algorithm with CGM rather than standard hourly glucose measurements, assessing also the effects of different levels of noise, different hypoglycemia alarms, and different bolus glucose interventions [69]. Although these systems need further study, it seems likely that the virtual patient will play an increasingly large role in the ongoing development of CGM systems and glycemic control protocols in the ICU setting.

The development of closed loop systems, which link CGM measurement with insulin delivery through control algorithms, is the most promising approach to improve glucose control once CGM becomes routinely available. Closed loop systems, which deliver insulin in a glucose responsive fashion modulated every 1 to 15 minutes, are being aggressively pursued in non-critically ill patients, and in the critical care setting they could additionally modulate glucose delivery to further reduce the risk of hypoglycemia. The feasibility assessment of automated closed-loop glucose control based on continuous subcutaneous glucose measurements and model predictive control in critically ill adults was associated with better glycemic control compared to a local sliding scale protocol [70].

Priorities for research

The expert group defined eight areas where research should help to advance glucose monitoring in the near future to the likely benefit of critically ill patients.

- The different devices for CGM need to be better validated in terms of accuracy and reliability. Head-to-head comparisons are needed, in particular of devices sampling from different compartments. Studies should also consider "human factor" issues in the use of CGM devices in the ICU environment.
- The clinical relevance of inaccuracies in glucose measurements should be shown in error grids adapted to current therapeutic algorithms.
- Glucose trends in critically ill patients and subgroups need to be more clearly characterized, so that better definitions of the rate of changes can be developed and, thereby, the frequency of sampling needed to describe clinically relevant trends.

- The effect of different insulin treatment algorithms on glucose variability should be studied with development of new and enhancement of existing glucose control protocols based on CGM.
- Development and validation of metrics for trend accuracy.
- Universal metrics to assess glycemic control and BG variability that could be used with continuous data as well as intermittent data should be defined and agreed upon.
- At a later time-point, randomized controlled trials (RCTs) assessing the effects of CGM systems vs intermittent protocols on outcome in critically ill patients, including assessment of patient-centered outcome measures (glycemic control and morbidity incidence), need to be conducted.
- Closed loop systems for glucose control in critically ill patients should be developed and eventually validated and assessed in RCTs as above.

Conclusion

CGM mandates the development of new approaches to the analysis of parameters of glucose regulation, such as glucose variability and glucose complexity, and also provides a tool to help effect these analyses. While CGM systems clearly have the potential to improve blood glucose control and patient outcomes, this remains a potential that has not yet been demonstrated in clinical practice. Future studies may be able to demonstrate real clinical benefits and reveal the optimal use of the different CGM-systems (which system for which patient). When discussing how best to assess CGM, different goals can be considered, including maintenance of specified target levels, which may vary in different patient populations; avoidance of hypoglycemic events; assessment of glucose variability; degree of glucose complexity. Most important, however, will be the impact of each device on clinical outcomes, including better glucose control and fewer hypoglycemic episodes; this is of far more relevance to clinicians and patients than small differences in accuracy.

Abbreviations

CGM: Continuous glucose monitoring

CLSI: Clinical and Laboratory Standards Institute

ICU: intensive care unit

MARD: mean absolute relative difference

PID: proportional, integral, derivative

POC: point-of-care

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Conflicts of interest

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Tom Van Herpe has one patent in the related field.

Robert Vigersky has received investigator-initiating grants from DexCom and has served as a consultant for Medtronic Diabetes Care, Sanofi-Aventis, Bayer, Abbott Diabetes Care, and Roche.

Jean-Charles Preiser has received speaker fees from Edwards, Fresenius, Maquet and Optiscan. He has also served as a consultant for Edwards, Medtronic and Optiscan.

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Box 1. Suggested criteria for the ideal CGM system [33]

* Rapid: very little lag between blood glucose and the measured value.
* Accurate: each measurement should be within accuracy guidelines suggested recently [1].
* Free of interference: minimal, if any, important interference, such as drugs or physiologic perturbations.
* Inert: the sensor should not react with the tissue or form a coating rendering the device inaccurate over time.
* Robust: the system must be able to perform within the dynamic and busy intensive care unit and operative setting.
* Minimally invasive
* Cost-effective

Figure legends

Fig. 1. Schematic representation of the potential advantages of using trends. A: If imprecision or noise is random or normally distributed, the trend line will filter it out; B: if the measurement system has a fixed bias, trend will not be affected but individual values could be; C: when trying to predict future events, trend may be clinically more important than the current absolute blood glucose value

Fig. 2. The clinical impact of hypo/hyperglycemia varies according to the degree away from normal values

Appendix: Summary of the current CGM devices (provided by the industrial sponsors of the meeting, listed in alphabetical order).

B. Braun: B. Braun Space GlucoseControl (SGC) is a decision support system for insulin therapy fully integrated in the Space infusion pump system. It is indicated for critically ill patients in a closely monitored environment, e. g., intensive care units (ICUs) or operating rooms (ORs). The system recommends an insulin dose rate and measurement interval using a model predictive control algorithm based on the patient's actual and previous blood glucose levels and under consideration of the current carbohydrate feeding which is automatically updated from enteral and parenteral nutrition pumps. Using SGC, glucose control can be significantly improved compared to manual control and effective glucose control can be established.

EchoTherapeutics: The Symphony® continuous glucose monitoring (CGM) system from Echo Therapeutics is a non-invasive, needle-free CGM system targeted for use with ICU patients. Symphony's color display of graphical trend information updated every minute, and customizable low and high glucose alerts, combine to provide ICU staff with an early warning system for potential glucose excursions. Symphony's transdermal approach to access interstitial glucose levels and its wireless transmission of glucose data from sensor to monitor minimize the risk of infection, inflammation, pain or discomfort that can be associated with other methods of glucose monitoring.

Edwards: The GlucoClear™ CGM system from Edwards Lifesciences measures blood sugar by glucose oxidase sensing technology through in-blood measurement. Blood is automatically drawn and analyzed every 5 minutes, with real time graphical display. Blood is then returned to the patient and the system automatically self-calibrates. GlucoClear CGM has been designed for ICU and OR patients. The GlucoClear CGM is designed to be highly accurate. In a recent ICU study, it was shown to be at least 95%, 10/15%*accurate with a mean absolute relative difference (MARD) of 5.05%. A 50-patient ICU accuracy study is currently underway with a further enhanced version of GlucoClear CGM.
** 10/15% is the proportion of the GlucoClear CGM's values within ± 10 mg/dL of YSI (for YSI ≤ 66.7 mg/dL) and within ± 15% of YSI (for YSI > 66.7 mg/dL).*

GluMetrics: The GluCath® Intravascular CGM System from GluMetrics, Inc. measures blood sugar by the quenched chemical fluorescence technique. The sensor is deployed through a radial artery catheter and optical measurements are made every 10 seconds. A five minute rolling average of analyzed glucose is the displayed result. The device is intended for use in post-cardiothoracic surgery patients in whom glycemic control is indicated. The device has been tested on seventy subjects in the critical care setting, comparing results from the device against hourly arterial samples tested on the blood gas analyzers of four surgical ICUs (results forthcoming).

GlySure: GlySure's intravascular blood glucose sensor uses optical fluorescence technology. Data are collected every few seconds and generate a continuous trend of blood glucose from the sensor, which is placed in the external jugular vein. The device is intended for use in management of glycemic control of Intensive care patients. Results from initial clinical evaluation were published at the ISICEM meeting in Brussels 2012, and a poster updating that progress w accepted for publication at the World intensive care congress in Durban, in August/September 2013. The device is not yet available commercially.

Maquet: EIRUS® from Maquet Critical Care is a device for continuous monitoring of blood glucose and blood lactate in hospitalized patients, including ICU patients and patients during surgery. The

system requires a special, multipurpose central venous catheter and the measuring principle is microdialysis. The glucose and lactate concentrations in the dialysate are in equilibrium with central venous blood concentrations and are analyzed every second. The measures are displayed every minute on the screen, with a delay of 5 minutes from actual sampling to displayed result. Accuracy of the device has been tested clinically in a critical care setting. As reference, arterial blood gas samples were analyzed in a blood gas analyzer. Paired glucose samples (607 and 994 paired samples) were analyzed using Clarke Error Grid and Bland-Altman analysis[v]. Lactate measurements (1601 paired samples) were analyzed using correlation coefficient and Bland-Altman analysis.

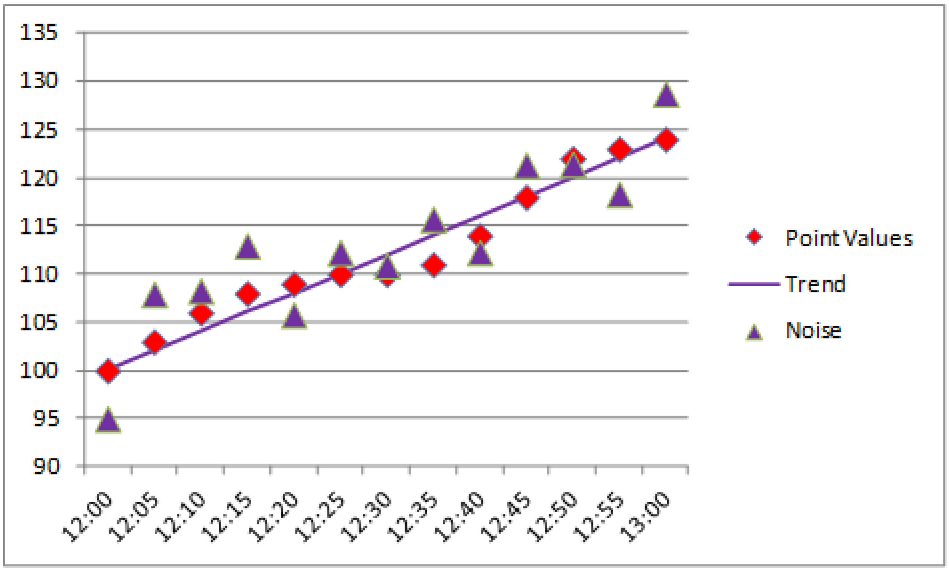
Medtronic: The Sentrino® System was designed to address the unique needs of critical care patients with a highly innovative design and unique ability to integrate into clinical protocols:

- The minimally invasive, subcutaneous sensor was customized for the critical care patient and inserts quickly and easily with low complication rates.
- Redundant sensing technology optimizes signal reliability for more accurate visibility of glycemic variability.
- A novel drug interference rejection technology ensures minimal interference with the wide array of pharmaceuticals used in critical care.
- The Sentrino CGM System is easily configured by clinicians and easily integrates into existing clinical workflow
- The compact, flexible system is easy to transport with the patient

Menarini: The GlucoMen®Day device (A. Menarini Diagnostics) measures blood sugar by the microdialysis technique, combining an intravascular probe with an external GOx-based amperometric biosensor, highly sensitive and immune to a wide range of endogenous/exogenous interfering chemicals. Dialysate samples downstream of the probe are analyzed each minute, with 2 minutes delay from sample to displayed result, wirelessly transmitted to a bed side monitor. The suggested indication of our device is critically ill patients. The device is presently investigational, and has been tested for 72 hours in T1DM subjects against venous standard, using point and trend accuracy metrics (e.g., Bias Plot, CEG, CG-EGA) to report performance.

Optiscan: The OptiScanner® measures blood sugar in plasma using mid-infrared spectroscopy. Its fluidics systems withdraw a sample of non-diluted whole blood every 15 minutes, applies heparin (without any heparin exposure to the patient), and centrifuges the sample to plasma. The OptiScanner® requires no calibration over several years. Clinical research supports usage of the OptiScanner® on in-hospital diabetics, acute myocardial infarction patients, and medical/surgical ICU patients. Blood access can be obtained through standard venous catheters: a central venous catheter, a peripheral intravenous access, or a peripherally inserted central catheter. OptiScanner®'s glucose accuracy has been published in three peer reviewed articles.

A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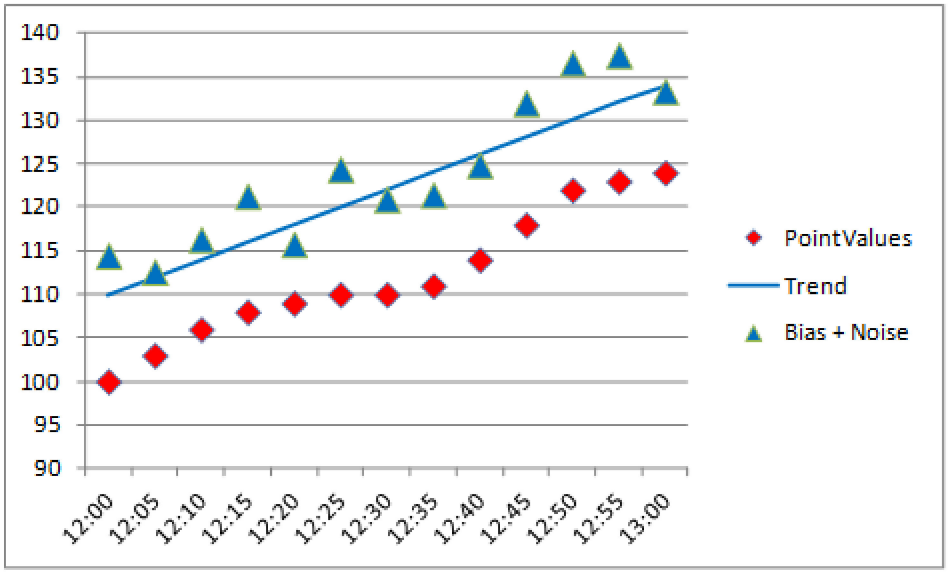
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C

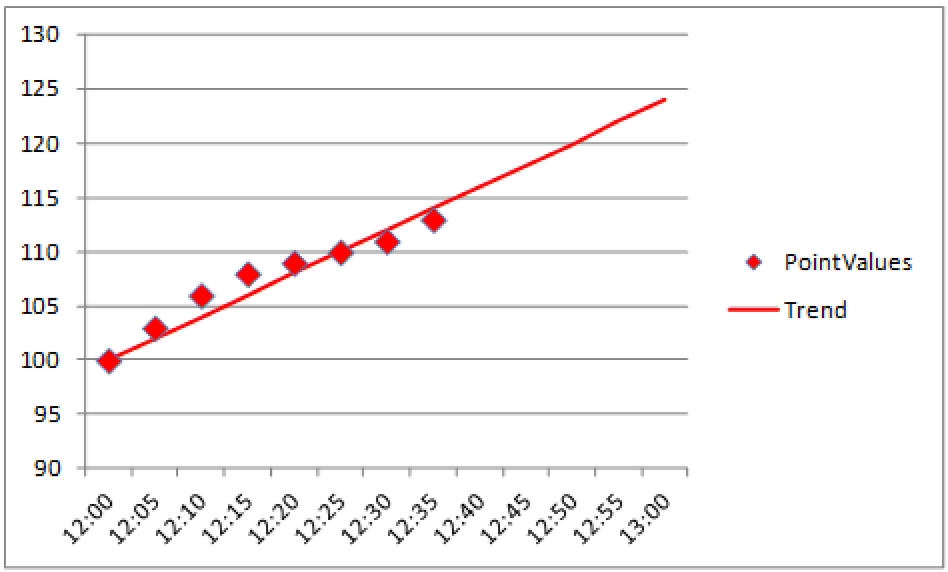
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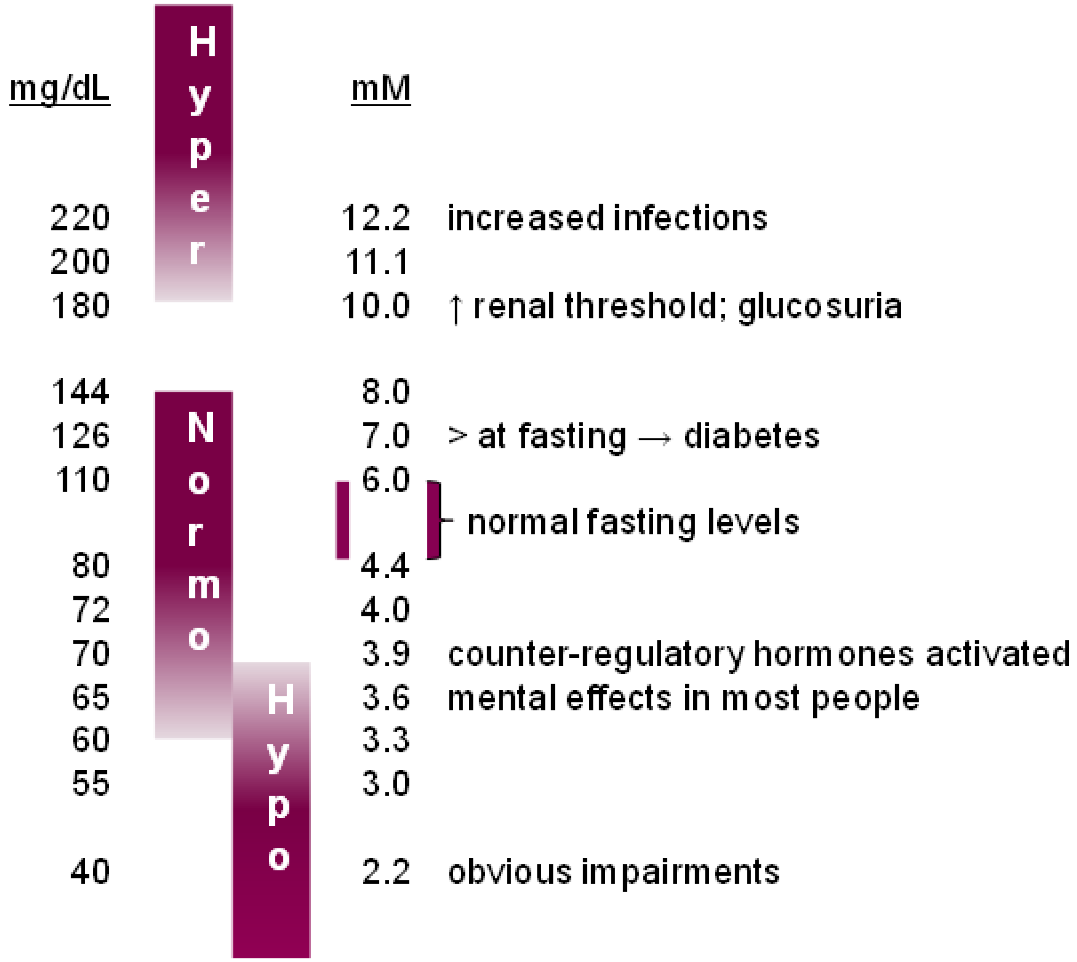
Figure 1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8.0
7.0
6.0
4.4
4.0
3.9
3.6
3.3
3.0
2.2
increased infections
↑ renal threshold; glucosuria
> at fasting → diabetes
normal fasting levels
counter-regulatory hormones activated
mental effects in most people
obvious impairments

Figure 2