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Impact of a computer-generated alert system on the quality of tight glycemic control in the ICU: a sequential cohort study

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Keywords

Intensive care - Critical illness - Blood glucose – Hypoglycemia - Computer assisted drug therapy - Insulin infusion system

ABSTRACT

Purpose: To assess the impact on quality of TGC in the intensive care unit (ICU) of a computer-generated blood glucose (BG) alert, generated by a Patient Data Management System (PDMS) and superimposed on a paper-based guideline.

Methods: TGC in the Leuven University Hospitals is done by nurses, using a paper-based guideline that allows anticipative, intuitive decision making. August 1st 2007, an electronic alert was implemented. A pop-up appeared in the PDMS at the following BG thresholds: >180 mg/dl, >110 mg/dl, 60-80 mg/dl, 40-60 mg/dl and <40 mg/dl. The impact was assessed by a sequential cohort study: the mean BG, the glycemic penalty index (GPI), the hyperglycemic index (HGI), the proportion of measurements per patient in the hyper- and hypoglycemic range, the number of hypoglycemic events, the standard deviation (SD) of the BG time series and the number of BG measurements per patient and per patient per day were compared in all adults admitted 6 months before ("pre-alert group", n=729) and after ("alert group", n=644) implementation of the alert.

Results: The alert resulted in a small reduction of mean BG (112 mg/dl versus 110 mg/dl, p=0.002), GPI (20 versus 19, p= 0.029), HGI (10 mg/dl versus 9 mg/dl, p= 0.004), and reduced the proportion of measurements per patient in the hyperglycemic range (32.9% versus 30.0%, p=0.008). The BG sampling rate was not affected (median 25 measurements/patient in both groups, p= 0.776; mean of 7.7 measurements per patient and per day, p=0.891). The alert reduced the proportion of patients experiencing an episode of hypoglycemia < 40 mg/dl from 6.5% to 4.0% (p=0.043). The hypoglycemic index, the proportion of measurements per patient in the hypoglycemic range, and the SD of the BG time series were not affected.

Conclusion: A simple computer-generated alert was able to statistically significantly improve the quality of TGC in ICU patients without increasing the need for blood sampling.

INTRODUCTION

Critical illness-induced hyperglycemia is common and associated with adverse outcome. The single center studies performed at the Leuven University in Belgium, 2 in adult patients [1-2] and 1 in pediatric patients [3] showed that targeting age-adjusted normoglycemia using insulin infusion lowered ICU mortality by an absolute 3% and reduced morbidity. Multicenter studies, using different control and/or intervention target ranges and using different methodology for BG measurement as well as different protocols for insulin administration, were not able to reproduce these results [4-6]. The exact reason for the discrepancies between these studies remains unclear. However, there is a broad consensus that keeping the BG between 80-110 mg/dl (4.1-6.6 mmol/L) in critically ill adults, is a complex procedure which bears an increased risk of inducing hypoglycemia. Although a causal relationship between brief hypoglycemia in the ICU setting and mortality has never been demonstrated [7], the hypothetical danger associated with hypoglycemia is an important reason why some centers are reluctant to implement tight blood glucose control.

To assess the 'quality' of glucose control, several indices have been proposed. Single blood glucose measurements such as admission BG, maximum BG or mean morning BG are not always representative for BG control throughout the patient's ICU stay. The mean of all BG values per patient can be strongly influenced by single outlying values. The hyperglycemic index (HGI) is defined as the area under the glucose curve above the normal range divided by the length of stay [8]. This index gives a good indication of overall BG control throughout the ICU stay, and compensates for an unequal time distribution of glucose measurements, although it does not account for hypoglycemic episodes. The glycemic penalty index (GPI) has been designed especially to compare different TGC algorithms [9]. For the calculation of the GPI, a penalty is assigned to each individual measured BG value. The index is the average of all penalties, and returns a number between 0 (no penalty) and 100 (the highest penalty), with a value below 20 indicating excellent control. Other studies have proposed the proportion of measurements in the desired range. A good summary of all the published quality indicators for tight glycemic control can be found in the review paper by Eslami et al [10]

Several recent studies in critically ill patients revealed an association between markers of intermittent exposure to elevated glucose, or "amplitude variation" of BG, and mortality, independent of baseline severity of illness [11-13]. Blood glucose amplitude variation, quantified by the mean of the difference between the daily minimum and maximum blood glucose, and by the standard deviation of the blood glucose signal, have shown to be a risk factor for mortality, independent of the level of BG control [14]. Hence, it may be important to report on the effect on blood glucose amplitude variation of different algorithms for TGC.

Since 2001, a paper-based guideline for TGC has been used in the ICU of the University Hospitals of Leuven. This guideline does not comprise explicit if-then rules but rather serves as a guide for the nurses to perform TGC in an anticipative, intuitive way. This way, with experienced nurses, good blood glucose control is obtained without computerized support [15].

An explicit computer algorithm has shown not to be superior over the nurse-driven TGC strategy in the Leuven ICU [16]. A simple computer alert has shown to decrease the incidence of venous thrombo-embolism in hospitalized patients, indicating that computerized decision support does not need to be complex in order to be effective [17].

In the present study, we hypothesized that a simple blood glucose level alert system that sends a message to the nurses via the ICU's Patient Data Management System (PDMS), is able to further improve TGC performed by an experienced team. The mean of all BG values per patients, the HGI, the GPI, the proportion of measurements in the hyper- and hypoglycemic range, the number of hypoglycemic events and the number of BG measurements per patient and per day were used to compare TGC before and after implementation of the computerized alert. The impact of such alert on BG amplitude variation was also investigated.

METHODS

Patients and setting

The study was performed in a 56 bed predominantly surgical ICU of a 1900 bed tertiary University Hospital. This unit admits patients after complex cardiac surgery and patients with medical complications requiring vital organ support after all types of surgery. The studied patient populations are described in Table 1 and 2.

TGC in the ICU of the Leuven University Hospitals

Since 2001, TGC is performed in all adult patients admitted to surgical ICU, targeting a BG level between 80-110 mg/dl by a continuous infusion of insulin (Actrapid®, Novo-Nordisk, Denmark). Insulin infusions are prepared as 50 IU insulin dissolved in 50 ml saline in a hard plastic syringe and tubings and using an accurate syringe-driven infusion pump (B. Braun Space®, B. Braun Melsungen AG) connected to the central venous line close to the patient on a separate lumen. Arterial blood is sampled every hour until in target and subsequently every 4 hours or more frequently according to the judgement of the bedside nurses. Sampling of undiluted arterial blood (discarding a volume of at least 4 times the dead space of the tubing system) is performed via the arterial line for BG monitoring. BG measurements are performed on a point-of-care bloodgas analyzer (Radiometer 800®, Copenhagen, Denmark) which is maintained and calibrated according to the company's prescription. There are 4 bloodgas analyzers on site for 56 beds. BG levels are reported as corrected to plasma glucose. The ICU nurses perform TGC in an autonomous way, responsible for the timing of additional BG samplings as well as the adaption of the insulin infusion rate. Nurses perform TGC using as a basis a concise guideline which does not contain strict "if/then" rules and which allows anticipative, intuitive decision making according to the needs determined by the individual condition of each patient. The guideline is published on the department's intranet homepage, but after extensive training and having gained experience with it for a few months, the nurses hardly ever consult it. In appendix 1, an English translation of the original guideline in Dutch is presented.

The electronic blood glucose alert system

The Leuven ICU has computerized patient records since 2006, when a PDMS (MetaVision®, iMD-Soft, Needham, MA, USA) was installed. This PDMS allows to detect critical values

of registered clinical and laboratory parameters and to send a message to users through an application called the EventManager®. Through an interface with the Laboratory Information System (LIS) and the Hospital Information System (HIS) (HIS and LIS, developed by the informatics department of the University Hospitals Leuven, in Java®, Sun Microsystems Inc., Palo Alto, CA, USA), the BG values from the blood gas analyzer are sent to the PDMS in a virtual real-time manner, as the delay is less than 1 minute between the BG measurement and the moment the result appears in the PDMS.

On August 1st 2007, an alert system was configured using MetaVision®'s EventManager®. At different BG thresholds, nurses received a pop-up alert at the bedside PC. This pop-up message required acknowledgement and validation by the user before it disappeared. Each pop-up contained a suggestion for the timing of a next BG measurement and an instruction to double-check caloric intake and the current insulin infusion rate and, when relevant, an advise for extra glucose infusion. The alert was configured to appear at 5 different BG thresholds.

Hypoglycemia: blood glucose value below 40 mg/dl

This hypoglycemia alert was a 'critical' event, as indicated by a red color. It was sent to all doctors and nurses logged-in on the patient's file, irrespective of the workstation that was used. It required acknowledgement by the nurse before the window could be closed. It advised to stop the insulin infusion, to check caloric intake interruptions, to administer 10g of IV glucose and to take a new blood sample within 30 minutes. The pop-up message is shown in Figure 1.

Hypoglycemia between 40 and 60 mg/dl

This hypoglycemia alert was a 'serious' event, also indicated by a red bar color, which was sent only to the nurse and only to the workstation at the bedside of this particular patient. It advised to stop the insulin infusion, to check caloric intake and to take a new blood sample within one hour. It required acknowledgement by the nurse before the window could be closed.

Hypoglycemia between 60 and 80 mg/dl

This hypoglycemia alert was an 'informative' event, as indicated by a yellow color. It was sent to the nurse at the bedside workstation of that particular patient. It advised to adapt the insulin infusion rate, to check caloric intake and to take a new blood sample after 1 hour.

Hyperglycemia above 110 mg/dl in a patient who cannot eat by himself

This hyperglycemia alert was an event that required 'attention' (dark yellow color), and was sent to the nurse whenever a blood glucose value exceeded 110 mg/dl. In order to avoid unnecessary alerts in patients who were eating, and who were no longer subjected to the strict TGC target range of 80-110 mg/dl as postprandial values often exceed 110 mg/dl, it was only triggered in those patients who had a caloric intake by meals of less than 500 kcal on the previous day. The pop-up advised to increase the insulin infusion rate, to check caloric intake, and to draw a new blood sample within 1 hour.

Hyperglycemia above 180 mg/dl in a patient who can take oral nutrition

This hyperglycemia alert applied only to patients who were able to eat at a blood glucose value exceeding 180 mg/dl. This was an 'informative' event (yellow color), which alerted the nurse when the blood glucose exceeded 180 mg/dl in a patient whose caloric intake by meals exceeded 500 kcal on the previous day. It advised to adapt the insulin infusion rate and to take a new blood sample after 1 hour.

Sequential cohort study design

A control cohort of 729 adult patients (>18y) admitted to the Leuven ICU between January 31st and July 31st 2007 (pre-alert group) was studied. Starting one month after implementation of the electronic alert, a second cohort was prospectively studied, comprising all 644 adults admitted to ICU between August 31st 2007 and February 6th 2008 (alert group). This one month interval was chosen to give the nurses the opportunity to get acquainted with the electronic alert. All data were extracted from the MetaVision® database. Baseline demographic data were registered and compared between the two study groups. All BG values stored in the PDMS were used for the analysis. The mean blood glucose per patient, the hyperglycemic index (HGI) [8], the glycemic penalty index (GPI) [9], the number of patients experiencing at least one episode of hypoglycemia <40 mg/dl and the number of BG samples taken per patient, and per patient per day were calculated and compared in both groups. The hypoglycemic index was calculated as the area under the curve of all

measurements below the 80 mg/dl level. The percentage of measurements in the hyperglycemic and hypoglycemic ranges per patient were calculated. As a measure of BG amplitude variation, the standard deviation (SD) of all BG measurements per patient was used, in analogy with Egi et al [12], and Meyfroidt et al [14].

Statistical analysis

Data are presented as number and percentages, means $\pm$ SD or medians with interquartile ranges, as appropriate. Differences among study groups were analyzed by the χ^2 test for comparison of proportions. Non-normally distributed numerical data are presented as medians (P25-P75) and are compared with a Mann-Whitney U test, normally distributed data are presented as means $\pm$ SD and are compared with a student's t-test. Two sided p -values of less than 0.05 were considered significant. Statistical analyses were performed using Stat View 5.0.1 for Windows (SAS Institute, Cary, NC, USA).

RESULTS

Baseline characteristics of the two patient cohorts are summarized in tables 1 and 2. There was no significant difference between the study groups for age, gender, body mass index, admission blood glucose of the patients, or in the admission categories, the number of unplanned admissions, ICU length of stay and mortality.

The results of the comparison between the pre-alert and the alert group are summarized in table 3.

The mean blood glucose values per patient were 112 (105-122) mg/dl before the alert, which were reduced after the alert to 110 (104-119) mg/dl ($p=0.002$). The GPI was reduced from 20 (14-28) to 19 (13-26) ($p=0.029$). In the hyperglycemic range, the alert reduced the HGI from 10 (5-17) mg/dl to 9 (4-15) ($p=0.004$), the proportion of measurements in the hyperglycemic range (>110 mg/dl) was reduced from 32.9% to 30% ($p=0.008$). In the hypoglycemic range, there was no reduction in the hypoglycemic index, or in the proportion of measurements in the hypoglycemic range (<80 mg/dl) but a significant reduction in the proportion of patients that experienced at least one episode of hypoglycemia (<40 mg/dl) from 6.5 % (47 patients) to 4.0% (26 patients) ($p=0.043$). The alert had no impact on the blood glucose amplitude variation, as there was no significant difference in the standard deviation of the blood glucose time series before [28 (22-38) mg/dl] or after implementing the alert [28 (13-57) mg/dl] ($p=0.566$). The alert did not lead to a higher number of blood glucose samples drawn per patient (median 25 measurements per patient in both groups, $p=0.776$), or per patient and per day (mean 7.7 measurements per patient per day in both groups, $p=0.891$).

DISCUSSION

A simple electronic alert system was able to further improve the quality of tight glycemic control in a surgical ICU, as shown by a reduced mean BG per patient, a lower GPI and HGI and a lower number of patients with hypoglycemia after implementation of the alert. The electronic alert did not have an impact on blood glucose amplitude variation. The number of blood samples drawn per patient to measure blood glucose was unaffected.

The finding that a simple electronic alert system can improve the quality and safety of TGC, even in a setting where TGC was already performed at a high level of experience, is striking. Indeed, the TGC methodology applied in the Leuven hospitals was developed in this center and used a paper-based guideline that allowed nurses to take anticipative, intuitive decisions. The electronic alert system did not alter this principle of autonomy, but assisted the nurses by reminding them when and how to further optimize TGC. This effectively resulted in a small but significant further decrease in the level of blood glucose, but much more importantly, it increased the safety of the intervention as the incidence of hypoglycemia, which in the pre-alert group was similar to the incidence reported in the clinical RCT that was conducted in this ICU [1], was further reduced.

The observation of improved quality and safety of TGC without increasing the number of blood samples taken per patient was somewhat unexpected. Perhaps a ‘big brother’ or ‘watch dog’ effect, giving the nurses the feeling that somebody is watching or controlling them, predominantly explains the observed beneficial effect on the glucose profile. Such an explanation cannot be excluded as we did not assess the nurses’ motivation before and after implementation of the alert. Alternatively, the knowledge that an electronic system is checking the risky situations may have rendered the nurses more secure, which could have avoided unnecessary blood sampling which may have outbalanced an increased sampling frequency where needed.

Many authors consider guidelines that allow intuitive decision making, as opposed to explicit and strict “if-then” protocols, problematic [18]. Theoretically, a strict if-then protocol offers many advantages [19, 20]. First, it does not require interpretation by the bedside users. Second, it ensures replicability of the protocol in other clinical settings. Third, it has previously shown to have the potential to increase clinician’s compliance with a guideline. Fourth, it may decrease the workload for the bedside user. For example, TGC as implemented in the NICE-SUGAR trial [6], was guided by a web-based computer treatment algorithm that comprised strict if-then rules. However, we have previously shown that a computerized explicit protocol with strict if/then rules did not improve TGC as compared with the nurse-driven implementation based upon a simple guideline that allows autonomous, intuitive, anticipative decision making by the bedside nurses [18]. Similarly, it was recently

confirmed that TGC can be significantly improved by switching from a strict physician-developed if-then protocol to a more intuitive approach led by the ICU nurses [20]. The reasons for this perhaps unexpected result remain unclear and should be further explored. Explicit protocols with if-then rules may fail to take into account certain aspects of BG control, such as concomitant medication and intercurrent infections that alter the insulin sensitivity, the impact of altered amounts of feeding or the anticipation required to prepare patients for an examination or an operation. The individual patient is a complex and dynamic organism, whose clinical condition evolves during the course of illness. Driving blood glucose safely into a narrow target range could be compared to driving a car, where it is crucial to look backwards in the mirrors as well as to anticipate on what lies ahead before deciding how far to turn the steering wheel or how strong to push the breaks. Some of the 'knowledge' of the patient's condition, and his response to changes in caloric intake, insulin infusion rate, drugs such as corticosteroids or disease states such as sepsis, is usually not incorporated in such explicit written or computerized TGC algorithms. The bedside nurses have experience with the patient's previous responses to insulin and caloric infusions, as well as insight in the future changes in the status of the patient, which they integrate when adjusting the insulin dose. For example, they know in advance when an interruption in the caloric intake of a patient is planned, when corticosteroids will be given, when adrenergic drugs will be administered or reduced in dose.

The present study did not compare the explicit with the more intuitive approach for TGC. However, we were able to demonstrate that an acceptable quality level of TGC can be achieved without the strict if-then rules, and that computers, by assisting the nurses in their anticipative, intuitive approach, can further improve the safety of the decision making process without imposing strict rules or increasing the need for blood samples.

The improvements in the level of success in reaching the preset target glucose range of 80-110 mg/dl control by the electronic alert, although statistically significant, were small. It is thus unlikely to expect that this small difference could result in a measurable effect on patient outcome. However, although it remains unclear whether brief hypoglycemia in the context of tight glycemic control causes damage [7], the reduced number of patients who experienced hypoglycemia is an important safety asset for clinicians. In the hypoglycemic range, the alert reduced the number of patients that experienced a deep and dangerous hypoglycemia of <40 mg/dl, whereas it did not impact on the indices that quantified hypoglycemia below 80 mg/dl.

This study has several limitations. First, the design of the study is observational in nature, lacking the level of evidence that a prospective randomized trial could have offered. Second, we did not study the effect of removing the electronic alert again which could have allowed a randomized cross-over design. Third, the results of this study can not be generalized to other

ICU settings or patient populations. The ICU in which the study was performed has a long standing experience with TGC, as reflected by the blood glucose values in the pre-alert group and the number of hypoglycemic events, that were quite similar to the values reported in the original randomized controlled study of surgical ICU patients (mean morning BG of 103 in the intensively treated group of the original study, and 5.1% of the patients experiencing hypoglycemia) [1].

CONCLUSION

Even in an environment with extensive experience in performing TGC in ICU patients, a simple computer-generated alert system was able to further improve the success of a paper-based, nurse-driven guideline allowing anticipative, intuitive decision making, by further lowering the level of glucose into the target range and by reducing the risk of hypoglycemia, without increasing the need for blood sampling.

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REFERENCES

1. Van den Berghe G, Wouters P, Weekers F et al (2001) Intensive insulin therapy in critically ill patients. *N Engl J Med* 345:1359-67
2. Van den Berghe G, Wilmer A, Hermans G et al (2006) Intensive Insulin Therapy in the Medical ICU. *N Engl J Med* 354:449-61
3. Vlasselaers D, Milants I, Desmet L, et al (2009) Intensive insulin therapy for patients in pediatric intensive care: a prospective, randomized controlled study. *Lancet* 373(9663):547-56
4. Brunkhorst FM, Engel C, Bloos F et al (2008) Intensive Insulin Therapy and Pentastarch Resuscitation in Severe Sepsis. *N Engl J Med* 358:125-39
5. Devos P, Preiser J, Melot C (2007) Impact of tight glucose control by intensive insulin therapy on ICU mortality and the rate of hypoglycaemia: final results of the GluControl study [European Society of Intensive Care Medicine 20th Annual Congress abstract 0735]. *Intensive Care Med* 33 (suppl 2):S189
6. Finfer S, Chittock DR, Su SY, et al (2009) Intensive versus conventional glucose control in critically ill patients. *N Engl J Med* 360(13):1283-97
7. Vriesendorp TM, Devries JH, van Santen S et al (2006) Evaluation of short term consequences of hypoglycemia in an intensive care unit. *Crit Care Med* 34:2714-2718
8. Vogelzang M, van der Horst IC, Nijsten MW (2004) Hyperglycemic index as a tool to assess glucose control: a retrospective study. *Crit Care* 8(3):R122-7
9. Van Herpe T, De Brabander J, Beullens M et al (2008) Glycemic penalty index for adequately assessing and comparing different blood glucose control algorithms. *Crit Care* 12(1):R24
10. Eslami S, De Keizer N, De Jonge E et al (2008) A systematic review on quality indicators for tight glycaemic control in critically ill patients: need for an unambiguous indicator reference subset. *Critical Care*, 12:R139 (doi:10.1186/cc7114)
11. Wintergerst KA, Buckingham B, Gandrud L et al (2006) Association of hypoglycemia, hyperglycemia and glucose variability with morbidity and death in the pediatric intensive care unit. *Pediatrics* 118; 173-179
12. Egi M, Bellomo R, Stachowski E et al (2006) Variability of blood glucose concentration and short term mortality in critically ill patients. *Anesthesiology* 105:244-252
13. Ali NA, O'Brien JM, Dungan K et al (2008) Glucose variability and mortality in patients with sepsis. *Crit Care Med* 36:2316-2321
14. Meyfroidt G, Keenan DM, Wang X, et al (2009) Dynamic characteristics of blood glucose time series during the course of critical illness: effects of intensive insulin therapy and relative association with mortality. *Crit Care Med*: in press

15. de Graaff MJ, Spronk PE, Schultz MJ (2007) Tight glycemic control: intelligent technology or a nurse-wise strategy? *Crit Care* 11(5):421
16. Cordingley JJ, Vlasselaers D, Dormand NC et al (2009) Intensive insulin therapy: enhanced Model Predictive Control algorithm versus standard care. *Intensive Care Med* 35(1):123-8
17. Kucher N, Koo S, Quiroz R et al (2005) Electronic alerts to prevent venous thromboembolism among hospitalized patients. *N Eng J Med* 352:969-77
18. Morris AH (2000) Developing and implementing computerized protocols for standardization of clinical decisions. *Ann Intern Med* 132 (5):373-383
19. Rood E, Bosman RJ, van der Spoel JI et al (2005) Use of a computerized guideline for glucose regulation in the intensive care unit improved both guideline adherence and glucose regulation. *J Am Med Inform Assoc* 12:172-180
20. Morris AH, Orme J Jr, Truitt JD et al (2008) A replicable method for blood glucose control in critically ill patients. *Crit Care Med* 36: 1787-1795
21. DuBose JJ, Nomoto S, Higa L et al (2009) Nursing involvement improves compliance with tight blood glucose control in the trauma ICU: a prospective observational study. *Intensive Crit Care Nurs* 25, 101-107

APPENDIX 1: THE LEUVEN GUIDELINE FOR TIGHT GLYCEMIC CONTROL

This is the original Leuven guideline for tight glycemic control, as published on the department of intensive care medicine's intranet homepage. This guideline should be used with caution and common sense by an experienced nursing team. The authors, and the department of intensive care medicine of the University Hospitals Leuven, deny any responsibility for adverse events that would occur in patients when applying this guideline in any other setting than the ICU's of the Leuven University Hospitals.

Normoglycemia (80-110 mg/dl) is targeted for all adult critically ill patients. In order to achieve this, a continuous infusion of insulin is used (Actrapid®, NovoNordisk®) dissolved in 50 ml of NaCl 0,9% at a concentration of 1 IU per ml. Exceptionally, in case of high insulin needs, a 2 IU per ml solution is required.

Blood glucose is measured at one to four-hour intervals with the use of an accurate blood glucose analyzer, incorporated in the blood gas analyzer (ABL 800, Radiometer Medical, Copenhagen). Whole blood is used; results are reported as calibrated to plasma glucose. Upon ICU admission of the patient, blood glucose is determined. From then on, the sampling frequency depends on the blood glucose level: every hour when the last value is out of the 4.4-6.1 mmol/L range, every 4 hours when in range.

The initial blood glucose stabilization is performed as follows. The nurses start the insulin infusion at 2 IU/h when the first blood glucose value exceeds 110 mg/dl (6.1 mmol/L), and 4 IU/h when it exceeds 220 mg/dl (12.2 mmol/L). When the control value exceeds 140 mg/dl (7.8 mmol/L), they should increase the infusion rate with 2 IU/h; when it is between 110-140 mg/dl (6.1-7.8 mmol/L), increase with 1 IU/h. As soon as the blood glucose comes close to normal values, adaptations are made with 0.1-0.5 IU/h steps. When blood glucose is normal, the insulin infusion rate is kept at a constant level.

After this initial stabilization, the following rules apply. When the blood glucose drops with more than 50%, the insulin infusion rate is reduced by half and more frequent blood glucose checks have to be performed. When the blood glucose is between 60-80 mg/dl (3.3-4.4 mmol/L), the insulin infusion rate should be reduced depending on the previous value, and blood glucose checked within the next hour. When blood glucose is between 40-60 mg/dl (2.2-3.3 mmol/L), it should be evaluated whether caloric intake has not been accidentally interrupted, and blood glucose should be checked within the next hour. When blood glucose is lower than 40 mg/dl (2.2 mmol/L), it should be evaluated whether caloric intake has not been accidentally interrupted, 10 g of glucose should be injected intravenously and blood glucose checked within the next hour.

Insulin sensitivity may change during the course of critical illness. It may happen that in a normoglycemic patient at a steady insulin infusion rate, blood glucose will drop, indicating a improved insulin sensitivity. In that case, the insulin infusion rate should be reduced with approximately 20% and blood glucose checked within the next hour. When the patient develops fever, especially when suspected to be caused by an infection, the insulin needs will increase; the insulin needs will decrease again when the infection is under control.

The maximal infusion rate of insulin is arbitrarily set at 50 IU per hour.

With regards to the caloric intake of the patients, the guideline advises as rule of thumb “insulin follow caloric intake” and more specifically as follows. In order to avoid excessive blood glucose fluctuations, it is advised to administer all intravenous glucose containing solutions with an infusion pump. Enteral nutrition in our ICU is administered in 10 hour blocks, and interrupted twice for 2 hours to measure gastric residue. During these interruptions, it is very important to reduce the insulin dose proportionally. For a patient who is exclusively fed through the enteral route, this usually implies stopping the insulin infusion during the interruptions, or in some cases maintaining a very low dose of insulin (especially in these patients with a previous history of insulin dependent diabetes mellitus). When a patient is transported from the ICU, enteral or parenteral nutrition and insulin is usually interrupted. In order to stimulate appetite in an extubated patient, caloric intake is usually reduced or stopped. Insulin infusion should be adjusted or stopped as well.

Glucocorticoids decrease insulin sensitivity. In that case, more insulin will be necessary to maintain normoglycemia. In order to avoid blood glucose fluctuations, it is advised to administer the daily doses of glucocorticoids as a continuous IV infusion.

When the urine output of the patient is being substituted using a glucose containing solution, this implies infusing glucose at a rate that may vary every hour. It is advised to neutralize the glucose in the bag by injecting an appropriate amount of insulin.

Upon ICU discharge, a less strict insulin regime is installed, aimed at maintaining the blood glucose < 200 mg/dl (11.1mmol/L) on the nursing ward. When patients require insulin to maintain blood glucose levels below this level, they are likely to have (previously undiagnosed) diabetes and should be followed-up by a diabetologist on the regular ward. Such a consult should be arranged before discharge of the patient.

TABLES

Table 1 Patient characteristics

	Pre-alert (n=729)	Alert (n=644)	<i>p</i> -value
Age in years [median (P25-P75)]	66 (55-75)	64 (53-73)	0.123
Male gender [n (%)]	476 (65.4)	403 (62.6)	0.280
BMI (kg/m ²)[mean (SD)]	26 (5)	26 (5)	0.738
Admission blood glucose in mg/dl [mean (SD)]	145 (67)	145 (52)	0.702
Emergency admission [n (%)]	280 (38.4)	258 (40.1)	0.531
Length of stay in days [median (P25-P75)]	3.2 (1.8-9.9)	3.6 (1.8-8.1)	0.932
ICU Mortality [n (%)]	51 (7.0)	42 (6.5)	0.727

Table 2 Diagnostic category [n (%)]

	Pre-alert	Alert	<i>p</i> -value
Cardiac surgery	410 (56.2)	364 (56.5)	0.917
Solid organ transplantation	78 (10.7)	72 (11.2)	0.776
Complicated abdominal surgery	47 (6.5)	50 (7.8)	0.903
Complicated neurosurgery/neurology	40 (5.5)	22 (3.4)	0.065
Multiple trauma	30 (4.1)	36 (5.6)	0.202
Complicated lung and esophageal surgery	34 (4.7)	27 (4.2)	0.672
Complicated or high risk vascular surgery	33 (4.5)	27 (4.2)	0.762
Complicated or high risk cancer surgery	17 (2.3)	15 (2.3)	0.997
Severe burns	11 (1.5)	8 (1.2)	0.178
Other	29 (4.0)	23 (3.6)	0.694

Table 3 Quality measures of tight blood glucose control

	Pre-alert	Alert	p-value
Measures of blood glucose level or range			
Mean blood glucose per patient in mg/dl: median (P25-P75)	112 (105-122)	110 (104-119)	0.002
Hyperglycemic index in mg/dl: median (P25-P75)	10 (5-17)	9 (4-15)	0.004
Hypoglycemic index in mg/dl: median (P25-P75)	0.5 (0.1-1.1)	0.5 (0.1-1.1)	0.460
Glycemic penalty index: median (P25-P75)	20 (14-28)	19 (13-26)	0.029
Proportion of measurements per patient in the hyperglycemic range >110 mg/dl (%): median (P25-P75)	32.9% (21.4-46.7%)	30.0% (19.7-41.2%)	0.008
Proportion of measurements per patient in the hypoglycemic range <80 mg/dl (%): median (P25-P75)	6.2% (0-10.4%)	5.8% (0-10.9%)	0.845
Number of patients experiencing at least one hypoglycemic event < 40 mg/dl: n (%)	47 (6.5)	26 (4.0)	0.043
Blood glucose amplitude variation: standard deviation of the blood glucose time series			
Standard deviation of blood glucose time series per patient (mg/dl) [median (P25-P75)]	28 (22-38)	28 (21-37)	0.566
Blood glucose level monitoring			
Number of blood glucose samples per patient: median (P25-P75)	25 (13-63)	25 (13-57)	0.776
Number of blood glucose samples per patient per day: mean (SD)	7.7 (2.6)	7.7 (2.3)	0.891

FIGURES

Figure 1

The screenshot displays a medical software window with a blue title bar. Inside, there are two tabs: 'Event' (selected) and 'Details'. To the right of the tabs, it shows 'Waarde: 2' and 'Tijd: 04/09/2007 20:25'. The main content area has a red header bar with the text 'Ev_hypo40' and 'Kritiek!' (Critical!). To the right of the header is a yellow progress bar. Below the header, the text reads: 'De laatste glycemiewaarde is lager dan 40 mg/dl :', 'Stop onmiddellijk de Actrapidrip , controleer de voeding en geef 10g Glucose IV .', and 'Controleer opnieuw na 30 min .'. To the right of this text are three vertical buttons: an up arrow, a middle button, and a down arrow. Below this is a section titled 'Opmerkingen' (Remarks) with a list of two items, each with a document icon and a down arrow. To the right of the list are three vertical buttons: an up arrow, a middle button, and a down arrow. At the bottom right of the window is a yellow button labeled 'Bewaar' (Save).

Event Details Waarde: 2 Tijd: 04/09/2007 20:25

Ev_hypo40 Kritiek!

De laatste glycemiewaarde is lager dan 40 mg/dl :
Stop onmiddellijk de Actrapidrip , controleer de voeding en geef 10g Glucose IV .
Controleer opnieuw na 30 min .

Opmerkingen

Bewaar

FIGURE LEGENDS

Fig. 1 Screenshot taken from MetaVision ®. This 'critical' event message appeared whenever the blood glucose dropped below 40 mg/dl (<2.2 mmol/L). The message (translated from Dutch) is as follows: "The last blood glucose value is below 40 mg/dl. Stop the Actrapid infusion, check nutrition and administer 10 g of Glucose IV. Take a new blood sample after 30 minutes".