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REVIEW

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Tight glycemic control and computerized decision-support systems: a systematic review

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Abstract *Objective:* To identify and summarize characteristics of computerized decision-support systems (CDSS) for tight glycemic control (TGC) and to review their effects on the quality of the TGC process in critically ill patients.
Methods: We searched Medline (1950–2008) and included studies on critically ill adult patients that reported original data from a clinical trial or observational study with a main objective of evaluating a given TGC protocol with a CDSS.
Results: Seventeen articles met the inclusion criteria. Eleven out of seventeen studies evaluated the effect of a new TGC protocol that was introduced simultaneously with a CDSS implementation. Most of the reported CDSSs were stand-alone, were not integrated in any other clinical information systems and used the "passive" mode requiring the clinician to ask for advice. Different implementation sites, target users, and time of advice were used, depending on local circumstances. All controlled studies reported on at least one quality indicator of the blood glucose regulatory process that was improved by introducing the CDSS. Nine out of ten controlled studies either did not report on the number of hypoglycemia events (one study), or reported on no change (six studies) or even a reduction in this number (two studies).
Conclusions: While most studies evaluating the effect of CDSS on the quality of the TGC process found improvement when evaluated on the basis of the quality indicators used, it is impossible to define the exact success factors, because of simultaneous implementation of the CDSS with a new or modified TGC protocol and the hybrid solutions used to integrate the CDSS into the clinical workflow.

Keywords Systematic review · Tight glycemic control · Insulin · Computerized decision-support system · Critically ill patients · Critical care

Introduction

Blood glucose control aiming at normoglycemia (i.e., blood glucose levels 80–110 mg/dl), frequently referred to as "tight glycemic control", has been shown to reduce mortality and morbidity of critically ill patients [1, 2] although its implementation bears the risk of hypoglycemia [1, 2]. Applying tight glycemic control (TGC), however, requires additional efforts, especially from the nursing staff who are expected to adhere to the TGC protocol. Such protocols are often complex, requiring specific timing of blood glucose level (BGL) measurements, and the availability of patient-specific data. One way to support nurses in adhering to protocols is by applying information technology, in particular clinical computerized decision-support systems (CDSSs).

In general, a CDSS is a computer program that is intended to help healthcare workers in making decisions [3]. A CDSS can be characterized by the level of support, the consultation mode, and the communication style. The level of support ranges from general to patient-specific: e.g., from merely displaying the protocol chart to suggesting the specific amount of insulin to be administered. Some systems are passive, providing advice only on demand, whereas others are active, providing feedback to the healthcare worker without being asked for it. Finally, regardless of the level of support and the consultation mode, a CDSS may operate in two communication styles: in the critiquing mode the system provides advice which is dependent on the adherence of clinical practice to a protocol (e.g., notifying the nurse that a BGL measurement has been expected but not performed), in the non-critiquing mode it provides advice regardless of whether a protocol is followed or not [4]. Notwithstanding the potential benefits of CDSSs, issues pertaining to their design, implementation, evaluation, and to critical success factors, are largely still open. Glucose regulation is specifically interesting as it forms an application in which a CDSS is applied in a highly controlled clinical practice. Therefore lessons learned from glucose regulation CDSSs can be used for other highly controlled clinical practices, for example mechanical ventilation and blood-pressure control.

The objective of this systematic review is to identify and summarize characteristics of CDSSs and to review their effects on the quality of the TGC process in published studies on the use of CDSS in TGC for critically ill patients.

Methods

We searched for relevant English language articles based on keywords in title, abstract and MeSH terms, using Ovid Medline and Ovid Medline In-Process (1950 to December 31, 2008). The final literature search was performed on January 11, 2008.

Figure 1 shows the applied search strategies and the corresponding search flowchart. In the first stage (A), we searched for terms related to glucose and insulin. In the second stage (B) we limited the search using the terms "critical illness" or "critical care" or "intensive care". In the third stage (C), keywords and MeSH terms referring to a decision-support system were searched. The results of these three stages were combined using the Boolean operator "AND". Searching was supplemented by scanning bibliographies from identified articles.

Two reviewers independently examined all titles and abstracts. Discrepancies among the two reviewers were resolved by consensus involving a third reviewer. Articles were selected if they reported original data from a clinical trial or observational study on critically ill adult patients and only if one of their main objectives concerned the evaluation of a given TGC protocol with a CDSS. A study was included if the TGC protocol implied an upper normoglycemia limit of, at most, 150 mg/dl. Opinion papers, surveys, and letters were excluded.

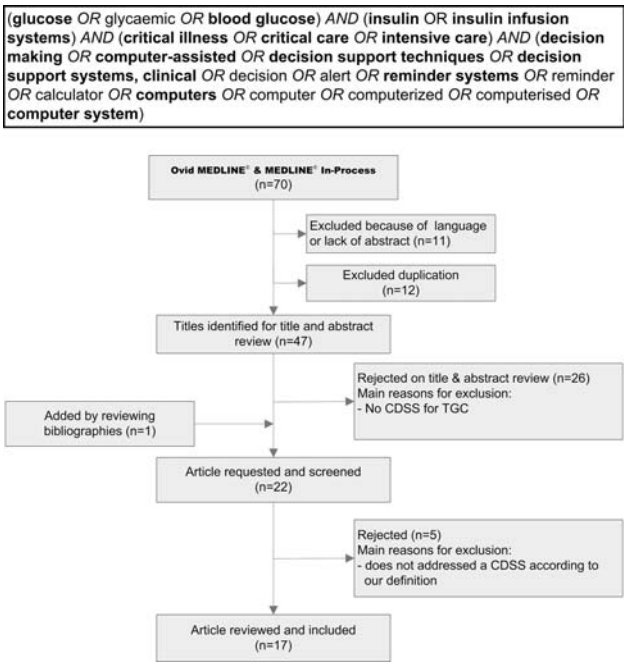

Fig. 1 The search strategies applied and the search flowchart. The *bold* terms are MeSH terms

From the selected papers, the same two reviewers extracted data on the following items:

1 method and study design aspects;
2 CDSS characteristics;
3 TGC quality indicators in terms of their definition and applicability; and
4 data on the effect of the CDSS on the quality of the TGC process or mortality or morbidity.

A quality indicator was defined as a measurable quantity of the TGC process that may, alone or in combination with other quantities, indicate some aspect of its quality. Discrepancies between the two reviewers were again resolved by consensus after involving the same third reviewer.

To obtain insight into the heterogeneous nature of these evaluation studies and according to the hierarchy of study designs developed by the University of California San Francisco Stanford Evidence-Based Practice Center we classified the studies into:

– randomized controlled trial (level I),
– non-randomized controlled trial (level II),
– observational study with controls (level III), and
– observational study without controls (level IV) [5, 6].

Results

Searching the online databases resulted in 70 articles. Initial screening of titles and abstracts rendered 21 articles eligible for further full-text review. One additional article was identified by reviewing bibliographies, yielding a total of 22 articles. Based on the full text review, five studies were excluded because they turned out not to address a computerized system, leaving 17 articles for detailed analysis.

Table 1 lists the materials (included patients and study locations), TGC target range, design, and results of these 17 studies. Table 2 summarizes the CDSSs' characteristics. Table 3 reports all the used quality indicators of the TGC process.

Methods and study design aspects

There were three randomized clinical trials, seven controlled before/after trials, and seven observational studies. In two studies only information was given on how often the CDSS was used, in one of these studies this information was only given for the three months after the study period.

In only one study the same TGC protocol was used before and after the implementation of CDSS. In five other studies a modified version of the TGC protocol was used after the implementation of the CDSS. Two of these five studies evaluated the same CDSS and the protocol used, but in another setting. Eleven out of seventeen studies evaluated the effect of a new TGC protocol introduced at the same time with the implementation of the CDSS. Three of these eleven studies also evaluated the same CDSS and the protocol in different settings.

CDSS characteristics

Most of the reported CDSSs (14 out of 17) were stand-alone and were not integrated in other clinical information systems, for example computerized physician order entry systems, patient data management systems, or intelligent pumps. CDSSs in all studies were "patient specific" and operated in the "critiquing" mode. This means that decision support was given if clinical practice for a patient was not according to the protocol. Reminders on the time of the next BGL measurement were "active" in nine out of seventeen studies. "Active" means that the users automatically received the reminder without manually asking for it. Support for insulin pump speed was "active" in one study only; the others used the "passive" mode for pump adjustments requiring the clinician to ask for advice.

In five studies the protocols were based on "if–then" statements on a sliding scale. They contained a list of simple rules, with a condition (the "if" part) and a conclusion part (the "then" part). The condition was based on the value of the current BGL measurement. The conclusion specified the corresponding insulin amount (or insulin pump speed) and the time interval until the next BGL measurement. In the other 12 studies the protocols were formula-based. Formula-based protocols rely on an familiar and simple equation: insulin dose/hour = [BGL − 60] × multiplier (insulin sensitivity) [7], which was sometimes adapted. In this group of studies, a default number for the multiplier was considered as the starting point for TGC. Based on the latest BGL values and a statistical model, the multiplier was recalculated and these values were used to calculate the required next pump speed.

In most studies (14 out of 17), users manually entered the BGL values and pump speeds into a separate CDSS database, because these data were not electronically available or they were not connected to the CDSS. In three other studies these data were electronically retrieved from a laboratory or a hospital information system.

Quality indicators

Twenty-four different indicators of glycemic control were extracted (Table 3). Hypoglycemia-related indicators were used in 14/17 studies as a proxy for safety. Six different thresholds varying between 40 and 70 mg/dl were used to define a hypoglycemia event. The most often used indicators were BGL summaries such as mean or median BGL (15/17 studies), the number of measurements in a predefined target range (10/17), the frequency of BGL measurements (9/17), the time needed to reach the defined BGL target (8/17), the time spent in the predefined BGL range (7/17), or compliance to protocol (6/17). Hyperglycemia-related indicators (number of hyperglycemia events and hyperglycemia index) (6/17) were other frequently used indicators. Because of different target ranges, comparing these indicators is difficult. Lower limits of target ranges varied from 80 to 100 mg/dl. Similarly, the upper limits of target ranges varied from 110 to 150 mg/dl.

Effect of the CDSS on the quality of the TGC process

All controlled studies reported on at least one quality indicator that was improved by introducing the CDSS (with or without the new protocol). Among controlled studies, one study reported that the number of hypoglycemia events increased, but without mentioning whether this increase was statistically significant. Among other

Table 1 Description of study design, TGC target range, and results of the 17 included papers on DSS for TGC implementation

Level	Ref.	Materials	Target range and monitoring interval	Design	Result
I	[23]	50 patients, nine-bed medical ICU, 72 h of ICU stay	TR: 80–110 M: NM	Prospective, five months, RCT	Median BGL and HGI were significantly lower in the CDSS group [BGL 106; HGI 7.2] than in control patients [BGL 133, $p < 0.001$; HGI 29, $p < 0.001$]. One hypoglycemic episode was detected in the CDSS group but none in the control group. Sampling interval was significantly shorter in the CDSS group [117 min vs. 174 min; $p < 0.001$]. Thirty out of thirty-four nurses answered the question of whether the algorithm could be applied in daily routine in the affirmative.
	[24]	40 patients with diabetes mellitus and scheduled cardiac surgery, Cardiothoracic ICU. Operation time and first 9 h in ICU	TR: 90–150 M: 15 min–4 h	Prospective, RCT	The mean BGL (147 vs. 126, $p < 0.01$) and the mean time to capture range (171 min vs. 40 min, $p < 0.001$) decreased during the ICU stay. Patients in the CDSS group spent more time in the desired range during both the intraoperative phase (49 vs. 27%, $p < 0.001$) and the ICU phase (84 vs. 60%, $p < 0.0001$). There were no statistical differences between groups in the number of hypoglycemia episodes.
	[8]	484 patients, 18-bed medical-surgical IC, ≥24 h in ICU	TR: 72–126 M: 15 min–3 h	Prospective, 10–6–10–4 weeks, before protocol–paper-based–randomized between paper-based or CDSS–paper-based protocol	In the paper-based period, 29% of the samples occurred with optimal timing; during the second period, this increased to 35.5% for paper-based and to 40.2% for computerized protocols. In the third study period timeliness scores reverted to the first period rates. The same occurred for late sampling and insulin dose compliance. For the second study period, the time that a patient's BGL fell within the target range improved for both the control (52.9%) and computerized (54.2%) groups compared with the first study period (44.3%), the third period (42.3%), and before TGC (22%).
II	[9]	552 trauma admissions, 31-bed ICU	TR: 80–110 M: 2 h in manual and 1–2 h in computerized protocol	Retrospective, 4 + 3 months, before/after	Median number of BGLs was 18 in control vs. 12 (4–54) in intervention group ($p = 0.27$). Mean BGL was lower (116 vs. 12; $p < 0.001$), and median BGL measurement interval decreased (2.79 vs. 2.14; $p < 0.001$). Percentage of range BGL increased (41.8 vs. 34.0%; $p < 0.001$), hyperglycemia and hypoglycemia frequency decreased (12.8 vs. 15.1% and 0.2 vs. 0.5%; both $p < 0.001$), and within 12 and 24 h more patients reached normalization (69.7 vs. 62.1%; $p = 0.47$ and 79.8 vs. 77.7%; $p = 0.88$). For post-initiation, computerized protocol entries compliance to protocol's recommendations was 98%.
	[22]	1,080 patients, four ICUs	TR: 80–110 M: 15 min–2 h in paper-based protocol and 1–4 h in computerized	Prospective, 22 months, controlled	Compliance with eProtocol-insulin advice was 91–98% among the four ICUs. Compared with the simple guideline, eProtocol-insulin BGLs in target increased from 21 to 39% ($p < 0.001$) and mean BGL decreased from 142 to 115 ($p = 0.001$). Number of measurements and patients with at least one hypoglycemic event did not change significantly.
	[10]	2,398 patients, progressive care unit and mixed medical-surgical ICU.	TR: 80–110 M: 15 min–2 h	Retrospective, 17 months, Observational, 3 + 3 before/after	61% of BGL were in target range, mean BGL was 106, and hypoglycemia frequency was 0.4%. After a hypoglycemia event the mean interval until next measurement was 26 min, and the mean next BGL measurement was 106. Achieving the target range (with mean BGL of 98) required 6.9 h. Percentage of measurements <110 increased from 32 to 52% due to intervention ($p < 0.001$). The frequency of hypoglycemia decreased from 0.5 to 0.4%.
	[25]	97 coronary artery bypass graft patients, six-bed Cardiothoracic ICU, first 48 h after surgery	TR: 80–120 M: 15 min–2 h	Retrospective, 5 + 5 months, before/after	There was a decrease in mean BGL (in first 48 h) from 154 (only type 2 diabetic patients included) to 118 in type 2 diabetic patients and 116 in non-diabetic patients ($p < 0.0001$), in percentage not in target range within 48 h (26 vs. 4.6% and 3.0%, $p < 0.0001$), in mean time to capture the target range (22.1 vs. 8.7 h and 5.9 h, $p < 0.0001$) and in hyperglycemia index (41.34 vs. 12.97 and 8.46, $p < 0.0001$). The hypoglycemia rate was not significantly increased after the intervention (1.14 vs. 1.42% and 1.94%, $p = 0.26$).
	[26]	129 + 128 trauma patients, ≥72 h in ICU	TR: 80–130 M: not mentioned	Retrospective, 6 + 6 months before/after	Significant reduction in mean BGL and total infection in all LOS categories were demonstrated after intervention. However, case mix adjusted mortality was significantly higher after the intervention. The percentage of hypoglycemic patients did not change (31 vs. 32%).
	[15]	351 patients, 21-bed surgical ICU, first five days in IC	TR: 80–110 M: 1 h in manual protocol and 1–2 h in computerized protocol	Retrospective, 32 + 49 days before/after	The computer-based protocol reduced time from first BGL measurement to initiation of insulin protocol, improved the percentage of in-range BGL (29.3 vs. 37.7%; $p = 0.006$), and patients on IIT for ≥24 h were on average 116 min more in target range ($p = 0.029$). The overall mean BGL for the first 5 days of IC admission were non-significantly lower in post-intervention group (129 vs. 134). Hypoglycemia was rare in both groups (0.2% of measurements).
	[11]	891 patients, 16-bed ICU, at least 24 h in IC	TR: 97–128 M: 30 min–4 h	Retrospective, 9 + 15 + 5 months before/after	The mean BGL decreased from 131 before intervention to 119 thereafter and then to 112 after the first revision. The proportion of values <144 increased from 69 to 81% and then to 89%. One episode of hypoglycemia was observed before the intervention, 13 after intervention and then six after revision. The hit counter added to the calculator after the end of study showed the monthly use was 1,175 hits on average.

Table 1 continued

Level	Ref.	Materials	Target range and monitoring interval	Design	Result
IV	[27]	661 patients, 16-bed ICU	TR: 97–128 M: 30 min–4 h	Prospective, 12 months, observational	Mean BGL was 121. There were 34 episodes of treated hypoglycemia 11 of which were on an IIT. There were two troughs in the time of data entry that corresponded with staff handover. There was no evidence of diurnal variation in BGL.
	[17]	2,800 patients, three ICUs (surgical, neurosurgical and cardiothoracic).	TR: 72–135 M: 30 min–12 h	Prospective, 30 months, observational	Patients were on GRIP-ordered pump rates 97% of time. Median measurement time was 5 min late (IQR 20 min early to 34 min late). Hypoglycemia was uncommon (7% of patients for <63; 0.086% for <40). Median time to capture target range was 5.6 h (0.2–11.8) and maintained for 89% (70–100) of the remaining ICU stay. The glucose variability was 22 (14.4–31.5). The frequency of measurements was 5.9 (4.8–7.3) per patient-day or once every 245 min.
	[28]	179, patients, ten-bed mixed medical-surgical ICU	TR: 81–135 M: 30 min–24 h	Prospective, 3 months, observational study	Mean BGL decreased from 166 without protocol to 138 with the final protocol implemented by a CDSS. BGLs were measured a total of 1,854 times in 179 ICU admissions during 553 ICU treatment days. The median BGL was 126, and 53.1% of BGLs were within the target range. One episode of hypoglycemia occurred (0.5% patients or 0.05% measurements).
	[29]	50 patients, 22-bed ICU, ≥24 h on mechanical ventilation	TR: 80–110 M: 15 min–4 h	Prospective, 6 month, observational study	Median time percentage in target range was 23%. BGL was 50% of time in the range 112–144. Median proportion of time spent in hyperglycemic range 180–200 and >201 was 2 and 1.4%. There were 28 hyperglycemic episodes including those of 15 (30%) patients treated with IIT protocol. Median time to capture the target range was 10.5 h. Median of 47% of sampling were not taken within the time frame stated in the protocol. Hypoglycemia occurred 14 times and in five (10%) patients.
	[7]	5,080 IIT run over 120,683 h IIT.	TR: 100–140 M: 20 min–2 h	NM, observational	The mean BGL reached <150 in 3 h. The prevalence of hypoglycemia was 2.6% among all runs. All episodes of hypoglycemia were recognized within 20 min. The mean of all BGL <60 was 49 and the follow up value in an average of 33 min was 83 ($p < 0.001$). No clinical symptoms due to hypoglycemia were reported.
	[16]	179 patients, 12-bed surgical ICU.	TR: 72–135 M: 30 min–12 h	Prospective, 4 months, observational	Severe and mild hypoglycemia rates were 0.6%, and 11.2%. In patients staying >24 h, time to capture target was 5.7 h and hyperglycemia Index was 17.3 mg/dl. Median time percentage for BGL in target range was 78% with median BGL of 88. Mean BGL change in the first 24 h was −21. After 24 h, mean BGL was 121. Nurses rated program as easy to work with and as an improvement over the paper protocol.
	[21]	NM, surgical ICU	TR: 100–150 M: 20 min–2 h	NM, observational	There was a significant improvement in glycemic control. The benefits to the participating institution were increased awareness of the importance of improving BG control, decreased calls to physicians, reduced need for sliding-scale insulin injections, increased nursing satisfaction because of fewer calls to physicians for insulin adjustment, and increased physician satisfaction because of improved BG control and fewer interruptive phone calls.

TR, target range; M, monitoring; NM, not mentioned
Unit of all BGL thresholds is mg/dl

Table 2 Characteristics of CDSS

Ref.	Type of protocol	Type of system	Consultation mode for: pump/next measurement	Users before/after new system	Evaluation of	Evaluation of usage, usability and satisfaction	Short description of CDSS
[23]	Model-based formula	Stand-alone	Passive/ active	Nurse/Nurse	CDSS + modified protocol	Usability	The system (called eMPC) runs on a bedside laptop computer. The model adapts itself to the input–output relationship observed during TGC, i.e., an incoming glucose measurement is used by the model to update insulin resistance taking into account previously administered insulin, parenteral and enteral glucose. At start-up, the algorithm requires the patient's ID and body weight. The input of the BGL measurement is the first step of a "wizard", subsequently querying the current status of enteral and parenteral glucose administration. Finally, any advice regarding the insulin infusion rate is given. Profiles of glucose level, insulin rate and the amount of carbohydrates infused by enteral and parenteral administration are displayed on the screen. A countdown timer signals the time until the next glucose measurement. When the enteral/parenteral carbohydrate infusion rate is changed then eMPC suggests a new insulin infusion rate without requiring a new BG measurement.
[24]	Model-based formula	Stand-alone	NM	NM	CDSS + modified protocol	No	This software (called EndoTool) upregulates and downregulates a quadratic insulin-dosing relationship based on the entered BG readings from a point-of-care device. It uses engineering-control mathematics that consider the previous four dose responses to regulate the dosing relationship. System recommends the insulin dose, glucose determination frequency, and a 50% dextrose dose (when appropriate) for hypoglycemia. How the necessary data should be entered (manually or electronically) was not mentioned.
[8]	"If–then" statements	Implemented in PDMS	Active/ active	Physicians/ physicians	CDSS	No	The system extracted the pump rate and BGLs from PDMS, and suggested the pump rate and the next BGL measurement time. It reminded when the next BGL measurement should be done according to the protocol. If the staff took no action, the message would pop up again within a few minutes. When the patient record was activated (bedside computer or any other workstation) the pop up windows would be shown.

Table 2 continued

Ref.	Type of protocol	Type of system	Consultation mode for: pump/next measurement	Users before/after new system	Evaluation of	Evaluation of usage, usability and satisfaction	Short description of CDSS
[9]	Model-based formula	Implemented in CPOE	Passive/ passive	Nurses/initiation by physicians and continuation by nurses	CDSS + modified protocol	No	Physician could initiate the CPOE-based insulin protocol, which the patient's nurse would carry out. Physicians should enter current BGL and target high and low limits. At initiation, a highlighted prompt reminds physicians to provide a dextrose source to prevent hypoglycemia. After verifying protocol the CPOE system generates corresponding orders for physician verification, and instructs the nurse to perform subsequent BGL testing. Nurses enter new BGL into the system, and adjust insulin drip rates based on the protocol provided. The nurse can override system pump suggestions and enter it manually based on his/her own decision. It included optional instructions for nurses to notify physicians about out-of-range values. BGLs below target threshold generate an order for intravenous dextrose dose; simultaneously, intravenous insulin infusion is withheld for 1 h.
[22]	Model-based formula	Stand-alone	Passive/ active	NM/mainly nurses but also physicians	CDSS + modified protocol	Kind of usability and satisfaction were mentioned (not formal)	Installed on stand-alone laptops. The laptops were distributed to clinical areas when patient care with e-Protocol insulin was started. Only in one ICU BGLs were automatically retrieved from the hospital electronic medical records. In other three ICUs, nurses manually entered the recent BGL and patient weight. Initial infusion rate was weight-dependent. Thereafter, the current infusion rate, the difference between the most recent entered BGL, the target, and the rate of change of BGL subsequently determined the insulin infusion rate. The e-Protocol-insulin bedside computer displayed the time remaining to the next BGL measurement. Clicking the electronic protocol screen signified an "intent to" accept the recommendation. The nurse still needed to verify drug administration through their usual medical record documentation. When a recommendation was declined, reason was recorded.

Table 2 continued

Ref.	Type of protocol	Type of system	Consultation mode for: pump/next measurement	Users before/after new system	Evaluation of	Evaluation of usage, usability and satisfaction	Short description of CDSS
[10]	Model-based formula	Stand-alone	Passive/ active	NM/nurses	CDSS + new protocol	No	Target range can be selected. It is menu-driven, and includes options for starting a new insulin drip, stopping/holding a drip, resuming a prior drip, entering a BG value, specifying the initial insulin sensitivity factor (ISF). First BG should be entered manually. Then the system calculates the initial pump rate and the amount of time until next BG measurement. Time and ISF are adjusted whenever a new BG is entered. Based on current and previous BGs, the new rate and next BG measurement time is announced by the program. At the scheduled time for the next measurement, the program sounds an alarm to remind nurse.
[25]	Model-based formula	Stand-alone, web-based	Passive/ passive	Nurses/nurses	CDSS + new protocol	No	A preprinted order was set on the web site that provided a direct link to an on-line calculator. Current, last BGL, and first multiplier should be entered manually. Therefore the computerized system calculates a new multiplier and pump rate. A list of patient non-specific recommendations related to the protocol was given by a computer interface without mentioning which one is more important.
[26]	Model-based formula	Stand-alone	Passive/ active	Physicians/ physicians	CDSS + new protocol	No	The system (called Glucommander) was used in combination with, but independently of, an insulin infusion pump and a glucometer. Nurse should enter the first multiplier and the BGLs manually. Except for the first multiplier, other multiplier and the next time for new BGL test was calculated automatically. Time for new BGL test was calculated for use by system reminders.
[15]	Model-based formula	Implemented in CPOE	Passive/ passive	Nurses/initiation by physicians and continuation by nurses	CDSS + modified protocol	No usage but not formal usability and satisfaction evaluation	Same system as mentioned in Ref. [9].
[11]	"If–then" statements	Stand-alone, web-based	Passive/ passive	Medical staff, pharmacists, and nurses/nurses	CDSS + new protocol	Usage for three months after end of study was mentioned	A nurse inputs current and last BGL and current pump rate into the bedside computer. Based on entered BGL and last BGL new pump rate was calculated and an interval for the next test was also suggested. A list of recommendations related to the protocol was given by the computer interface.
[27]	"If–then" statements	Stand-alone, web-based	Passive/ passive	Nurses	CDSS + new protocol	Usage was mentioned	A slightly modified version of the protocol and web-based calculator mentioned in Ref. [11] were used in this study. The system was modified to record entered insulin, BGL, and patient's bed number, and the date and time of calculation.

Table 2 continued

Ref.	Type of protocol	Type of system	Consultation mode for: pump/next measurement	Users before/after new system	Evaluation of	Evaluation of usage, usability and satisfaction	Short description of CDSS
[17]	Model-based formula	Stand-alone	Passive/ active	NM/nurses	CDSS + new protocol	Only usability and satisfaction were evaluated	Slightly modified version of mentioned protocol and CDSS in Ref. [16] was used in this study. More safety features such as label printing and other features rendering the entire procedure paperless were added.
[28]	"If–then" statements	Stand-alone	Passive/ passive	Physicians/nurses	CDSS + new protocol	No	Current, last BGL, current insulin rate and hourly rate of feeding should be entered manually. Therefore the computerized system calculates needed bolus insulin, pump rate, and next measurement interval. A list of patient-non-specific recommendations related to the protocol was given by a computer interface without mentioning which is most important.
[29]	"If–then" statements	Stand-alone	Passive/ passive	Nurses	CDSS + new protocol	No	A nurse inputs BGL and current pump rate into the system in the bedside computer. Based on entered BGL and last BGL a new pump rate was suggested by the system. 50% tolerance for delay in BGL test was accepted because the nurses manually entered the BGLs into the system.
[7]	Model-based formula	Stand-alone	Passive/ active	NM/physicians and nurses	CDSS + new protocol	No	Same system as mentioned in Ref. [26] but now system is connected to the pump and can adjust it directly.
[16]	Model-based formula	Stand-alone	Passive/ active	NM/nurses	CDSS + new protocol	Only usability and satisfaction were evaluated	The system (called GRIP) extracts new BGLs from the hospital information system. Nurses should validate these BGL values and also could change them. Nurses should enter current insulin pump rates, intravenous glucose dose, related drug doses, etc. Nurses can see the new rate suggestion and can accept or change it. Time for next BGL test is used in system reminders.
[21]	Model-based formula	Stand-alone	Passive/ active	NM physicians and nurses	CDSS + new protocol	Not formal satisfaction evaluation	Same system as mentioned in Refs. [7] and [26].

NM not mentioned

Table 3 List of quality indicators used

Indicator	Measurement description	Refs.
Blood glucose levels over a time period	Represented as mean and/or median BGL values. Each BGL measurement or each patient was considered as the unit of observation. Mean or median BGL was also calculated in the morning (6:00–12:00, morning BGL) [11], after the target range was achieved [10], after 24 h [16, 17], at different time of a day [27], or at starting TGC [29].	Fifteen articles [9–11, 15–17, 21–29]
Measurements in predefined blood glucose ranges	Represented as the number or percentage of measurements in a predefined BGL range during the study, after the target is achieved [10] or among early, on time, or late measurements (based on protocol) [17]. Each BGL measurement was considered as the unit of observation.	Ten articles [9–11, 15, 17, 22, 24, 25, 27, 28]
Frequency of measurements during the study	Represented as: mean or median per patient [9, 22, 25, 28] or per patient treatment day [15–17, 28]; mean sampling interval (time) [9, 17, 23, 29]; frequency overall [24] per day [15]; and mean number of measurements before first in-range BGL [22]	Nine articles [9, 15–17, 22–25, 28, 29]
Time to capture defined blood glucose target	Represented as mean and median of time or by Kaplan–Meier curve [10, 25]	Eight articles [7, 9, 10, 16, 17, 22, 24, 25]
Time in predefined range	Represented as mean of percentage of time per patient [15, 24], median of percentage of time per patient [16, 17, 29], or cumulatively for all patients [8, 17, 25]	Seven articles [8, 15–17, 24, 25, 29]
Protocol compliance	A comparison of measurement times suggested by protocol to actual times of measurements and/or pump speed suggested by protocol to actual pump speed during TGC or at the time of hypoglycemia events.	Six articles [8, 9, 17, 22, 23, 29]
Hyperglycemic index	Represented as median area between glucose–time curve and upper normal range divided by time per patient during the trial. Upper ranges were 110 [23], 117 [16], 120 [25], and 135 [17].	Four articles [16, 17, 23, 25]
Hyperglycemia events	Represented as: percentage of measurements >180[a] [25] or percentage of time >150 [9, 25, 29] and percentage of measurements and patients with at least one BGL >180 for more than 2 h [29]	Three articles [9, 25, 29]
Number of patients who achieved predefined range	Represented as number and percentage of patients who achieved the target range overall [22], within 12 and 24 h after starting IIT [9].	Two articles [9, 22]
BGL change over time	Represented as BGL change in first 24 h.	One article [16]
BGL variability	Represented as standard deviation of all measurements per patient.	One article [17]
Number of patients who did not achieve predefined range	Represented as number and percentage.	One article [25]
Odds ratio of achieving certain BGL	Per additional IC day and per used drugs.	One article [11]
Time until first BGL	Represented as mean of time [16].	One article [15, 16]
Time until starting IIT	Proportion of patients per time [15].	One article [15, 16]
Hypoglycemia-related indicator (*proxy for safety*)		
Hypoglycemia events	<40 [7, 9, 15, 22, 23, 25, 27], ≤40 [9, 22, 25, 28], <50 [7, 10, 11, 26], <60 [7, 24], and <70 [25] were used as thresholds for defining a BGL as hypoglycemia event.	Twelve articles [7, 9–11, 15, 22–28]
Severe or marked hypoglycemia events	<40 [16, 17] and ≤40 [15, 16, 29] were used to define a BGL as severe hypoglycemia event. In one study clinical findings defined severe hypoglycemia [7]	Five articles [7, 15–17, 29]
Mild or moderate hypoglycemia events	<63 was used define a BGL as a mild hypoglycemia event.	Two article [16, 17]
Next BGL after hypoglycemia	Represented as mean BGL.	Two articles [7, 10]
Time until next in predefined range after hypoglycemia	Represent as mean time.	Two articles [7, 10]
Need for glucose injection	<40 have to inject and <72 should be considered.	One article [27]
Time until hypoglycemia recognition	Represented as maximum time until hypoglycemia recognition.	One article [7]
Time until next BGL after hypoglycemia	Represented as mean time.	One article [10]

[a] Unit of all BGL thresholds is mg/dl

controlled studies one study did not report [8], six studies reported no change, and two studies [9, 10] even reported a reduction in the number of hypoglycemia events. Seven observational studies also reported that the number of hypoglycemia events was in an acceptable range. No clinical symptoms attributable to hypoglycemia were reported in any of the studies. The observational studies also used efficiency-related indicators, for example mean BGL or time to capture TGC in the acceptable range by introducing the CDSS (with or without a new protocol).

Discussion and recommendations

In this review we have summarized the design, characteristics, indicators, results, and limitations of 17 published studies on glucose regulation CDSSs in intensive care. Although most studies reported a positive effect on at least one quality indicator the diversity of studies in term of case-mix, insulin therapy, associated therapies, and indicators used (varying in their definition and the ways of calculating them) severely hamper comparison of the studies. Therefore, although meta-analysis is theoretically possible, the results will not be reliable. In addition only three papers reported on an RCT. Our search included all synonyms known to us of TGC, for example "intensive insulin therapy" (IIT). A limitation of our search is that we only addressed studies whose main objective concerned evaluation of a given TGC protocol with a CDSS; we might have missed some studies with a limited evaluation and TGC quality measurement focus.

The implementation of paper-based TGC protocols with decision tables or charts for adjusting the insulin rate is cumbersome and time-consuming [11]. Although for many studies without CDSS implementation results were acceptable [12, 13], frequent measurements are crucial in TGC. Furthermore, a paper-based TGC protocol cannot remind the users about the time for the next measurement. For these reasons, CDSSs may improve glycemic control and help implementing TGC. To the best of our knowledge this is the first review exclusively dedicated to supporting the TGC protocol with a CDSS. Existing reviews on TGC focused on the range of TGC, the effects, and advantages, regardless of the implementation strategy of the TGC protocol, such as a CDSS [12, 13]. The remainder of this section will discuss the findings on study design, CDSS characteristics, and TGC quality indicators and will provide recommendations on these subjects for future research.

Study design

Most of the studies used a before–after design and introduced the CDSS together with a new protocol. Therefore, it is difficult to conclude that the CDSS itself was the causative reason for observed improvements in glucose regulation. The fact that in some studies the users differed before and after the introduction of the CDSS (based on a new protocol) further hampers identification of success factors for improved glucose regulation. Future research should carefully choose a study design in order to clearly separate the effect of the TGC protocol and the contribution of the CDSS.

CDSS characteristics

To achieve the optimum effect of TGC, the protocol should be integrated into clinical workflows [14]. It should put the knowledge for clinical decision-making at the point of care. The question is, however, what is the best place and time for presenting the knowledge to the user. Boord et al. [15] used the computerized physician order entry (CPOE) as the starting point and integrated the CDSS into this. They believe this provided a "one stop shop" by capturing BGL and other patient data from the clinician at the bedside, generating new orders, and logging the data into the electronic medical record. Clinicians should first initiate an order in the CPOE before the CDSS could generate advice. Both pump adjustment and next measurement time reminders were passive. In contrast, Vogelzang et al. [16, 17] believe that because most nurses spend some time near the glucose analyzer until the result of the analysis is known, a computer situated next to the analyzer is the ideal spot for the system to interact with the nurses. This system generated an active reminder but it could be shown only when nurses were near the analyzer, missing other clinicians. As a final example, Rood et al. [8] evaluated a system which got the necessary data from a patient data-management system (PDMS), generating reminders during care at the bedside computer, and logging the data into the electronic medical record. This system provided an active reminder but it is unknown what happens with a reminder if the user was logged out or was away from the computer. Altogether more research is necessary to investigate the most appropriate implementation site, target user, and time of advice. This will also depend on local circumstances such as technical infrastructure and responsibilities of TGC implementation.

TGC quality indicators

We found no uniform indicator set of glycemic controls was used in the studies reviewed. Most indicators differed in their definitions among the studies although they are all meant to measure the same underlying concept. For example the sampling frequency of measurements plays a crucial role in TGC but it was reported in nine out of 17 studies. In these nine articles, six different ways were used to calculate the

sampling frequency (e.g., mean or median per patient or per patient treatment day or mean sampling interval). Thus reproducibility and comparability of research results are hampered by this lack of unambiguous definitions. The choice of quality indicators used was not explicitly mentioned in any of the studies. We could not find an association between indicator selection and patient population, diseases, or specification of the designed protocols.

Because hypoglycemia is the main risk of TGC implementation, almost all studies reported on at least one indicator related to hypoglycemia. The number of hypoglycemic events before and after TGC implementation and/or the management of these events form the main safety-related indicators of TGC. However, we found several definitions and ambiguous terminology for rendering a BGL measurement (or a set thereof) as a hypoglycemic event. Most of the studies reported no change or even a reduction in the number of hypoglycemia events. This finding is in contrast with some studies, including a recent meta-analysis [18], showing that TGC implementation increased the risk of hypoglycemia events. TGC, semantically, excludes the occurrence of hypos because it is "tight". Thus, if one is applying a TGC protocol but hypoglycemia occur then the culprit resides in the implementation of the regulatory process. CDSSs are used to improve adherence to TGC protocols; therefore, if the protocol is sound a CDSS contributes to keeping BGL in range and hence to reducing the risk of hyperglycemia and hypoglycemia.

The strong relationship between hyperglycemia and mortality and morbidity is well known from the literature. Hence hyperglycemia reduction is the main objective of TGC. Surprisingly, only six studies explicitly defined a hyperglycemic event and/or hyperglycemia index, but they used different definitions of such an event.

The increased number of blood-glucose measurements, especially in well regulated patients, may increase the number of measurements with low glucose levels and may thus reduce the mean and median plasma glucose level of the whole group, giving a false impression of improvement of the studies.

There is almost no literature that compares different glycemic metrics to relevant clinical outcomes, such as severity-associated mortality [19]. It is, therefore, hard to evaluate and qualify these indicators. Deciding upon a common glycemic vocabulary is hence essential.

Applying the results of highly controlled clinical trials like those evaluating TGC to everyday practice is difficult [20]. The need for frequent measurements and pump adjustments increases the need for CDSSs. If a passive CDSS is implemented, we cannot be sure that the users ask for support on time. In such a case usage of the system (frequency) should be clearly described. If an active CDSS is implemented based on the content of these highly controlled protocols, the reminders will be shown many times. Showing many pop-up reminders usually irritates users, resulting in the alerts being ignored [5, 6]. Also, in an active CDSS it is not clear how many times the messages are actually seen on time and not too late, because of users being logged off or away from the computer. Therefore, in future research it is necessary to report the usage, usability, and satisfaction with such CDSSs.

Data verification is very important, especially when the values are entered manually in information systems. Button et al. [21] implemented double data entry as a data-verification tool. Morris et al. [22] mentioned this issue, although they did not implement any data verification techniques. They are of the opinion that enabling bedside nurses to use CDSS with minimum effort outweigh the theoretical advantage of additional security and double data entry. Similar to others, in their study the accuracy of manually entered values and the possibility of introducing new kind of errors were not reported or discussed. Using CDSSs without a data-verification process might be a critical safety issue and hence authors ought to address this issue when discussing their results.

Conclusion

While most studies evaluating the effect of CDSS on the quality of the TGC process found improvement when evaluated on the basis of the quality indicators used, it is impossible to define the exact success factors. This is mainly because of the lack of standard agreed-upon indicators of glycemic control, the simultaneous implementation of the CDSSs with new treatment protocols, and the various solutions used for integrating the CDSS into the users' workflow. This systematic review provided key recommendations and information for researchers and ICU managers who want to develop and evaluate CDSSs for glucose regulation or other highly controlled clinical practices.

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