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Towards closed-loop glycaemic control

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Blood glucose control performed by intensive care unit (ICU) nurses is becoming standard practice for critically ill patients. New algorithms, ranging from *basic protocols* to *elementary computerized protocols* to *advanced computerized protocols*, have been presented during the last years aiming to reduce the workload of the medical team. This paper gives an overview of the different types of algorithms and their features. Performance comparisons between different algorithms are avoided as *blood glucose sampling frequencies* and *protocol durations* were not similar among different studies and even within studies. Particularly advanced computerized protocols can potentially be introduced as *fully*-automated blood glucose algorithms when accurate and reliable near-continuous glucose sensor devices are available. Furthermore, it is surprising to consider in some of the described protocols that the original blood glucose target ranges (80–110 mg/dl) were *increased* (due to fear of hypoglycaemia) and/or that glycaemia levels were determined in *capillary* blood samples.

Introduction

Critically ill patients, typically admitted to the ICU, show hyperglycaemia and insulin resistance associated with adverse outcomes. It has been demonstrated that strict blood glucose control results in an important reduction in mortality and morbidity.[1,2] Current therapy requires a manual and

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rigorous administration of insulin (''intensive insulin therapy'') by following a set of guidelines aiming at blood glucose levels between 80 and 110 mg/dl. Nevertheless, a survey study in England and the Netherlands revealed that only approximately 25% of the ICU wards of the hospitals under study effectively set the normoglycaemic target range at 80–110 mg/dl.[3,4] Some aspects may hamper the general application of tight glycaemic control (TGC) explaining why TGC is far from standard clinical practice at present.

A first important limitation of the intensive insulin therapy is the **increased workload** for the nurses. In general, the protocol requires blood glucose levels to be measured every four hours (or more frequently, especially in the initial phase or in case of complications). Next, the flow of the continuous insulin infusion is adjusted based on this insulin titration schedule which, however, only comprises *recommendations* giving the medical staff the ability to appropriately adapt the proposed insulin infusion rate depending on patient-specific features. Accordingly, this empirical protocol is no simple 'if-then' protocol and requires lots of clinical experience to correctly interpret the guidelines. Further, the insulin needs have drastically increased since the introduction of the intensive insulin therapy (due to the lower blood glucose target) such that nurses spend more time in preparing and refilling the insulin infusion pumps.

The threat of administering too much insulin to the patient (leading to **hypoglycaemia**) is a following barrier to intensive insulin therapy and may result in a rather 'conservative' (conventional) insulin treatment (characterized by **blood glucose target ranges higher** than 80–110 mg/dl).[5–7] The diagnosis of hypoglycaemic events in the ICU is more complicated than with patients with diabetes as sedation can mask (hypoglycaemic) symptoms of neuroglycopenia. Moreover, the counter-regulatory responses to hypoglycaemic events may be impaired in the critically ill.[8]

Finally, glycaemia control requires the **frequent monitoring** of the blood glucose. To safely target normoglycaemia in ICU patients, intensivists and ICU nurses anxiously await the availability of accurate and reliable near-continuous glucose sensors.[7,9–12] As these sensor devices may export glucose values every second or every minute, the fear of provoking hypoglycaemic episodes due to delivering too much insulin would significantly diminish.

Since the introduction of the intensive insulin therapy, different alternative algorithms and control systems that potentially provide *tight* (i.e., normoglycaemic) and *safe* (i.e., reduction of hypoglycaemic events) glucose control and that can reduce the nursing workload, have been proposed. Additionally, an 'objective' and approved computerized protocol (that is independent of the experience/skills of the nurse) may further facilitate the application of the intensive insulin treatment to critically ill patients word-wide. In this paper an overview of most known protocols and algorithms is given. However, a detailed *qualitative* comparison of these protocols is not straightforward as not all algorithms were described in detail. Further, a *quantitative* comparison (in terms of the obtained results) between algorithms is difficult since an assessment depends on the selected measure (e.g., average blood glucose) and the design of the study (e.g., blood glucose sampling frequency and duration that the algorithm was applied, which is related to the duration of stay in the ICU) as recently shown.[13] Therefore, the results that are obtained with each of these protocols are not compared to each other. The main focus of this review paper is the description of the different types of insulin infusion algorithms and their specific features.

Overview of different types of algorithms

Leuven guidelines

The two TGC landmark studies[1,2], performed in the Leuven University hospital, were based on a set of written guidelines applied by the nursing teams.[14] These guidelines only aim to *guide* the nurses in determining the insulin dose and are certainly **not** a strictly defined protocol. The need for insulin depends on insulin production reserves, insulin sensitivity before and during critical illness, caloric intake, and the severity and nature of the underlying disease.[15] Additionally, the occurrence of infections and the administration of medication (e.g., glucocorticoids) may severely affect the insulin resistance and the need for exogenous insulin, consequently. *Nurse-wise experience* is a major condition for adequately controlling blood glucose in this type of patients when applying these guidelines. For

this reason alternative algorithms that aim to reduce the nursing workload and to limit the prevalence of hypoglycaemia have been proposed.

Basic protocols or nomograms

The first type of alternative insulin protocols is the 'basic' protocol or nomogram. This is a detailed plan providing the nurse specific instructions concerning the treatment of patients. Nomograms have the advantage that implementation in the currently existing treatment therapy is rather simple and does hardly need any training of the personnel. When these protocols are sufficiently detailed such that patient-specific instructions are generated without judgment by a clinician, they are called 'explicit'.[16] The efficiency of these basic protocols, however, may be frequently insufficient since they are aimed to be used for a large group of patients leading to rather general protocols. Accordingly, nurses just follow the respective instructions avoiding any deviation from the protocol.

This group of protocols can be further subdivided in 'sliding scale protocols' and 'dynamic scale protocols'.[17,18] The first subgroup is characterized by the delivery of a predetermined insulin flow defined by the glycaemic range in which the actual blood glucose lies. Consider the following example. When the patient's blood glucose is between 110 mg/dl and 140 mg/dl, 1U/hr of insulin is administered; when the blood glucose is between 141 mg/dl and 170 mg/dl, 2U/hr of insulin are delivered; etc. The second subgroup comprises basic protocols that are founded on a dynamic scale. In that case, the next insulin rate is determined based on the previous insulin flow and the actual blood glucose. Even glycaemia trend information can be incorporated here. For example, if the patient's glycaemia lies between 110 mg/dl and 140 mg/dl, the previous insulin rate is increased by 1U/hr. Some known basic protocol examples, but not limited to this list, are given below:

Balkin et al.[19]

In this work the authors presented different tables for determining the amount of insulin. Depending on the previous insulin flow and the current and previous blood glucose the amount by which the insulin flow was changed could be easily found. This dynamic scale protocol could be labeled as pure 'feedback' as no future disturbances were taken into account. The default glycaemia sampling interval was two hours and the goal glycaemic range was 100–120 mg/dl although the protocol was only commenced at glycaemia levels above 150 mg/dl. In total, the protocol was applied to 188 patients (with a minimum duration of protocol application of 12 hours) divided over three different hospitals. The lowest obtained average blood glucose was 134 ± 44 mg/dl.

Chee et al.[20,21]

A closed-loop system, based on a sliding scale algorithm, was tested on five critically ill patients. The insulin dose was computed using a formula that consisted of three parameters: the basic dose (the basic sliding scale), the offset (that was related to the glycaemia trend), and a shutting-off parameter for insulin in case of hypoglycaemic events. The target glycaemic range was 108–180 mg/dl, which was significantly higher than that of the Leuven guidelines (80–110 mg/dl), and the insulin infusion rate was adjusted every hour. The computed mean blood glucose for these 5 patients (trial during 24 hours) was 189 ± 43 mg/dl.

Taylor et al.[22]

Two nurse-driven insulin infusion protocols were compared with a conservative physician-initiated protocol (i.e., no target blood glucose). The nurse-driven protocols were similar to each other but differed in thresholds for initiating and discontinuing insulin. The target glycaemic range was 120-150 mg/dl for the first protocol and 80–110 mg/dl for the second. There were 71 patients who received a physician-initiated insulin infusion, 95 patients who were involved in the study for the first nurse-driven protocol, and 119 patients for the second nurse-driven protocol, respectively. Further, this dynamic scale protocol was only based on the actual blood glucose and the glycaemia trend. The glycaemia sampling interval varied from one to four hours depending on the glycaemic stability. The average blood glucose in the group with the second nurse-driven protocol (132 mg/dl) was lower than

that of the group with the first nurse-driven protocol (163 mg/dl) and that of the group with the physician-initiated protocol (190 mg/dl).

Goldberg et al.[23,24]

The protocol defined in this study was another typical dynamic scale protocol that determined the next insulin rate based on the actual and previous (trend information) blood glucose and the previous insulin flow. The glycaemia sampling period was set at 1 hour and the target blood glucose range was 100-139 mg/dl. The protocol was applied to 52 medical ICU patients and 118 cardiothoracic ICU patients. The mean blood glucose of the first patient group was 125 ± 12 mg/dl for patients with a history of diabetes and 121 ± 18 mg/dl for patients without any history of diabetes. The duration of protocol application was variable ($\geq$72 hours in 48% of the cases). Mean blood glucose levels for the second group were 122 ± 17 mg/dl and 119 ± 14 mg/dl depending on the hospital.

Chant et al.[25]

The dynamic scale nomogram presented in this work was founded on the actual blood glucose value, the glycaemia trend, and the previous insulin flow. The target blood glucose range equaled 90-144 mg/dl and the glycaemia sampling interval mostly varied from 1 to 2 hours. The protocol was applied to 44 patients (admitted to a medical/surgical ICU) resulting in an average morning blood glucose of 128 ± 32 mg/dl. These results were compared to the glycaemic behaviour of 42 patients receiving a non-standardized insulin sliding scale (i.e., patient-specific alterations by the medical staff were permitted). In this last group an average morning blood glucose of 176 ± 50 mg/dl was obtained.

Kanji et al.[26]

Similar to the previous protocols, the next insulin rate was determined based on the actual and previous blood glucose and the previous insulin dosage. The sampling interval of this dynamic scale protocol varied from 30 minutes to 2 hours. The target blood glucose range was the same as used in the landmark studies: 80–110 mg/dl. The protocol was applied to 50 critically ill patients admitted to a mixed medical/surgical ICU. The results were compared to another patient group (50 patients) receiving a conservative physician-initiated treatment. Target glycaemia was achieved more rapidly and fewer patients experienced severe hypoglycaemia when using the proposed protocol. Nearly half of the glucose measurements (47%) fell in the target blood glucose range supporting the concept of standardizing intensive insulin therapy.

Chase et al.[27–29]

The Specialized Relative Insulin and Nutrition Tables (SPRINT) approach was an alternative dynamic scale protocol aiming to provide an easy-to-use 'paper' protocol (compared with the computerized protocols, see below). The SPRINT protocol comprised an insulin and a feed *wheel*. This protocol was progressive due to the presence of two manipulated variables: both insulin as well as nutritional input could be modulated. Accordingly, the actual and the previous glycaemia value, the previous insulin dosage, and the previous nutrition feed rate were used to determine the insulin and nutrition intervention for the next interval. The patient's age, body frame size, and gender could further influence the nutrition manipulation variable. The target glucose range was 72–108 mg/dl and glycaemia was measured every 1–2 hours. This SPRINT protocol was applied to 371 critically ill patients (with a varying duration in the ICU) and compared to a standard glucose management algorithm (with a significantly lower glucose sampling frequency) that was applied to 413 critically ill patients. The SPRINT protocol resulted in an average *lognormal* blood glucose of 108 ± 27 mg/dl with 54% of the measurements in the 80–110 mg/dl glucose range whereas the standard protocol returned an average *lognormal* blood glucose of 130 ± 43 mg/dl with 30% of the measurements in the 80–110 mg/dl glucose range.

Elementary computerized protocols

This category consists of standard computerized insulin infusion protocols that are based on rather rudimentary control laws. These protocols (e.g., computerized 'if-then' rules) mainly act as *decision*

support tools aiming to facilitate glycaemia control in the ICU. The obtained results dramatically differ depending on the considered protocol and may not give a clear view on the general effect of computerizing protocols.[30] Protocol examples of this category, not limited to this list, are illustrated below:

Rood et al.[31]

In this study a blood glucose regulation guideline was implemented in paper and computerized form. The actual and previous blood glucose combined with the previous insulin infusion rate determined the next insulin flow. The recommended time interval between two glycaemia measurements could range from 15 minutes to 3 hours and the target glycaemia range was set at 72–126 mg/dl. The computer protocol was tested on 66 patients and compared to the paper protocol that was applied to 54 patients. The duration of algorithm application did not remain constant. The time that was spent in the target range was 54% for the computerized and 53% for the paper protocol explaining that this difference was too small to be clinically significant. Compared to the results obtained with the paper protocol before (44% in target range) and after (42% in target range) this test phase, a clinically relevant improvement was found showing that integrated computerized guidelines are useful.

Davidson et al.[32]

The 'Glucommander' algorithm that was presented in this study was founded on the formula $F_I = (G\text{-}60)\,m$, where m symbolized a variable multiplier with starting value usually set at 0.01 or 0.02. Depending on the glycaemia trend and the actual glycaemia value, this multiplier was adapted leading to alteration of the insulin flow. The suggested time interval for the next sampling varied from 20 to 120 minutes with a target blood glucose range of 100–140 mg/dl. Data (>120000 glucose measurements), not limited to critically ill patients (most of the patients were admitted to general medical and surgical wards with a variable duration of algorithm application), were analysed giving mean glucose levels <150 mg/dl achieved in 3 hours. The authors claimed the proposed algorithm could be used in all units of any hospital, would be easy to use by nurses (no need for deviation from the algorithm), and could lead to a lower prevalence of hypoglycaemia (compared with the Leuven protocol). A derivative of this algorithm, with a target blood glucose range lowered to 80–110 mg/dl, was recently proposed by Boord et al.[33] The computer-based insulin protocol outperformed the manual nurse-driven protocol in terms of time spent in the target range.

Thomas et al.[34]

An electronic insulin dose calculator was developed based on the Leuven protocol but with a higher glycaemic target range: 97–128 mg/dl. The suggested insulin rate was determined based on the actual and previous glucose measurement and the previous insulin dose. The time interval between glucose measurements varied from 30 minutes to 4 hours. The study population comprised 288 patients (before introduction of protocol), 502 patients (after its introduction), and 101 patients (after introducing a modified protocol) and led to a decrease of the mean blood glucose (131 ± 32 mg/dl vs. 119 ± 29 mg/dl vs. 112 ± 23 mg/dl, respectively). The duration of algorithm application was not kept constant. The mortality rate remained similar during the study in spite of the tighter glycaemic control (possibly due to the higher target blood glucose compared to the Leuven trials) but the study was also not designed for showing potential survival improvements with TGC.

Meynaar et al.[35]

The computerized protocol presented in this study was based on a set of 'if-then' rules that considered the actual and previous blood glucose, the previous insulin flow and the amount of feeding (either ≤25 ml/hr or >25 ml/hr) as inputs to the system. The target blood glucose range was 81–135 mg/dl and mean blood glucose decreased from 166 mg/dl (without protocol) to 138 mg/dl (with protocol, 179 patients and with a variable duration of algorithm application). The time to the next glucose measurement could vary from 30 minutes to 4 hours.

Shulman et al.[30]

An insulin protocol was implemented into a bedside clinical information system aiming at blood glucose levels between 80–110 mg/dl. A relative adaptation of the insulin flow was suggested based on

the actual and the previous measured glucose. Blood glucose was sampled every 15 minutes, every one or two hours or even every 4 hours depending on the observed glucose profile. The protocol was applied to 50 critically ill patients (with a variable duration of algorithm application) leading to a median 23% of the time spent in the target range (nearly half of the time the measured glycaemia values fell in the range 111–144 mg/dl). The rather low percentage in the target range explained why the authors concluded that the used protocol (independent of the paper or computerized format) was not efficient for TGC.

Vogelzang et al.[36]

This work presented a computer program, GRIP (Glucose Regulation for Intensive care Patients), that recommended insulin infusion adaptations mainly based on the mean insulin flow over the last 4 hours, the deviation from the actual blood glucose to the target glycaemia (that was set at 117 mg/dl), the glycaemia trend over the last 4 hours, and changes in the administration of enteral or intravenous glucose calories. The advised sampling interval could vary from 30 minutes to 12 hours. The GRIP system was tested on 179 patients (with a variable duration of algorithm application and a median 4.9 glucose measurements per day). The target blood glucose range (72–135 mg/dl) was achieved for 78% of the time favoring the use of computer-driven protocols over nurse-driven protocols.

Morris et al.[37]

Recently, the 'eProtocol-insulin' algorithm was tested in four different ICUs in four hospitals (ranging from 31 to 458 patients). This new protocol had a target range of 80–110 mg/dl. The initial insulin infusion rate depended on the patient's body mass and the initial blood glucose. Relative adjustments of the insulin dose were based on previous insulin flow, current blood glucose and glycemia trend over the last two measurements. The 'eProtocol-insulin' algorithm was compared with a simple guideline and a paper-based protocol leading to better results for the 'eProtocol-insulin' algorithm in terms of higher number of glucose measurements within target range (39–42% for 'eProtocol-insulin') and lower mean blood glucose (115–116 mg/dl for 'eProtocol-insulin'). Blood glucose sampling intervals and durations of algorithm application were not similar among the different study groups. Since 91 to 98% of the 'eProtocol-insulin' recommendations were effectively accepted by bedside clinicians, the proposed protocol was labeled replicable and exportable.

Advanced computerized protocols

The last (and probably most promising) category of protocols is founded on more advanced engineered *controllers*. Advanced control theory (typically optimization-based) is considered in this type of algorithms. Most efficient and used control technique in this category is model based predictive control (MPC). A MPC strategy is explicitly founded on a model (set of mathematical equations) that describes the dynamic glucoregulatory system of a patient. This 'patient model' is used to *predict* the effect of future (known) disturbances on the blood glucose. Accordingly, future known disturbance factors can be taken into account (using this 'patient model') when determining the most *optimal* insulin infusion dose. Examples of advanced computerized protocols are listed below:

Chase et al.[38–40]

A control algorithm (*different from MPC*) modulating intravenous insulin infusion and bolus with an enteral feed rate was developed in this work. Therefore, a two-compartmental model was used to determine nutritional flow variations. Further, the insulin sensitivity was initially estimated with the glucose data of the first hour (sampling interval equaled 15 minutes) and adapted as a function of previously computed insulin sensitivities. The target blood glucose range was 72–108 mg/dl though the target glycaemia reduction in the control algorithm was set at only 10–15% per hour in case of blood glucose values larger than the target range. Every hour, the insulin bolus size, insulin infusion rate and nutritional feed could be iteratively determined based on the estimated insulin sensitivity, the used model, and the glucose values (sampled every 30 minutes) with the aim to achieve the target glycaemia at the end of the next hour. The system was applied to 8 proof-of-concept clinical trials of

whom the duration of algorithm application was 10 hours for seven patients and 24 hours for one patient showing acceptable stepwise glycaemia reduction.

Hovorka et al.[41,42]

These studies presented the clinical feasibility of using a MPC format for normalizing blood glucose in the critically ill. The model was based on former studies in patients with diabetes.[43] Incoming glucose measurements were used to update the model parameters. The blood glucose profile, the previous insulin flow, and the (future) carbohydrate calories determined the next insulin infusion dosage. The target blood glucose range was set at 80–110 mg/dl and the sampling frequency was variable (depending on the estimated prediction accuracy). The initial study[42] considered a one hour glycaemia sampling interval, which was found to be too short for use in clinical practice.[44] The updated MPC version was applied to 30 critically ill patients and compared to a standard glucose management algorithm (also 30 patients). The duration of algorithm application was set at 24 hours and the average sampling interval was 1.5 ± 0.3 hours (compared to 2.1 ± 0.2 hours for the standard protocol). The obtained average blood glucose values were 112 ± 20 mg/dl for the MPC approach and 130 ± 20 mg/dl for the standard approach. The percentage of the measurements in the target range was found to be 60% for the MPC approach and 27% for the standard approach. Though the comparisons between the two approaches may be partly falsified (due to the different average blood glucose sampling frequencies in both groups), this study clearly shows the potential of using MPC to normalize blood glucose in critically ill patients.

Van Herpe et al.[45,46]

This work introduced the design of a similar MPC approach that, however, incorporated the developed Intensive Care Unit – Minimal Model (ICU-MM)[47] as patient model, which was especially designed for describing the glucoregulatory system of the critically ill. So far, this predictive controller was tested only in simulation using the first 48 hours-after-admission data of 19 critically ill patients. The ICU-MM was initially estimated with the near-continuously monitored glucose data of the first 24 hours and the glucose profiles were simulated (using the insulin flows determined by the MPC) for the next 24 hours and compared with the real data of the second 24 hours. Accordingly, the duration of algorithm application was set at 24 hours. The controller was able to adapt the insulin infusion rate every hour or every four hours based on the measured glucose signal, the recent insulin dosage profile, and the (future) flow of carbohydrate calories. The simulation results were satisfactory in terms of control behaviour (reference tracking and the suppression of unknown disturbance factors). The proposed control system is potentially suitable to control glycemia in the ICU and will be soon tested in real-life.

Discussion

The previous overview presents the evolution of the Leuven TGC guidelines to some basic insulin infusion protocols to elementary computerized protocols and to more sophisticated blood glucose controllers. Particularly the use of the last group of controllers can potentially lead to *fully*-automated TGC (automated adaptations of the insulin flow, without confirmation by nurses, aiming at normoglycaemia) reducing the workload of the nursing team and the prevalence of hypoglycaemic episodes. A few remarks should be stressed, however.

First of all, it is surprising to see that the **blood glucose target values** were raised in many of the studies presented above although the two landmark Leuven studies[1,2] clearly showed a significant reduction of mortality and morbidity in case of TGC between the narrow limits 80–110 mg/dl. The most important reason for this is the fear of hypoglycaemia as the lower glycaemia threshold (80 mg/dl) appears to be *too low*. In general, hypoglycaemia is defined as blood glucose values lower than 50 mg/dl with neuroglycopenic symptoms or blood glucose values lower than 40 mg/dl in the absence of these symptoms.[7] Infusing insulin (aiming at normoglycaemia) bears the risk of inducing life-threatening hypoglycaemic events, particularly in sedated patients[7,41] and explains why this strict target range was elevated in many protocols: hypoglycaemia is often considered more dangerous than hyperglycaemia.

Though the incidence of hypoglycaemia was comparable to the Leuven landmark studies (11%), two trials were prematurely stopped due to the apparently unacceptable high number of hypoglycaemic events. The German VISEP (Volume Substitution and Inulin Therapy in Severe Sepsis) trial[48], which was stopped after the inclusion of 488 patients, reported 12% for incidence of hypoglycaemia in the intensive treatment group without any significant reduction of mortality. The European GLUCONTROL study[49], that was stopped after the inclusion of 1109 patients, notified 10% as relative number of patients who have experienced at least one hypoglycaemic episode. The median blood glucose was found to be 118 mg/dl (IQ range: 109–131 mg/dl). It is obvious that the applied insulin infusion protocol in these two studies was not adequate to achieve TGC as patients were exposed to increased hypoglycaemic risks (incidence of hypoglycaemia was comparable to the intensive insulin patient group of the Leuven trials) without bringing the benefit of TGC (i.e., reaching normoglycaemia leading to a reduction of mortality and morbidity). Moreover, both studies were underpowered such that any conclusion concerning the mortality rate could not be statistically validated.

Nevertheless, some authors advise to set higher blood glucose targets (e.g., target glycaemia $<$140–150 mg/dl to avoid these hypoglycaemic risks[49]). However, as often unstressed in articles, the Leuven landmark studies[1,2] compared the *intensive* insulin treatment (aiming at blood glucose levels between 80–110 mg/dl) with the *conventional* treatment (administration of insulin only if the blood glucose level exceeded 215 mg/dl and then maintenance of glucose at a level between 180–200 mg/dl). In the conventional treatment, however, blood glucose was not *forced* to lie in this 180–200 mg/dl target range.[1,2] In other words, when glycaemia was below 180 mg/dl the insulin flow was *not* adapted aiming at blood glucose values between 180–200 mg/dl. Accordingly, the obtained average morning blood glucose of the conventional patient group was 153 ± 33 mg/dl for the first[1] and 153 ± 31 mg/dl for the second landmark study.[2] Surprisingly, these averages are similar to the recommended target blood glucose mentioned in some studies described above. The landmark studies clearly showed the relation between mortality/morbidity reduction and TGC (80–110 mg/dl) suggesting the conventional treatment may be harmful to patients. The studies from above, however, illustrate that some newly proposed insulin titration algorithms still use 'more conventional' target blood glucose ranges which are *not* related to the mortality/morbidity reduction.

Application of the intensive insulin therapy in the critically ill is expected to reduce absolute mortality by 3 to 4% and even to 8% when the therapy is continued for at least three days.[1,2,50] Confirmation of this 3 to 4% absolute mortality reduction in similar studies (with a sufficient power) would require a sample size of at least 5000 to 6000 patients.[50] The Australian and New Zealand NICE-SUGAR (Normoglycaemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation) multicenter trial[51], which is currently still ongoing, may have sufficient statistical power to confirm the mortality reduction when applying TGC in a mixed medical/surgical patient population. While awaiting the results of the NICE-SUGAR study it is recommended to consider 80–110 mg/dl as target blood glucose range in the critically ill as many studies have already shown that many lives were saved with the intensive insulin therapy.[1,2,52,53] Indeed, hyperglycaemia is more deleterious than hypoglycaemia in this type of patients. Moreover, incidental, brief episodes of hypoglycaemia may not cause serious harm when appropriately and rapidly treated[4,54,55] confirming the recommended compromise between perceived safety concerns (avoiding hypoglycaemia) and published evidence (avoiding hyperglycaemia). Finally, it is important to stress that no association between hypoglycaemia and early or late mortality was found in a recent study.[55]

Secondly, it is **hard to compare** the results of different studies due to the non-uniform evaluation strategy and the different study designs. In most studies a new (computerized) insulin infusion algorithm is compared to a more conservative (nurse-driven) protocol. However, the selected assessment measure (e.g., mean morning blood glucose, mean blood glucose, time spent in target range, hyperglycaemic index (HGI)[56], number of hypoglycaemic events, etc.) or the combination of measures differ over the mentioned studies. Moreover, definitions of the target glycaemic range, hypoglycaemia, and others are dependent on the study. The use of the glycaemic penalty index (GPI), as recently presented[13], can potentially lead to a uniform evaluation strategy in future studies. Next, the

study design can falsify the obtained results.[13] At least the *duration that the algorithm is applied to the patient* (related to the time spent in the ICU) and the *blood glucose sampling frequency* can mislead evaluations when they are not similar among patient groups. Accordingly, performance comparisons of algorithms published in different studies (e.g., computer protocol 1 presented in study 1 versus computer protocol 2 presented in study 2) or even within a study (e.g., computer protocol versus nurse-driven protocol) may be false.

Thirdly, it is remarkable that some studies **tend to compare** the results obtained with a newly proposed algorithm **to the results of the Leuven landmark studies** without taking into account the influence of external factors. For example, the reduction of the number of hypoglycaemic events or the improvement of the TGC level (compared with the Leuven trials) are often mentioned without considering possible study design differences regarding blood glucose sampling frequency, duration of algorithm application, type of patients, etc. (see for example[9,32]). Furthermore, it is important to note that the Leuven nursing team only applied some titration *guidelines* instead of fixed 'if-then' rules. However, in simulation studies these Leuven guidelines are typically transformed to an 'if-then' protocol, which is obviously not identical to the real set of guidelines (that allow interpretation by the nurses) generating misleading conclusions (see for example[28]).

Next, most of the present insulin infusion algorithms have only one **manipulation variable** (i.e., insulin). Few exceptions are the studies described by Chase and co-workers[27–29,40] in which both insulin flow and rate of nutritional calories are determined by the control algorithm. From a control perspective, the incorporation of this additional manipulation variable may give more freedom to the algorithm to improve the performance of the control system. However, widespread use of a system with two manipulation variables does not seem to be accepted yet for clinical standard practice as the rate of nutritional calories is typically based on a set of measured patient-specific parameters. Moreover, it was shown that intensive insulin treatment works irrespective of the load of parenteral glucose calories[57] explaining there is no urgent need to have the flow of nutritional calories determined by the control algorithm. An alternative approach to potentially increase the performance of a control system could be the inclusion of a glucose/glucagon manipulation variable that is only aimed to pick up rapidly evolving hypoglycaemic episodes. Accordingly, the fear of hypoglycaemia due to the intensive treatment with insulin could diminish. Nonetheless, it is likely that this extra feature may only be incorporated in the first commercial (fully-)automated blood glucose control system if a *reliable* near-continuous glucose sensor is available.

Finally, it is remarkable that some studies were based on **capillary** glucose measurements (i.e., the 'fingerstick' which is typically used for glucose monitoring by patients with diabetes).[19,22,25–27,32,35,40,58] Capillary samples should be avoided to be used with unstable ICU patients as hypoperfusion can lead to unreliable glucose measurements at the capillary level as previously shown.[59–63]

Summary

The interest to design a computerized algorithm (control system) for semi- or fully-automated blood glucose control in the ICU is increasing.[64] During the last years different control strategies, evolving from basic protocols to intelligent technology algorithms, have been presented. Particularly the use of advanced computerized protocols can potentially lead to the introduction of TGC worldwide (even leading to a further reduction of the mortality/morbidity rate) while reducing the incidence (and fear) of hypoglyceamia. The use of *fully*-closed-loop systems in the ICU may only be feasible if a reliable near-continuous glucose sensor (validated in the critically ill) is available. Current *semi*-closed-loop systems (that require confirmation of the proposed insulin dosage by the nurse) are expected to be commercially available as soon as the required blood glucose sampling frequency is acceptable (e.g., sampling intervals between 1 and 4 hours). Further, when comparing/validating control systems the similarity conditions (with regard to, at least, the blood glucose sampling frequency and the duration of algorithm application) and the efficiency of the measure (e.g., HGI, GPI) should be taken into account.

Practice points

- Blood glucose target values in many algorithms developed for controlling glycaemia in the critically ill are raised (due to fear of hypoglycaemia) compared to the original landmark targets (80–110 mg/dl).
- The blood glucose sampling frequency and the duration of algorithm application should be similar among patient groups when comparing algorithms.
- Most blood glucose protocols contain only one manipulation variable (insulin) though the inclusion of an additional variable (glucose/glucagon) may improve the level of control.
- Particularly advanced computerized protocols can potentially improve the level of TGC while reducing the workload of the medical personnel.

Research agenda

- A reliable and accurate near-continuous glucose sensor to be used in the critically ill is still under development and requires an appropriate validation in a similar patient group.
- Further research is warranted to design more advanced computerized protocols (that can potentially be used in *fully*-automated blood glucose control systems). Adequate evaluations and comparisons with nurse-driven protocols based on large patient data sets are required.

Conflict of interest

The authors declare that they have no competing interests.

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