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HOSPITAL MANAGEMENT OF DIABETES (A WALLIA AND JJ SELEY, SECTION EDITORS)

Hypoglycemia Prevention by Algorithm Design During Intravenous Insulin Infusion

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Abstract

Purpose of Review This review examines algorithm design features that may reduce risk for hypoglycemia while preserving glycemic control during intravenous insulin infusion. We focus principally upon algorithms in which the assignment of the insulin infusion rate (IR) depends upon maintenance rate of insulin infusion (MR) or a multiplier.

Recent Findings Design features that may mitigate risk for hypoglycemia include use of a mid-protocol bolus feature and establishment of a low BG threshold for temporary interruption of infusion. Computer-guided dosing may improve target attainment without exacerbating risk for hypoglycemia. Column assignment (MR) within a tabular user-interpreted algorithm or multiplier may be specified initially according to patient characteristics and medical condition with revision during treatment based on patient response.

Summary We hypothesize that a strictly increasing sigmoidal relationship between MR-dependent IR and BG may reduce risk for hypoglycemia, in comparison to a linear relationship between multiplier-dependent IR and BG. Guidelines are needed that curb excessive up-titration of MR and recommend periodic pre-emptive trials of MR reduction. Future research should foster development of recommendations for "protocol maxima" of IR appropriate to patient condition.

Keywords Hypoglycemia · Critical care · Insulin protocol · Insulin infusion · Best practices · Critical care protocols

Abbreviations

BG	Blood glucose
CGM	Continuous glucose monitoring
ICU	Intensive care unit
IR	Infusion rate of insulin
IV	Intravenous
MR	Maintenance rate of insulin infusion

Introduction

Excellent guidelines provide principles for safe and effective use of intravenous (IV) insulin infusion in the intensive care unit [1, 2]. Modifiable factors extrinsic to the insulin dosing rules may reduce risk for hypoglycemia [3]. Our goal in this review is to examine algorithm design features that may mitigate risk for clinically significant hypoglycemia < glucose

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54 mg/dL or glucose alert value ≤ 70 mg/dL, while attaining glycemic control during IV insulin infusion [4–6].

Optimal glycemic targets for specific populations remain controversial. The importance of time-to-target is not well established. Lower glycemic targets and higher insulin doses may be associated with hypoglycemia. Insulin resistance and nutritional exposure modify the relationship between target selection, insulin dose, and hypoglycemia risk. With respect to insulin infusion rate (IR), it is not clear whether a high IR upon initiation is superior to lower rates. One could argue that hourly insulin requirements should be approached gradually, from an initial underestimation. However, insulin resistance and nutritional exposure may change rapidly. A gradual approach to discovery of admission insulin requirements could lead to late snowballing of insulin effect at a time when insulin requirements are abating rapidly, with resultant hypoglycemia.

When a tabular user-interpreted algorithm or multiplier algorithm is to be initialized, we will argue in favor of using patient characteristics to assign a maintenance rate of insulin infusion (MR), either explicitly or as a column assignment, or to assign a multiplier. We also will suggest that a rule assigning MR-dependent IR as a strictly increasing sigmoidal function of BG may offer hypothetical advantages over a rule assigning multiplier-dependent IR as a linear function of BG.

Saturation Dynamics and Tincture of Time

Several lines of reasoning lead to the premise that high-dose IV insulin therapy should not be sustained for prolonged time intervals, even in the presence of hyperglycemia, without periodically testing the possibility that a lower dose might achieve the same result.

Recognize Saturation Dynamics

To our knowledge, there has not been a randomized trial comparing glycemic or medical outcomes that might result from use of higher vs. lower insulin infusion rates when aiming at the same glycemic target. Experimental and observational evidence suggest that saturation dynamics pertain to IV infusion of insulin. Although higher IRs may be tolerated, It has been suggested that an IR exceeding 8 units/h seldom may be necessary [7•, 8–10, 11••, 12].

Anticipate Improvement of Insulin Sensitivity

Insulin resistance associated with critical illness may decline rapidly in the early hours of critical illness [13•, 14]. The SPRINT and STAR protocols employ a parameter that can be re-calculated during the course of treatment to quantify overall insulin sensitivity, utilizing a model that incorporates glycemic response to exogenous insulin and nutrition in order to estimate insulin sensitivity and recommend future adjustments of insulin and/or nutrition therapy [12, 13•]. In a study of 124 patients from a single ICU after commencement of use of the SPRINT protocol, the maximum improvement of insulin sensitivity occurred within the first 12–18 h, with improvement of cohort and per-patient median insulin sensitivity levels increasing by 34 and 33% ($p < 0.001$) between days 1 and 2 of the ICU stay [13•].

Recognize Persistence of Insulin Effect After Reduction of IR

The action of IV insulin involves passage of insulin from the intravascular space to the extravascular space, binding to tissue insulin receptors, and activation of post-receptor events. Saturation of tissue receptors is thought to be nearly complete at relatively low rates of insulin infusion. Although the half life of an IV bolus of insulin in the circulation is brief (commonly assumed to be about 5 min), the duration of biologic effect from a given IR is measured in hours, with a half time for deactivation of effect, after interruption of continuous infusion, of about 63 min [15]. Peripheral tissues may serve as a reservoir for insulin. Renal failure, if present, prolongs the effect of insulin. In the ICU setting, clearance and pharmacodynamic effect of insulin may be delayed, creating risk for late hypoglycemia as a complication of previously aggressive IV insulin treatment.

Note Instances of Late Hypoglycemia

Late hypoglycemia has been associated with failure to reduce the rate of insulin infusion during recovery from hyperglycemic emergencies [16]. Late hypoglycemia also may be noted after interruption of IV insulin that had been used for routine critical care [17]. In a population of patients having heart transplantation at Northwestern Memorial Hospital, the fractions of patients who experienced hypoglycemia < 70 mg/dL, from lowest to highest quartile according to peak IV insulin infusion rates, respectively, were 7/18, 8/18, 10/18, and 8/17, such that the occurrence of hypoglycemia was judged to be equally distributed according to quartile of insulin resistance. In the highest quartile of peak insulin rate, the minimum was 14.7 and maximum was 64 units of insulin per hour. The authors noted a small subgroup of six patients who required high drip rates between 14 and 65 units/h, sometimes with boluses, and whose insulin resistance later suddenly plummeted, such that five developed hypoglycemia [18•].

Design of Intravenous Insulin Algorithms

The reader is referred to earlier reviews of algorithm designs, some aspects of which are at least partially proprietary [19, 20].

Response to Actual or Impending Hypoglycemia

Many algorithms or hospital protocols provide rules for temporarily suspending the insulin infusion in case of impending or actual hypoglycemia and include reference to a hypoglycemia treatment protocol [19, 21–23]. As we will discuss later, in order to deliver temporarily negligible insulin effect as a short-term response to hypoglycemia, we strongly favor sharp reduction of IR in preference to temporary suspension of the infusion. Most institutions use a standardized treatment response for hypoglycemia, with administration of oral glucose or an IV bolus of dextrose, or for those unable to swallow and lacking IV access, a standardized dose of glucagon, and often include provisions for revisions of IR and/or continued carbohydrate exposure [3]. The protocol for treatment of hypoglycemia typically may be placed as "prn" instructions with parameters for use, so that nursing staff may initiate treatment without having contacted a provider for an order [24].

In a before-and-after study of introduction of a hypoglycemia treatment protocol for critically ill patients, in order to avoid overcorrection the grams of dextrose to be administered depended upon the severity of the hypoglycemia. Recurrent hypoglycemic events were not reduced, but dextrose use was reduced and the coefficient of glucose variability improved from 49.3 to 40.9% ($p = 0.048\%$) [25].

A supposition occasionally utilized is that the severity of hypoglycemia or excessive rate of fall of BG may determine the amount of dextrose necessary for correction [21, 25–29]. Such a supposition does not control for differences in the risk of relapsing hypoglycemia from persisting effect from insulin previously administered. Nevertheless, avoidance of overtreatment with dextrose may help blunt oscillations between hypoglycemia and hyperglycemia that otherwise might be seen during IV insulin infusion.

In order to reverse a trend toward hypoglycemia, even during treatment of type 1 diabetes, persistence of insulin effect may justify brief temporary interruption of insulin infusion. Multiplier algorithms or column-based MR algorithms thus may specify temporary interruption of IR, such as the withholding of insulin for 30 min until glucose > 60 mg/dL [23]. A published version of the Cleveland Clinic algorithm called for interruption of the infusion for BG 71–85 when combined with decline of BG by ≥ 30 mg/dL or for BG ≤ 70 mg/dL [30]. The University of California- San Francisco (UCSF) adult critical care IV insulin protocol calls for interruption of insulin infusion for BG < 80 [29]. The STAR algorithm published in 2012 specified interruption of insulin infusion for BG < 90 mg/dL or for current BG value more than 18 mg/dL below the 5th percentile that had been forecasted at the previous intervention under the stochastic protocol [11••]. The Yale protocol, in its earlier computer-guided version targeting BG 100–139 mg/dL, was studied for contributory factors associated with hypoglycemia. It was found that 42.1% ($n = 201$) of the hypoglycemic readings occurred in association with continuation of insulin while below the low target range of 100 mg/dL, under protocol titration rules which called for continuation of insulin infusion albeit at a lower rate [31]. A protocol revision calling for interruption of insulin infusion for glucose < 100 mg/dL, together with upward adjustments of target to a single value of 140 mg/dL, and recommendation for a tighter testing frequency, was associated with subsequent reduction in the rate of hypoglycemia < 70 mg/dL from 0.998 to 0.256% of readings or from 17.2 to 5.8% of treatment courses [32].

When interruptions of insulin infusion occur, monitoring of glucose should not be interrupted. Ideally, cancelation of IV insulin infusion should occur only if specified by provisions of the protocol or by provider order. Staff must reliably execute a protocol for retesting and forced resumption of the infusion within a specified timeframe [3]. Classification of diabetes as type 1 may not be apparent to caregivers and may have escaped identification, especially if a patient could not speak for himself or herself upon admission. The occurrence of in-house diabetic ketoacidosis (DKA) for a patient having known type 1 diabetes should be a "never" event. In the absence of adequate subcutaneous insulin effect, ketoacidosis could result within hours of interruption of the infusion [22].

Monitoring and resumption of IV insulin infusion may be forgotten or delayed once the infusion has been turned off, even if the protocol calls for re-testing and provides parameters for re-starting of the infusion. Inexperienced or overextended caregivers may treat the protocol-driven interruption as the equivalent of cancelation. Rather than interrupting the infusion for BG < 100 mg/dL, we speculate that similar protection against BG alert value ≤ 70 mg/dL could be achieved by sharply reducing IR to a low restraining rate, for BG below an acceptable range. Such a strategy requires infusion pumps and use of insulin concentrations capable of delivering insulin in increments as low as 0.1 units/h [17, 33]. The strategy of continued insulin delivery at a negligible rate might serve as a gentle reminder that insulin infusion has not been canceled. The strategy also might be preferred if it reduces rebound hyperglycemia following treatment of hypoglycemia.

Partial Replacement of Continuous IV Infusion with Recurring Small Doses of Intravenous Bolus Therapy

A lenient schedule for re-testing when hypoglycemia occurs, or excessive work burden of staff that prevents timely

re-testing of BG, could delay a necessary reduction of IR. Therefore, it has been proposed that supplementation of continuous infusion with small IV boluses of insulin may improve safety with respect to hypoglycemia, when compared to delivery of similar total hourly insulin doses entirely by continuous infusion [8, 10, 11••, 32].

The SPRINT protocol from Christchurch New Zealand was designed from the early days of its development as a bolus-based treatment with some use of background IV insulin infusion, intending to modulate insulin bolus, insulin infusion, and feeding rate according to the algorithm. The SPRINT protocol described in early reports and its successor, the STAR protocol, limited total insulin prescribed to 6.0 units/h [8, 10, 11••, 12, 34]. Background insulin at a rate of 0.5 to 1.0 units/h was mandated for type 1 diabetes and was also used at typical rates of 0.5 to 2.0 units/h for those known to have type 2 diabetes. IV insulin otherwise was given predominantly in bolus form, "avoiding infusions being left on at levels inappropriate for evolving patient condition" [8]. However, any protective effects of the bolus feature might be difficult to differentiate from another protective effect against hypoglycemia that characterizes the SPRINT and STAR protocols, i.e., having a protocol maximum rate of insulin administration of 6.0 units/h.

Modifications of the Yale protocol introduced over time have included revision of the rules of the original protocol, computerization, raising the glycemic target, attention to protocol adherence including BG timing, and introduction of a "midprotocol bolus" feature [32, 35, 36]. The authors, comparing their protocols before and after the incorporation of the midprotocol bolus rules, reported that the "addition of midprotocol boluses ($n = 105$ protocol use periods) further improved overall glycemic control, reduced the need for D50 boluses, and lowered overall continuous insulin infusion requirements." They also noted an associated overall decreased incidence of BG < 70 mg/dL when compared to earlier versions of the Yale protocol ($P = 0.03$) [32].

Priming or loading doses of IV bolus insulin may be used differently than recurring bolus doses [30, 35, 37–41]. A priming dose, sometimes relatively large, may be given at initiation of IV insulin therapy with the effect of hastening time to target. Tanenberg et al. noted a reduction in hypoglycemia after restricting the maximum bolus to 10 units [42].

Essential Assumptions, Inputs, Computations, and Outputs of Validated Algorithms

Algorithms generally acknowledge either a glycemic target or a target range, provide rules for IR assignment at the time of initialization appropriate to patient characteristics and medical condition, during treatment require determination of the rate of change of BG, and may respond to other time-variant inputs concerning the patient. Necessary inputs thus include the previous and most recent time-stamped BG measurements and time between those measurements. Inputs also include either the most recent insulin infusion rate (IR) or information about its determinants, such as the most recent multiplier or column assignment together with previous BG (see below). Inputs about patient condition and feedings may improve the performance of any algorithm. The final output of most algorithms provides for modification of the IR and a recommendation for the next test time. Although most adult algorithms express IR in terms of insulin units/h, expression of IR in terms of insulin units/kg-h enables applicability to children.

Rules for Assignment of IR

Our goal is not to characterize or classify all published algorithms. Several published algorithms are mentioned here that have demonstrated satisfactory performance. Modifications of IR may be defined as incremental direct adjustments to the most recent antecedent IR according to rules that take into account the current BG and the rate of change of BG, as in the Yale protocol [35, 36]. A proportional-integral-derivative (PID) algorithm utilizes BG distance from target, recent cumulative deviation from target, and rate of change of BG to assign IR [43]. To assign the next IR, a validated e-protocol relies upon rate of change, the current IR, and a mitigating factor related to distance from mid-target [44, 45]. The computerized Endotool® protocol utilizes multiple functions to assign infusion rates based on patient-specific inputs [42, 46, 47]. Complex model predictive control systems have been highly effective [20, 48, 49].

Our goal is to focus on multiplier algorithms or user-interpreted tabular algorithms. Each type of algorithm requires repeated re-determination of an intermediary variable reflecting insulin resistance and carbohydrate exposure, namely the multiplier or the column assignment (MR). Multiplier algorithms and user-interpreted tabular algorithms both create a family of functions, linear in the case of multiplier algorithms, and potentially non-linear in the case of tabular algorithms, such that each function requires an identification of a value for multiplier or MR and then gives IR as a function of BG (Fig. 1). Insulin resistance and carbohydrate exposure influence rate of change of BG in response to therapy, permitting re-assignment of the multiplier or the column-associated MR. Thus, column-based and multiplier algorithms are "dynamic" protocols, seeking and revising approximations of the MR or optimal multiplier.

Together with rules for assigning the value of the multiplier, a multiplier algorithm typically uses a simple linear equation:

$$[\mathrm{IR} = \mathrm{multiplier} \times (\mathrm{BG}–60\ \mathrm{mg/dL})]$$

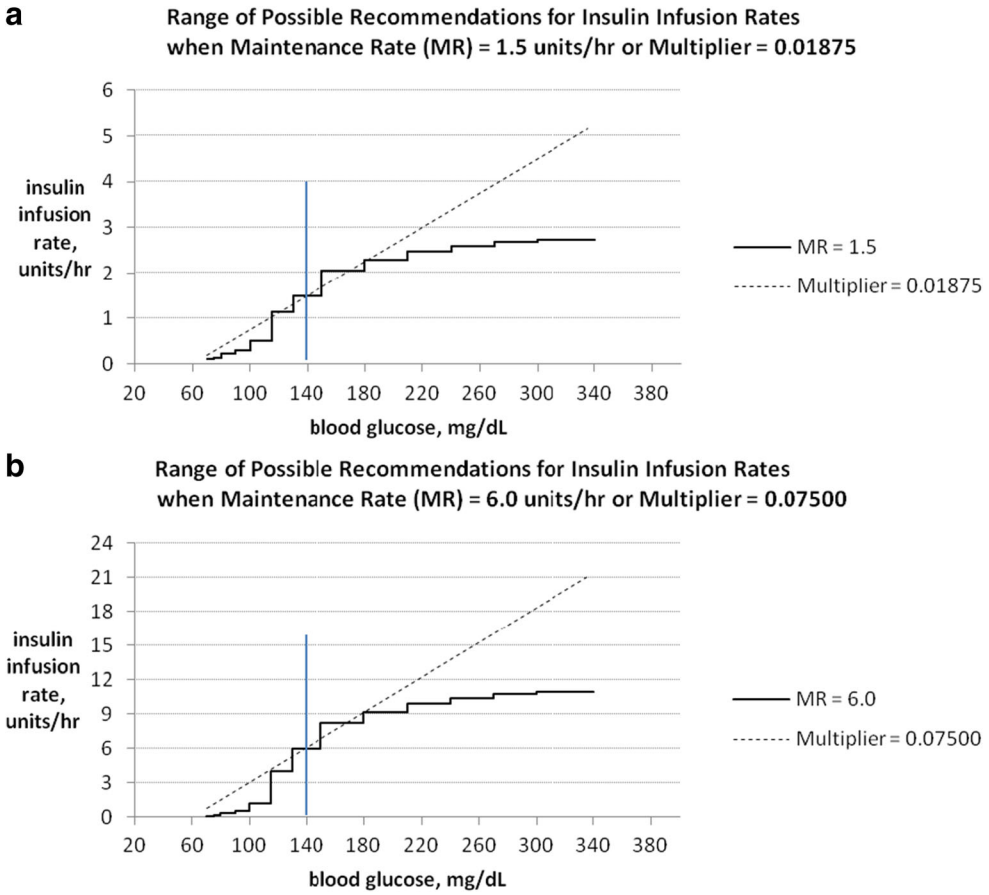

Fig. 1 Comparison of recommended insulin infusion rates under a nearly sigmoidal MR-dependent algorithm vs. a hypothetical multiplier-dependent algorithm**.** After initialization, depending upon response to previous iterations of the algorithm a patient may repeatedly be reassigned to a new MR or a new multiplier, which, together with current BG, will determine the next IR. A caregiver reasonably might target BG ≈ 140 mg/dL for some patient situations. A multiplier algorithm commonly may state the multiplier to two decimal places [21]. The depicted examples of the MR algorithm are derived from a seven-column tabular algorithm that associates each column with a specific MR [17, 33, 50]. For the examples depicted above, values of the multiplier were defined artificially to five decimal places such that identical IRs would be recommended for BG = 140 mg/dL by each of the two algorithms, the MR algorithm, or the multiplier algorithm. The comparison is shown at two different levels of insulin sensitivity represented within the tabular MR algorithm, requiring specifically 1.5 units/h (**a**) or 6 units/h (**b**) for maintenance of target range control. The figure compares recommended IRs across a spectrum of other possible BG values, showing that for given MR, the asymptotic rules of the sigmoidal MR-dependent algorithm effectively determine a protocol maximum infusion rate (IR). Incremental adjustments of IR for BG deviations from target must be followed by repeat BG testing within a recommended timeframe. For BG below an acceptable range but not frankly hypoglycemic, it is speculated that continuation of insulin infusion at a sharply reduced rate may be preferable to continued infusion at a linearly reduced rate, or preferable to interruption of infusion (adapted from Devi et al. [17])

A multiplier algorithm is readily computerized, or it may be expressed in tabular form displaying the linear relationship for different values of the multiplier [21, 26–28, 51–57].

A user-interpreted tabular algorithm typically associates a specific value of MR with each of several columns and a range of BG values with each row. Column change rules provide a mechanism for discovering and reassigning the column (i.e., the MR), based on response to previous therapy. The column-based MR together with the current BG then are used at the beginning of the next iteration of the algorithm in order to reassign the IR [17, 24, 33, 39, 50, 51, 58–61]. When BG is at goal, the IR that is recommended equals the column MR. Algorithms that were tabular in original design have been integrated into electronic systems and may announce the output without requiring the user to refer to a look-up table [24].

Performance of Intravenous Insulin Algorithms

The limiting factor in algorithm performance is not likely to be discovery of important patient characteristics, nor the

ability to specify the use of those inputs appropriately. Rather, the limiting factor is likely to be the human factor, i.e., supervision and nurse training in the case of user-interpreted algorithms, and the burden of timely data entry and therapeutic response in the case of both paper user-interpreted and computer-guided dosing algorithms. Protocol violation, deviation, or non-compliance (so-called) have been implicated in association with hypoglycemia [31, 47, 54, 62–65]. However, protocols must be designed and implemented realistically, avoiding excessive frequency of interaction and allowing some margin of discretion with respect to timing. Institutions or healthcare systems must provide for staff training, resources for assistance of inexperienced personnel, and quality improvement programs.

Advantages of Computerization

We note advantages of computerization without providing detailed description of proprietary aspects of algorithm design. Detailed description of the mathematical design of commercialized products may be not readily available. Several studies have suggested that software-guided therapy produces favorable results compared to alternative strategies outlined as a paper guideline [20, 27, 28, 31, 32, 42, 44, 46, 47, 49, 52, 53, 55–57, 66–77]. Computerization creates a new workload burden of data entry. However, without changing algorithm design, computerization by announcing algorithm outputs thereby relieves nursing staff of the greater burden of mentally rehearsing their understanding of the written algorithm rules prior to taking action. It has been suggested that advantages of computerization include the forcing of more BG monitoring, providing information on insulin sensitivity, adjusting to rapidly falling BG levels, and creating a database in real time [28].

Several institutions have reported successful use of a computer-guided version of a multiplier algorithm. The Tufts surgical ICU, targeting BG 95–135 mg/dL in a before-and-after study of replacing a paper protocol with the Glucostabilizer® computerized multiplier algorithm, reported an increase of BG tests per day per patient from mean (SD) 8 ± 4 to $17 \pm 6 < 0.001$ and an improvement of time in target and reduction of time < 70 mg/dL, but similar percentages of patients with any BG < 70 mg/dL, being under the paper protocol 31.8% of 110 patients, and under the software guided protocol 31.0% of 87 patients. Patients were followed for a mean ± SD of 6.3 ± 8.6 and 5.7 ± 8.3 days in the two groups, respectively [28]. The Rush University group assigned differing targets according to patient population, 120–160 and 140–180 mg/dL for surgical and medical patients, respectively. With use of the Glucostabilizer® system, overall 9.8% of 210 patients experienced BG < 70 mg/dL [57].

Computerized and fully automated administration of both insulin and dextrose by infusion pumps with use of continuous glucose monitoring (CGM) may be the optimal solution, potentially using intravascular sampling for BG monitoring [76, 78]. Such technologies, not yet available commercially in the USA, hold promise for the future [49, 78–83]. Regulation of enteral feedings can be a component of a computer-guided algorithm [12]. With use of a sensor and a controller for pumps delivering insulin and regulating carbohydrate exposure, a fully closed loop system may prevent hypoglycemia and control glycemic oscillations [82].

In general, for comparison of user-interpreted algorithms vs. computer-guided control, the available randomized trials compare algorithms that utilize differing logic, so that computerization is not the only variable (Table 1). Each algorithm was treated as a package, generally without evaluation of component features singly. In several randomized trials, the ability of computerization to attain target range control was a more consistent finding than was reduction of hypoglycemia [46, 47, 56, 70, 75, 80, 84, 85].

Process Improvement Reports Concerning Insulin Infusion Algorithms

Glycemic outcomes such as time-to-target, time-in-target, or risk for hypoglycemia will reflect not only algorithm design but also revisions of target range that have occurred over time. The recommended target ranges for glycemic control now are higher than targets that were widely advocated shortly after the Leuven, Belgium, study reported in 2001 [1, 24, 86, 87]. Reduction of hypoglycemia may occur after introduction of process improvement efforts focusing on standardization of practices under protocols, staff education especially nursing, analysis of outlier events and protocol violations, attention to work flow of nursing staff, and opportunities for preventive intervention [2, 24, 31, 32, 47, 64]. Under the Yale protocol, over years of development, there has been progressive reduction in hypoglycemia in comparison to its earlier performance [35, 36]. Identified factors contributory to hypoglycemia included protocol-directed continuation of the insulin infusion when BG was < 100 mg/dL protocol deviations including late glucose checks, and insufficiency of recommended frequency of testing [31]. Hypoglycemia subsequently was minimized by protocol upgrades, including target revision to a single value of 140 mg/dL, and the introduction of use of midprotocol bolus therapy, as discussed above [31, 32]. A rendition of the Yale protocol has been used successfully at other sites. Progressive reduction in hypoglycemia was reported from Ohio State University, tracked over several years [88]. A retrospective comparison of the Yale and the Leuven Belgium protocols utilizing pooled data from CGM studies suggested superior control under the Yale protocol [89]. With respect to hypoglycemia, in a comparison of paper protocols conducted at a single site in France, an adaptation of the Yale protocol compared favorably with a fixed dose regimen [90].

Table 1 Randomized trials of intravenous insulin infusion comparing user-interpreted algorithms vs. computer-guided dosing

Reference	Setting and patient population	User-interpreted vs. computer-guided dosing algorithms, number of patients	Target range	Definition of low BG	User-interpreted vs. computer-guided dosing algorithms, control of hyperglycemia	User-interpreted vs. computer-guided dosing algorithms, low BG
[46] Saager 2008	Single-center, patients treated after induction of anesthesia and for the first 9 h in the cardiothoracic ICU	Standard paper-based insulin protocol, $n = 20$, vs. computer-guided glucose management, system (Endotool®), $n = 20$	90–150 mg/dL	< 60 mg/dL	Mean BG in ICU: 147 ± 27 vs. 126 ± 18 mg/dL, $p = 0.01$	1 vs. 5 events (3 in a single patient) (N.S.)
[84] Blaha 2009	Single-center, consecutive ICU patients after heart surgery	Matias protocol based on the absolute glucose value, $n = 20$, vs. Bath protocol based on the relative glucose change, $n = 20$, vs. computer-based model predictive control algorithm (eMPC) with variable sampling rate, $n = 20$	4.4–6.1 mmol/L	In risk of hypo-glycemia, 2.9–4.3 mmol/L	Average BG ± SEM: Matias 6.7 ± 0.1 vs. Bath 6.5 ± 0.2 vs. eMPC 5.9 ± 0.2 mmol/L, $p < 0.05$ for ePMC vs. each other protocol	Time in risk of hypoglycemia after reaching target (% ± SEM): 10.9 ± 1.5 vs. 13.1 ± 1.6 vs. 22.2 ± 1.9, $p < 0.05$ for ePMC vs. each other protocol Compared to the other two protocols, ePMC produced no severe hypoglycemic episode (< 2.3 mmol/L) whereas one and two episodes did occur during treatment under each of the other protocols respectively.
[70] Cavalcanti 2009	Multicenter, 5 ICUs	Leuven protocol, $n = 58$, vs. conventional subcutaneous insulin protocol, $n = 53$, vs. computer-assisted insulin protocol (CAIP), $n = 56$	80–110 mg/dL, ≤ 150 mg/dL, or 100–130 mg/dL, according to study group	BG ≤ 40 mg/dL	Mean ± SD of patients' median BGs: 127.1 ± 32.2 vs. 158.5 ± 49.6 vs. 125.0 ± 17.7 mg/dL; Leuven vs. CIAP, $p = 0.34$; conventional treatment vs. CAIP, $p < 0.001$	Percentage of hypoglycemic BG measurements per patient, mean: 0.55 vs. 0.03 vs. 0.43%; Leuven vs. CIAP, $p = 0.04$; conventional treatment vs. CAIP, $p = 0.007$
[56] Newton 2010	Multicenter, 5 medical ICUs	Standard paper protocol, $n = 76$ vs. Glucommander computerized protocol, $n = 77$	80–120 mg/dL	BG < 60 and < 40 mg/dL	Glucose mean ± SD, during infusion: 131.0 ± 24.6 vs. 115.5 ± 20.7 mg/dL, $p < 0.001$ Once at target: 117.3 ± 16.5 vs. 103.3 ± 8.8 mg/dL, $p < 0.001$	Percentages of patients with at least one episode, < 60 mg/dL: 31.9 vs. 42.9%, (N. S.) < 40 mg/dL: 5.6 vs. 3.9%, (N.S.)
[47] Dumont 2012	Single-center, cardiovascular surgical ICU	Paper protocol, $n = 159$, vs. computerized insulin dosing calculator (Endotool®), $n = 141$	80–150 mg/dL	BG < 60 and < 40 mg/dL	Percentage of BG in target range ± SD: 61.6 ± 17.9 vs. 70.4 ± 15.2%, $p < 0.001$	Number of hypoglycemic events < 60 mg/dL: 18 vs. 7 (N.S.); < 40 mg/dL: 2 vs. 0 (N.S.)
[75] Van Herpe 2012	Single-center, mixed ICU population	Paper guideline for tight glycemic control, $n = 150$ analyzed, vs. LOGIC computerized algorithm guided control, $n = 140$ analyzed	80–100 mg/dL	BG < 70 and < 40 mg/dL	Percent time in target range ± SD: 60.1 ± 18.8 vs. 68.6 ± 16.7%, $p = 0.00016$	Number (%) of patients having BG < 70 mg/dL: 73 (48.3%) vs. 48 (32.2%), $p = 0.0048$ < 40 mg/dL: 5 (3.3%) vs. 0 (0%), $p = 0.060$
[80] Leelarathna 2013	Single-center, neurosciences critical care patients	Local paper-based IV insulin protocol, $n = 12$, vs. automated closed-loop system utilizing continuous glucose monitoring and a laptop computer running a model predictive control (MPC) algorithm, $n = 12$	6.0 to 8.0 mM	BG < 4.0 mM	Percent time spent in primary target range, median (IQR): 18.5% (0.1 to 39.9) vs. 54.3% (44.1 to 72.8), $p = 0.001$	No events in either group
[85] Mesotten 2017	ICUs of three hospitals, medical and surgical patients	BG control by trained nurses, $n = 773$, vs. LOGIC computerized algorithm guided control, $n = 777$	80–110 mg/dL in two ICUs, 90–145 mg/dL in one ICU	BG < 70 mg/dL, BG < 60 mg/dL, and BG < 40 mg/dL	Percent time in target range: 47.1 vs. 67.0%, $p < 0.001$.	Number (%) of patients experiencing at least one episode of hypoglycemia missed significance for BG < 60 mg/dL: 78 (10.1%) vs. 58 (7.5%), $p = 0.07$ Percent of BG < 70 mg/dL: 1.8 vs. 1.5%, $p = 0.02$ Percent of BG < 60 mg/dL: 0.7 vs. 0.5%, $p = 0.02$ Percent of BG < 40 mg/dL: 0.05 vs. 0.04, $p = 0.9$

Algorithm Design Features That May Reduce Risk for Hypoglycemia

Independent of whether or not an algorithm is computer-guided, there may be insulin dose-determining strategies that promote safety with respect to hypoglycemia.

Set Initial IR, MR (Column Assignment), or Multiplier Appropriate to Condition

Determinants of insulin infusion rates ideally include patient factors additional to BG [91]. Overloading a patient with insulin could be unnecessary for attainment of goal range control, could have little or no effect upon time-to-target, and could lead to late hypoglycemia.

Concerning treatment of diabetic coma, some readers may remember published recommendations for an initial IV insulin bolus as high as 200 units [92]. Such high-dose treatment given historically, though sometimes tolerated, now is understood to be not necessary [39]. Might developing evidence soon justify similar restraint when assigning initial insulin doses for other critically ill patients?

Predictors of early insulin resistance may include cardiac surgery, organ transplantation, corticosteroid treatment, or high preadmission doses of insulin. Predictors of early insulin sensitivity may include type 1 diabetes, cystic fibrosis, malnutrition, or renal or hepatic failure. Patient characteristics may guide selection of a rendition of an algorithm or may be announced to computerized systems as user inputs [17, 24, 29, 42, 56, 57]. At given BG, column-based MR or multiplier algorithms may specify the initial MR or multiplier appropriate to patient condition, rather than specifying an initial IR. Then, at any given BG, based upon the assigned multiplier or MR-based column assignment, the algorithm will specify a higher initial IR for patients presumed to be insulin-resistant, compared to those judged more insulin-sensitive (Fig. 2).

A standard user-interpreted paper algorithm in a multicenter randomized trial initiated treatment for most patients on the lowest of four columns, except for those requiring > 80 units/day of insulin as outpatients or those on glucocorticoids, who were started on the second column. A patient was reassigned to the next higher column if BG targets were not achieved and the BG had not decreased by at least 60 mg/dL in the preceding hour [56]. The IV insulin algorithms at University of California, San Francisco, specify an initial rate for DKA and for cardiac surgery [29]. The Dignity Health System in California uses a computer-guided column-based IV insulin infusion protocol with algorithms numbered 1–7 in ascending order of aggressiveness, starting on column 1 for most patients. For patients who are status post-cardiac surgery, receiving glucocorticoids, or treated with more than 80 units of insulin daily as an outpatient, the recommendation is to start on column 2 [24].

Curb Your Enthusiasm for Progressive Upward Adjustments of Column Assignment (MR) or Multiplier

Up-titration of insulin administration after initialization should not be governed by impatience. A reasonable approach, amenable to evidence-based analysis, could be to sacrifice expectations of rapid time-to-target in favor of greater safety with respect to hypoglycemia. A logical approach after initialization could be to "curb your enthusiasm" for up-titration of MR or multiplier, either from an initially conservative or an initially aggressive starting point. An aggressive algorithm could be available to satisfy needs that could arise in specific situations of insulin resistance, but otherwise would not be routinely favored.

Under the Dignity Health protocol mentioned above, the higher rates under column 7, between 4 and 43 units/h, are recommended after failing to achieve control on the lower columns [24]. Notably, the rules of the protocol restrict column up-titration to instances of BG > 160 mg/dL with failure of BG to have declined by at least 50 mg/dL. The protocol requires that the IR may not exceed 18 units/h without having a prescriber order. As the protocol implementation matured across the 9-hospital healthcare system through the efforts of the improvement teams, the rate of patient days with BG < 70% decreased by 0.4% (0.06-0.6%, 95% CI) from 4.5 to 4.1% [24].

Downscale Column Assignment (MR) or Multiplier Pre-Emptively

If the choice of initial or re-assigned MR is appropriate, then the MR-dependent IR will begin to oscillate around the assigned MR, as BG stabilizes close to target. Once attainment and stable maintenance of reasonable control have been demonstrated during a treatment course, it is also appropriate to "downscale pre-emptively" (Table 2). By making small downward adjustments of the presumed MR, a dynamic algorithm periodically tests the possibility that insulin resistance has begun to improve. In case the assumption is disproven by a subsequent rise of BG, the up-titration rules of the algorithm provide for prompt reversal.

Employ a Sigmoidal Relationship Between BG and MR-Dependent IR

It may be a feature of feedback regulation that a sigmoidal relationship exists between regulator and regulated substance [93]. For any given MR (column assignment), rather than a linear multiplier rule, we favor an ascending sigmoidal relationship between IR and BG (Fig. 2).

In the Presence Health System, for non-pregnant critically ill adults not experiencing a hyperglycemic crisis, we have three institutional column-based user-interpreted algorithms, designated as the aggressive, standard default, and

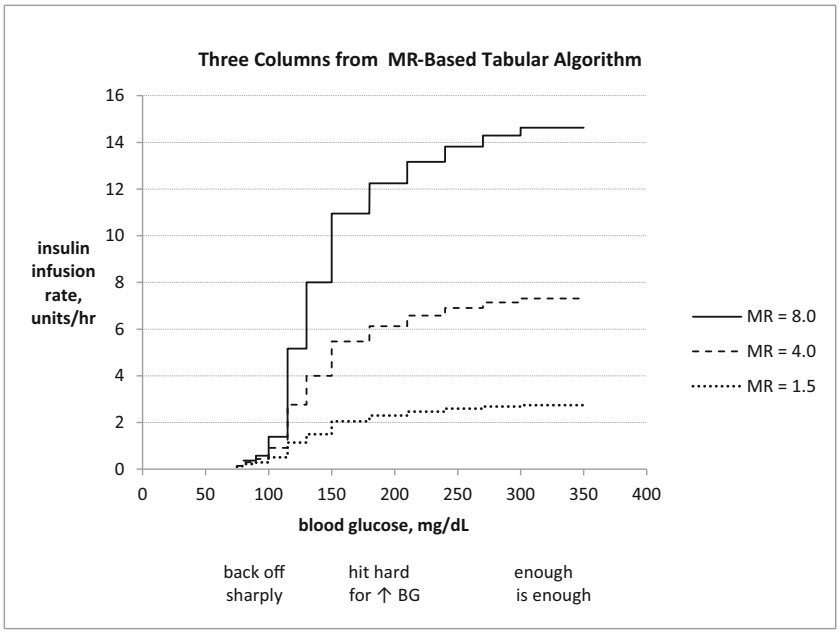

Fig. 2 Three members of a family of curves are drawn from the columns of a tabular user-interpreted algorithm having BG goal 130–149 mg/dL and acceptable BG range 100–149 mg/dL. Initial column assignment may be determined by patient characteristics. The column-based maintenance rate of insulin infusion (MR) may be re-assigned based on response to therapy. Column reassignment also reflects the principles described in the text as CYE (curb your enthusiasm) and DSP (downscale pre-emptively). When BG is 130–149 mg/dL, within each curve, the IR equals MR. Each function demonstrates the following principles for assigning MR-dependent IR as a function of BG: (1) Hit hyperglycemia hard, with greatest incremental adjustments of IR for BG deviations just above target. (2) Enough is enough, for extreme BG elevations. (3) Back off sharply, for BG below goal (adapted from Devi et al. [17])

conservative algorithms, which have an identical BG goal range, 130–149 mg/dL, and an identical acceptable range, 100–149 mg/dL, but differing initiation and titration rules. We have separate algorithms for hyperglycemic crises (diabetic ketoacidosis and hyperosmolar hyperglycemic state). In the Presence Health System, in order to meet the capabilities of equipment available in all ICUs, the adult non-pregnant algorithms now have been modified from their original design by the replacement of extremely low rates of infusion, formerly 0.1 to 0.4 units/h, with rates that are temporarily zero during intervals of low BG. Otherwise, IRs shown in the current versions of the protocols have been actively in use in the Presence Health System since at least June 2012 as user-interpreted paper tabular algorithms, from which pilot performance data previously was published [17, 33, 39].

A statement of strategy for design of algorithms that announce MR-dependent IR might be paraphrased as shown in Table 3. We hypothesize that computerization of an MR-based algorithm design like that in the Presence Health System could preserve glycemic control while reducing hypoglycemia risk if the following features are incorporated:

1. Assign the initial MR (identified by column in some tabular algorithms) or multiplier according to population and patient characteristics.
2. Follow rate of change of BG as the principal input governing revision of MR or multiplier.
3. Evaluate feasibility and establish guidelines for use of additional inputs governing revision of MR or multiplier.
4. Curb your enthusiasm for rapid or excessive upward adjustments of MR or multiplier.
5. After attainment of target during a treatment course sustained for a specified sustained time interval, periodically test whether it is possible to downscale the MR or multiplier by making a pre-emptive reduction or MR or multiplier
6. For IR assignment among algorithms relying upon estimation of MR, assign the MR-dependent IR as a sigmoidal strictly increasing function of BG, centered around the target range BG.

Midprotocol bolus use may reduce reliance upon higher IV infusion rates and reduce hypoglycemia, but it does add one more dimension to the complexity of care required of nursing staff. Assuming BG monitoring occurs on schedule, recurring use of intravenous (IV) bolus doses of insulin may be similar to hitting hard for hyperglycemia but backing off sharply under a sigmoidal rule for IR assignment. If a sigmoidal curve relating IR to BG can be shown to reduce hypoglycemia, then nursing staff during conduct of intravenous insulin infusion could be relieved of the burden of the second recurring process of delivering a bolus.

Table 2 Column down-titration rules for intravenous insulin infusion

The conservative and standard default algorithm recommend:

- If BG is less than 100 mg/dL, go to next lower column
- If insulin is increased in TPN, go to next lower column.
- Go column 1 if there occurs any of the following:
  - Reduction of dextrose-containing IV maintenance fluid rate by 50% or more
  - Interruption of tube feeds
  - Glucocorticoid dose reduction by at least 50%
  - Increase of insulin dosage in TPN by greater than 35 units
  - Interruption of continuous veno-venous hemodialysis

The conservative algorithm recommends:

- If on column having maintenance rate ≥ 2 units/h for the past 4 h, and if BG less than 150 mg/dL at all times for 8 h, go to next lower column.

The standard default algorithm recommends:

- If on column having maintenance rate ≥ 2 units/h for the past 8 h, and if BG less than 150 mg/dL at all times for 8 h, go to next lower column.

The aggressive algorithm retains column down-titration rules for some of the indications above and additionally recommends:

- If on column having maintenance rate ≥ 2 units/h for the past 4 h, and if BG less than 180 mg/dL at all times for 4 h, go to next lower column. If already on the lowest column of the aggressive algorithm, switch to the standard default algorithm, lowest column.

Algorithm down-titration rules for insulin are paraphrased from the Presence Health System tabular column-based algorithms for critically ill non-pregnant adults. Separate rules exist for column up-titration. The algorithms for hyperglycemic crises are not shown. The conservative and standard default algorithms share seven identical columns, for which the maintenance rates during euglycemia are 1.0, 1.5, 2.0, 3.0, 4.0, 6.0, or 8.0 units/h, and column maximum rates are 1.8, 2.7, 3.7, 5.5, 7.3, 11.0, and 14.6 units/h. The algorithms both specify starting on the column that has a maintenance rate (MR) of 1.5 units/h and range of rates between 0.5 to 2.7 units/h for BG 100 to > 299 mg/dL (column 2), unless the order for insulin infusion specified a different starting column. The aggressive algorithm has seven columns, for which the maintenance rates during euglycemia in units/h are 1.5, 2.0, 3.0, 4.0, 8.0, 12.0, or 16.0 and column maximum rates are 2.7, 3.7, 5.5, 7.3, 14.6, 21.9, and 29.2 units/h. The aggressive algorithm specifies starting on the column that has MR 3.0 units/h, unless the order for insulin infusion specified a different starting column. For all three algorithms, the goal range is 130–149 mg/dL, and the acceptable BG range is 100–149 mg/dL, below which the user is advised to switch to the next lower column (for BG < 100 mg/dL, the original design of the standard default protocol formerly showed rates of 0.1 to 0.6 units/h, as previously published [17, 33]; rates formerly assigned as 0.1 to 0.4 units/h now have been replaced with 0.0 units/h). The protocols invoke a hypoglycemia treatment protocol for BG < 70 mg/dL. Pending re-testing of BG under protocol, insulin infusion later is resumed under the reassigned lower column, unless the order for IV infusion has been canceled by provider order

Table 3 Attributes favored in the design of algorithms that announce MR-dependent IR

MR assignment rules (column assignment):

- Assign MR (or column) initially not according to BG elevation, but rather according to estimated insulin resistance and anticipated continuous carbohydrate exposure, starting conservatively in most cases
- Curb your enthusiasm for upward column adjustment
- Downscale between columns pre-emptively

IR assignment rules for MR-dependent IR, as sigmoidal function of BG.

For given MR (i.e., within-column):

- "Hit hyperglycemia hard" with greatest incremental adjustments of IR, as a function of BG, when just above target
- "Enough is enough" for extreme BG elevations
- "Back off sharply" for BG below goal

The maintenance rate of insulin infusion (MR), reflecting insulin resistance and carbohydrate exposure, is the insulin infusion rate (IR) that would preserve euglycemia during intervals of stability. The MR may change over time. The magnitude of incremental adjustments of IR, responsive to deviations from euglycemia, may be specified to be dependent upon the MR. In a typical tabular protocol, each column is associated with a value for MR, and each row is identified with a range of BG. During a treatment course, the usual minimum inputs that are required for column re-assignment include rate of change of BG (with consideration of the range within which the current BG lies) and special rules in case of recent hypoglycemia, planned change in carbohydrate exposure, or other inputs. The user during a treatment course applies rules of the algorithm first to assign the patient to a column, then uses the current BG to assign the patient to a row, and finally looks at the cell where the column and row intersect. Within that cell, the recommendation for the next IR is given

Future Directions; Aims and Objectives

It is relevant to evaluate the performance of paper algorithms in achieving their stated goal range BG results, and their safety with respect to hypoglycemia. The hope is to develop a computer-guided algorithm modeled on mathematical principles similar to those of our Presence Health user-interpreted column-based algorithms [94]. It is anticipated that such a computer-guided algorithm will minimize hypoglycemia and safely attain glycemic targets for most patients within 4–8 h, and thereafter maintain control within goal range, with availability of renditions of the algorithm that will target each of several different goal ranges for BG. Two algorithm damping parameters are envisioned that are analogous to column change rules of the Presence algorithms. The damping parameter CYE (curb your enthusiasm) will be used mathematically so as to restrict the rate of increase of the MR, and the damping parameter DSP (downscale pre-emptively) will be used mathematically so as to force a reduction of the MR after an interval of satisfactory control. The outputs of the sigmoidal functions giving MR-dependent IR as a function of BG can be computed in advance and stored in a lookup table.

Conclusion

It is hypothesized that algorithm design features may mitigate risk for hypoglycemia during intravenous insulin infusion. Risk for hypoglycemia increases with insulin dose in general. Further research is needed to define protocol renditions or algorithm parameters for members of populations anticipated

to have high insulin resistance, such as post-cardiac-surgery patients, organ transplant recipients, corticosteroid-treated patients, or patients receiving high doses of insulin prior to hospitalization, and also for those patients whose characteristics predict high risk for hypoglycemia, such as patients having type 1 diabetes, cystic fibrosis, malnutrition, or renal or hepatic failure. Are high doses of intravenous insulin necessary, or are they simply tolerated? Should there be "protocol maxima" for IV insulin infusion rates, according to patient condition, that would minimize hypoglycemia without loss of control of hyperglycemia? Would "protocol maxima" result in clinically important prolongation of time to target? There is not yet sufficient evidence to clearly answer these questions.

Compliance with Ethical Standards

Conflict of Interest Susan Shapiro Braithwaite has a patent for an insulin algorithm which has not yet been embodied as a device (U.S. Patent No. 8,721,584 issued). She is on the Editorial Board for Endocrine Practice, as an Associate Editor. She also receives honoraria form the American Diabetes Association for book reviews.

Lisa P. Clark, Thaer Idrees, Faisal Qureshi, and Oluwakemi T. Soetan declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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