Curr Diab Rep (2017) 17: 133
https://doi.org/10.1007/s11892-017-0963-3

Hypoglycemia Reduction Strategies in the ICU

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Published online: 2 November 2017

Abstract
Purpose of Review We reviewed the strategies associated with hypoglycemia risk reduction among critically ill non-pregnant adult patients.
Recent Findings Hypoglycemia in the ICU has been associated with increased mortality in a number of studies. Insulin dosing and glucose monitoring rules, response to impending hypoglycemia, use of computerization, and attention to modifiable factors extrinsic to insulin algorithms may affect the risk for hypoglycemia. Recurring use of intravenous (IV) bolus doses of insulin in insulin-resistant cases may reduce reliance upon higher IV infusion rates.
Summary In order to reduce the risk for hypoglycemia in the ICU, caregivers should define responses to interruption of continuous carbohydrate exposure, incorporate transitioning strategies upon initiation and interruption of IV insulin, define modifications of antihyperglycemic therapy in the presence of worsening renal function or chronic kidney disease, and anticipate the effects traceable to other medications and substances. Institutional and system-wide quality improvement efforts should assign priority to hypoglycemia prevention.

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

This article is part of the Topical Collection on *Hospital Management of Diabetes*

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Introduction

The problem of hypoglycemia and its association with mortality have dampened enthusiasm for strict glycemic control in the ICU for at least some populations, leading to upward revision of glycemic targets in recent years and interest in predictors of hypoglycemia [1–24, 25••, 26–48, 49•, 50–56]. The prognostic importance of dysglycemia and the optimal targets for control may depend upon the hospital setting and the medical condition being treated, the pre-admission presence or absence of diabetes, and, among those having diabetes, the severity and chronicity of hyperglycemia prior to admission. In the critical care setting, in general, a higher target blood glucose (BG) may be associated with reduced occurrence of hypoglycemia, although not invariably so, and increased occurrence of hypoglycemia may accompany greater glycemic variability [1, 9–11, 13, 19, 21, 24, 29, 31, 33–36, 45, 47, 49•, 53, 54]. The prevalence of hypoglycemia in the ICU may vary by hospital type and geographic region [32]. Hypoglycemia traditionally has been identified as a glucose result < 70 mg/dL, the approximate threshold for the release of counter-

regulatory hormones and severe hypoglycemia as glucose < 40 mg/dL [57]. Most recently, based on recommendations from the International Hypoglycaemia Study Group, no threshold for severe hypoglycemia is specified, but clinically significant hypoglycemia has been defined as < 54 mg/dL (3.0 mmol/L), while a glucose alert value is defined as ≤ 70 mg/dL (3.9 mmol/L) [58–60].

Harms Associated With Hypoglycemia in the ICU

From the results of randomized trials designed to compare outcomes during strict vs. more lenient glycemic controls in the ICU, the greater occurrence of hypoglycemia among the more tightly controlled groups has provoked concern about the possibility of an adverse impact of hypoglycemia on outcomes [1, 2, 6, 10, 13, 25••]. A meta-analysis of 14 trials comparing intensive insulin therapy to conventional glycemic control in the ICU found that the pooled risk ratio for hypoglycemic events was 6.0 with intensive therapy (95% CI 4.5–8.0, $p = 0.08$) [11]. A systematic review of studies comparing intensive vs. conventional control confirmed the pattern of hypoglycemia in the treatment arms assigned to intensive therapy [19].

Among critically ill patients, studies of hypoglycemia in the ICU have identified factors independent of antihyperglycemic therapy that may promote both hypoglycemia and adverse outcomes, analyses of which have shown that ICU hypoglycemia is associated independently with adverse outcomes [3, 5, 7, 8, 12, 14–17, 20, 23, 25••, 26, 37, 51, 55] (Appendix Table 1). Although the confounders of the relationship between hypoglycemia and adverse outcomes are expected to differ according to setting, when the study population is not restricted to ICU admissions, there is an association between hospital hypoglycemia and hospital deaths [26]. The risk of adverse outcome may increase with greater frequency of hypoglycemic events [17, 25••, 37, 55]. In one ICU study, during the use of an effective glycemic control protocol, nonsurvivors were shown to have greater insulin sensitivity than survivors [56]. In the Normoglycemia in Intensive Care Evaluation—Survival Using Glucose Algorithm Regulation (NICE-SUGAR) study, the hazard ratio for death in association with moderate or severe hypoglycemia was greater in the absence of insulin treatment [25••]. From a report in the setting of acute myocardial infarction, similarly, the increased mortality risk associated with hypoglycemia was confined to patients who developed hypoglycemia spontaneously, without insulin therapy [12]. However, not all studies have confirmed a stronger association with mortality for spontaneous hypoglycemia in comparison to medication-induced hypoglycemia [51].

Simplistically, when trials have been designed to compare two glycemic targets, the strategies used to attain lower targets have been associated with higher average doses of insulin [1, 6, 13]. For example, 50.2 ± 38.1 vs. 16.9 ± 29.0 insulin units/day ($p < 0.001$) were used in the intensive vs. conventional groups of the NICE-SUGAR study [10]. At given insulin doses, nutritional exposure and insulin resistance affect the risk for hypoglycemia. These factors also reasonably might be expected to modify the insulin dose requirement necessary to achieve a given glycemic target. For patients having type 2 diabetes (T2DM) with A1C ≥ 7%, an observational study contrasting liberal vs. standard targets for glycemic control suggested that treatment initiated at a higher glycemic threshold did not reduce average insulin delivery, and despite a reduction of risk for "relative hypoglycemia" at 4.1–6.0 mmol/L, the reduction in risk for moderate or severe hypoglycemia did not reach statistical significance [47]. Another study of patients with pre-existing diabetes, assigned to differing targets of 80–140 mg/dL for A1C < 7% or 110–160 mg/dL for A1C ≥ 7%, showed a significantly higher insulin dose requirement in the higher A1C group (i.e., the group treated to a higher target, speculatively the more insulin-resistant group), without significant difference in the percentage of patients experiencing hypoglycemia (Appendix Table 2) [53].

Statistical reports showing the association between hypoglycemia and adverse ICU outcomes generally do not link those outcomes to specific hypoglycemic events [2, 6, 13–17, 23, 26, 55, 61]. It is suspected that inflammatory mediators and cardiac arrhythmias may indirectly mediate some adverse outcomes associated with hypoglycemia [62–65]. Some events may be traceable to direct central neurologic or cardiovascular consequences of a hypoglycemic event [4]. Such events might include temporary or long-term alteration of consciousness or mental status, seizures, arrhythmia, and death. Iatrogenic harm during insulin therapy is most convincingly demonstrated if the event occurs within the time frame of insulin action, together with documentation of hypoglycemia [51].

It is recommended that ICUs have a hypoglycemia treatment protocol. Between published sources, the treatment protocol details differ slightly [27, 66–68, 69•, 70]. Assuming patients will have access and receive insulin by intravenous (IV) infusion, the suggested components of hypoglycemia treatment protocols for the ICU generally instruct the nurse to do the following:

- recognize BG value that defines hypoglycemia
- detect hypoglycemia by scheduled monitoring
- recheck BG for confirmation when hypoglycemia is detected if the patient is asymptomatic
- treat with concentrated dextrose bolus or increased rate of dextrose infusion
- (optional) use a graduated scale for dextrose dose according to BG

- temporarily interrupt (T2DM) or sharply reduce IV insulin infusion rate (T1DM)
- notify prescriber
- perform posthypoglycemic recheck within the defined time
- retreat if posthypoglycemic recheck is below the pre-specified goal
- recheck again according to BG within the time defined by protocol to prevent recurrence
- automatically resume ordered antihyperglycemic therapy at revised dose and under conditions of recovery from hypoglycemia as pre-specified by protocol, unless canceled or revised by prescriber.

Strategies to Reduce Risk for Hypoglycemia During Intravenous Insulin Infusion

Several strategies to mitigate risk for hypoglycemia during intravenous insulin infusion are applicable to physician orders, given in response to BG reports, or to nurse-implemented therapy conducted under explicit titration rules of user-interpreted paper protocols. Computerization of insulin algorithms as a decision support tool may improve protocol adherence while simplifying the burden of interpretation and decision-making for nursing staff and prescribers [49•, 71, 72]. A discussion of design features of dose-determining insulin infusion algorithms is beyond the scope of this review. It may be probable that recommendations for "protocol maxima" for insulin delivery could be developed for specific populations without loss of control of hyperglycemia. However, for a given level of insulin resistance and carbohydrate exposure, the risk of hypoglycemia probably is greater with higher insulin doses (Appendix Table 2) [21, 25••, 33, 45, 47, 49•, 52, 53, 73–76, 77•]. The future may hold increasing interest in the use of recurring doses of IV bolus therapy to help mitigate the risk of hypoglycemia during IV insulin infusion therapy [78]. Recurring conservatively dosed IV insulin "pushes" may comprise part of the intended hourly rate of IV insulin delivery (Appendix Table 3) [21, 49•, 77•, 79–82]. Within user-interpreted paper protocols guiding IV insulin infusion therapy, some reports describe rules for recurring doses of IV bolus therapy or for subcutaneous (SC) prandial insulin therapy preparatory to transitioning from IV infusion to subcutaneous insulin therapy. Computer-guided IV insulin infusion protocols also may provide for recurring doses of IV insulin bolus therapy [49•, 77•].

In the sections that follow, we will discuss the strategies for hypoglycemia prevention that require consideration of not only a sequence of timed BG measurements, but also patient factors and clinical course. The strategies may be referenced by hospital insulin algorithms and/or embedded within ICU glycemic management policies, protocols, and procedures, which often result from interdisciplinary hospital- or system-wide quality improvement efforts [69•, 83, 84••].

Define Responses to Interruption of Continuous Carbohydrate Exposure

Interruption of IV dextrose, parenteral feedings (PN), or continuous enteral feedings (EN) may result in sudden changes of insulin requirements [3]. The American Society of Health-System Pharmacists (ASHP) Research and Education Foundation has recommended that protocol-driven and evidence-based order sets be developed for insulin use and BG monitoring during planned and unplanned interruptions of EN or PN [85]. Principles of inpatient nutrition recently have been reviewed in this publication [86]. Rules for insulin dosing during continuous carbohydrate administration generally employ assumptions about an insulin-to-carbohydrate ratio for initialization and gradually provide for an increase of insulin delivery as needed. Continuation of basal insulin delivery for patients having type 1 diabetes (T1DM) is required even when nutritional insulin coverage suddenly needs to decline [80, 87, 88]. The Dignity Health algorithm recommends that in case the PN/EN feeding is stopped or the rate is reduced by 50% or more, then, the insulin infusion rate should be reduced by 50% for 1 h, the protocol should be used to determine subsequent rate changes, and BG should be checked hourly until in range × 4 h [84••]. Management with subcutaneous insulin usually necessitates preventive infusion of dextrose-containing fluids in case of unexpected interruption of PN/EN feedings.

Incorporate Transitioning Strategies Upon Initiation and Interruption of IV Insulin

Most algorithms for IV insulin infusion initialize treatment conservatively, with exceptions for specific circumstances. Patients with T1DM when transitioning to an IV insulin infusion during nihil per os (NPO) status will require at minimum an hourly infusion rate that ensures continuation of their usual true basal insulin requirement. IV dextrose, sufficient to meet energy needs and prevent ketogenesis, will require additional insulin coverage. For patients with T2DM treated with insulin prior to hospitalization, transition from ambulatory insulin requirements to IV insulin therapy cannot be based on an assumption that equivalent doses will be required in the hospital setting. Unusually high insulin doses in the ambulatory setting do not necessarily predict equally high doses upon admission to the hospital. Established subcutaneous U-500 regular insulin doses may be found to be excessive after conversion to U-100 insulin subcutaneous insulin, once the patient is in the inpatient setting [89–91]. On the other hand, defined stresses or corticosteroids may augment insulin

requirements to doses greater than those used in the ambulatory setting [27]. The insulin requirements for previously normoglycemic patients having stress hyperglycemia differ according to condition. A dynamic algorithm should quickly discover adjustments necessary to match changing conditions of hospitalization.

During IV insulin infusion, at the time of introduction of oral feedings for a patient previously NPO but before transition to subcutaneous basal insulin therapy, some centers not only maintain basal control by continuing insulin infusion but also provide prandial rapid-acting subcutaneous insulin to supplement the insulin infusion [79, 81, 82, 84••]. Subcutaneous insulin analogs may have onset of action within 5 to 15 min, with a peak action at 30 to 90 min and a duration of action of 4 to 6 h [92]. Prandial coverage with subcutaneous insulin analogs may restrain oscillations of BG which otherwise could destabilize control by leading to postprandial hyperglycemia and subsequent overestimation of the hourly insulin infusion requirement. Dungan and colleagues argued that the introduction of prandial insulin overlapping with IV insulin infusion was intended to allow more precise calculation of basal insulin requirements [81]. The practice of introducing prandial coverage during ongoing IV insulin infusion is prevalent during recovery from open heart surgery [81, 93]. By preventing a postprandial excursion that could lead to miscalculating insulin requirements at the next titration, both hyper- and hypoglycemia may be prevented. We strongly advocate this approach for patients who are eating but who are not ready to transition off of IV insulin.

Transition from IV insulin infusion to subcutaneous insulin therapy is a time of risk for hypoglycemia [81, 82, 93, 94]. The ASHP has recommended order sets for transition from IV to subcutaneous administration of insulin, specifying monitoring recommendations and guiding insulin use based on the patient's nutritional status [85]. The pharmacodynamic profiles of long-acting and rapid-acting insulin analogs have been summarized, describing their suitability for basal and prandial coverage, respectively, for patients who are eating [92, 95]. We have insufficient evidence in the inpatient setting concerning the "follow-on" bio-similar U-100 insulin glargine, longer-acting basal (U-100 degludec), or new insulin concentrations (U-200 degludec, U-300 glargine) to compare these with the older formulations that have been referenced in most discussions of inpatient care, and we look forward to future studies that might establish their relative safety in the hospital setting in comparison to U 100 glargine, detemir, or neutral protamine Hagedorn (NPH) insulin.

When SC insulin is used to provide basal and continuous EN coverage, safeguards are required in case of unforeseen interruption of carbohydrate exposure [82, 87, 96]. In one study, successful transition from IV insulin infusion to basal and prandial coverage was defined as half or more of all first-day BG values in the strict ranges of 100–140 mg/dL before meals and 100–180 mg/dL after meals. High mean doses of IV insulin infused in the 24 h preceding the transition predicted unsuccessful transition, (≥ 1.6 units/h, OR 2.202, 95% CI 1.045–4.640) [94]. In this study, 7.7% of patients experienced hypoglycemia on the first day of SC therapy and 26.8% within the first 3 days [94].

Because of the short half-life of IV regular insulin, for those who will continue to require insulin after transition, including all patients having T1DM, it is essential to start the first dose of intermediate- or long-acting subcutaneous insulin at least 2 h prior to discontinuation of the insulin infusion [96]. The pharmacodynamics of IV regular insulin infusion are complex, dependent in part upon patient condition and insulin dose [97, 98]. In one study examining the effect of IV infusion of regular insulin upon incremental glucose disposal rate, the 50% activation times were between 21 ± 2 and 74 ± 6 min, and the 50% deactivation times were between 31 ± 6 and 78 ± 5 min, depending upon the dose of insulin and the presence or absence of obesity [97]. In another study, among non-diabetic subjects, the 50% activation time was 32 ± 5 min and deactivation time was 63 ± 5 min (mean ± SE), with persistence of action for 90 min or more [98]. Glycemic effects of the previous infusion may continue to occur for 90 min or more. If IV insulin infusion will terminate at a time of day when the first dose of long-acting insulin analog is not yet due, a bridging dose of NPH and/or regular insulin may be used once, to be given at least 2 h (for NPH) or 1 h (for regular insulin) before interruption of IV insulin infusion, until the patient can begin to receive a once-daily dose of long-acting insulin analog at the usual time of administration [14]. A 2012 prospective randomized study of 61 patients with known T1DM or T2DM showed a benefit in starting long-acting insulin within 12 h of the time of inception of the IV infusion, with intent to reduce rebound hyperglycemia at the time of discontinuation of the infusion. This approach prevented rebound hyperglycemia without increasing the risk of hypoglycemia. Since this practice has not been examined specifically among patients having doubtful absorption of subcutaneous insulin, it may be less applicable to hemodynamically unstable ICU admissions [99].

Basal requirements may be overestimated at the time of transition to SC insulin. We suggest excluding the postprandial time frames when averaging IV insulin infusion requirements to estimate basal requirements. In stable situations, the 24-h requirement for scheduled basal long-acting analog insulin that is to be started or added then may be ~ 80% of the 24-h amount of IV insulin, extrapolated from the observation of insulin requirement during the most recent 6 to 8 h of IV insulin infusion during a time frame during which there have been no meals, such as midnight to 0800 hours. In order to use the 80%

guideline, observation should be made during a time frame of relatively stable insulin resistance; there must be no change of carbohydrate-containing maintenance fluids, enteral feedings, or PN at the time of transition to SC insulin therapy; there must have been independence from vasopressors and continuous veno-venous hemodialysis (CVVHD); and there must be no change of corticosteroid dose. Otherwise, a more conservative starting rule for SC basal insulin should be used. In the setting of recovery from heart surgery, a randomized study of 82 patients by Dungan and colleagues suggested that the initiation of basal SC therapy with 50% of the 24-h basal insulin requirement as projected from IV insulin infusion rates, rather than 65 or 80%, provided similar control of mean glucose but better protection against hypoglycemia, which otherwise occurs for some patients within the 72 h subsequent to transition when higher doses were used [81].

Define Modifications in the Presence of Worsening Renal Function or Chronic Kidney Disease

It is recommended that during IV insulin infusion, in the presence of chronic kidney disease (CKD), there should be conservative BG goals and insulin infusion rates [17, 36, 100, 101]. Exogenous insulin bypasses first pass hepatic extraction, which is normally responsible for removal of about 40–60% of endogenously secreted insulin. The kidney is therefore the main organ responsible for metabolizing exogenous insulin [101]. In the setting of acute or chronic renal failure, insulin clearance consequently is reduced and the half-life of exogenous insulin is prolonged. The renal contribution to gluconeogenesis may be compromised. In the critical care setting, renal failure increases the risk for hypoglycemia during insulin therapy [5, 17, 22, 36].

Dickerson et al. conducted a study to evaluate the safety and efficacy of a modified IV insulin algorithm for glycemic control in critically ill ventilator-dependent adult trauma patients with renal failure [102]. The modified insulin algorithm, compared to a discontinued historical algorithm, was adapted for patients with renal failure by having a higher threshold of BG for both the reduction and increase of the infusion rate. Mean BG was higher in the modified algorithm group ($n = 25$) compared with historical control group ($n = 21$): 145 ± 10 mg/dL vs. 133 ± 14 mg/dL ($p = 0.001$). The proportions of patients treated with the modified algorithm compared to the discarded historical algorithm who experienced moderate hypoglycemia (BG 40–59 mg/dL) or severe hypoglycemia (BG < 40 mg/dL) were decreased (32 vs. 76%; $p = 0.001$) and eliminated (0 vs. 29%; $p = 0.006$), respectively. The new algorithm provided the best combination of glycemic outcomes, first by improving patient safety as evidenced by the absence of episodes of severe hypoglycemia and second, by still achieving therapeutic efficacy within a broader therapeutic BG range.

At the time of transitioning from IV insulin infusion, for a population of trauma patients receiving continuous enteral feedings and therefore at risk for unexpected interruptions of feedings, in preference to using long-acting insulin analog, the same site favored the greater safety of using NPH at 12-h intervals, supplemented by IV correctional regular insulin as needed. The transition protocol entailed the initiation of NPH in divided doses every 12 h, starting with a daily dose of about 30–50% of the insulin requirement that had been established during the 24 h of IV infusion prior to transition, with IV correctional regular insulin at 3–4-h intervals as needed. When this regimen was titrated to a plateau of NPH dose, typically after about 5 days, then approximately two thirds of the total daily dose of insulin was NPH, and one third was correctional regular insulin [103].

Anticipate Effects Traceable to Other Medications and Substances

Hypoglycemia may result from use of antihyperglycemic drugs, other drugs, or alcohol or from failure to taper antihyperglycemic therapy during tapering of corticosteroids [57, 61, 96, 104, 105]. In the ICU setting, the simultaneous use of octreotide and insulin has been associated with hypoglycemia [3]. If sulfonylureas were used immediately prior to ICU admission, then, the treatment of severe hypoglycemia requires IV dextrose infusion and monitoring to detect any relapse. A protracted time frame of risk for relapsing hypoglycemia among sulfonylurea users is most likely to occur when renal excretion of the active metabolite is required and renal function is compromised, especially in older adults and those having impaired renal function.

A systematic review of available evidence for drugs reported to cause hypoglycemia with exclusion of those used to treat hyperglycemia found that of the 164 drugs associated with hypoglycemia, none had high-quality evidence supporting the associations, only 7 drugs had moderate-quality evidence, and 5 had low-quality evidence [61]. The most commonly cited drugs were gatifloxacin, pentamidine, quinine, beta-blockers, angiotensin-converting enzyme inhibiters, and IGF. The majority of cases did require hospitalization, suggesting to the authors that drug-induced hypoglycemia may cause significant morbidity. Caution is recommended in prescribing these drugs to elderly patients as well as patients with sepsis, renal, or hepatic disease or in patients taking other antihyperglycemic agents known to cause hypoglycemia.

Glucocorticoids are commonly used in the setting of organ transplantation, graft-vs.-host reactions, treatment of inflammatory conditions, and chemotherapy regimens [105]. Management of treatment-induced hyperglycemia from these agents begins with monitoring of point-of care BG and

obtaining an A1C, if one has not been performed in the past 2–3 months for persons with diabetes. Hyperglycemia in the ICU may be best managed with IV insulin infusion to cover basal insulin requirements [59, 84••, 105]. Protocols for IV insulin infusion may recommend an anticipatory reduction of aggressiveness at the time of interruption or tapering of glucocorticoid dose [14]. During any tapering of glucocorticoid therapy after transition to subcutaneous therapy, anticipatory tapering of insulin should occur [104, 105].

Conclusion

For institutions not using proprietary software, insulin-dosing strategies to mitigate risk for hypoglycemia during IV insulin infusion may include the development of recommended "protocol maxima" rates of insulin delivery appropriate to patient condition and supplementation with recurring doses of SC or IV bolus insulin to substitute for the part of the dose that otherwise would be delivered by IV insulin infusion. Reduction of hypoglycemia may require appropriate response to interruption of continuous carbohydrate exposure, transitioning strategies between the use of IV and subcutaneous insulin, modification of antihyperglycemic therapy in the presence of changing renal function or CKD, anticipation of effects traceable to other medications, and process improvement efforts to address protocol violations and nursing burden. Institutional quality improvement efforts should assign high priority to glycemic management programs, including hypoglycemia prevention strategies.

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. 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.

Dharmesh B. Bavda, 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.

Abbreviations *ASHP*, American Society of Health-System Pharmacists Research and Education Foundation; *BG*, Blood glucose; *ICU*, Intensive care unit; *CKD*, Chronic kidney disease; *CVVHD*, Continuous veno-venous hemodialysis; *IV*, Intravenous; *NPO*, Nihil per os; *NPH*, Neutral protamine Hagedorn; *SC*, Subcutaneous; *PN*, Parenteral nutrition; *EN*, Enteral nutrition

Appendix

Table 1 Mortality associated with ICU hypoglycemia

Mortality, ICU hypoglycemia, and associated factors				
Reference	Study design	Patients	Factors	Mortality associated with hypoglycemia
Vriesendorp [3, 4]	Single site medical and surgical ICU including cardiothoracic and neurosurgical patients; all admissions over 2 years; nested case control method	156 patients with glucose value < 45 mg/dL, 155 control patients, from cohort of 2272 patients	Continuous veno-venous hemofiltration with bicarbonate-based substitution fluid, failure to adjust insulin infusion for decreased nutrition, diabetes mellitus, insulin use, sepsis, and need for inotropic or vasopressor drugs were associated with hypoglycemia.	Mortality: no association found, but data set judged too small to exclude the possibility
Krinsley [5]	Single site; consecutive medical, surgical, and cardiac ICU admissions; case-control study	102 patients with at least one episode of severe hypoglycemia (SH) < 40 mg/dL from cohorts of 2666 patients before and 2699 after implementation of a tight glycemic control protocol, each matched to 3 controls	Diabetes, septic shock, renal insufficiency, mechanical ventilation, severity of illness reflected by acute physiology and chronic health evaluation II score with the age component deleted, and treatment in the tight glycemic control period were associated with SH.	Mortality: 57/102 (55.9%) among SH patients vs. 121/306 (39.5%) among the control cases, $p = 0.0057$; multivariable regression analysis for SH as an independent predictor of mortality: OR (95% CI) = 2.28 (1.41–3.70), $p = 0.0008$

Table 1 (continued)

Mortality, ICU hypoglycemia, and associated factors

Reference	Study design	Patients	Factors	Mortality associated with hypoglycemia
Bagshaw [7]	24 ICUs; multivariable analysis	9122 patients having early hypoglycemia < 4.5 mmol/L (< 81 mg/dL) within 24 h of admission, among 66,184 admissions over a 6-year study period	Female sex; having any co-morbid illness, specifically end-stage kidney disease or liver disease; being immune-compromised; medical patients; non-elective admissions; higher severity of illness by APACHE II scoring; primary admission diagnoses of sepsis; and metabolic disturbance and/or poisoning were associated with hypoglycemia.	Adjusted OR (95% CI), presence vs. absence of early hypoglycemia: ICU mortality 1.41 (1.31–1.54), hospital mortality 1.36 (1.27–1.46)
Egi [15]	2 ICUs; analysis of six bands of hypoglycemia; multivariate models	1109 patients having hypoglycemia < 81 mg/dL among 4946 ICU patients	Illness severity by APACHE II score was independently associated with increased overall mortality.	Severity of hypoglycemia independently associated with higher mortality ($p < .001$); unadjusted hospital mortality among 1109 hypoglycemic patients vs. 3837 controls: 36.6 vs. 19.7%, $p < 0.001$
Hermanides [16]	Single site medical/surgical ICU; adjusted incidence rate ratio of ICU death	5961 patients treated with a computerized insulin algorithm to target 72–126 mg/dL; 288 with severe hypoglycemia ≤ 45 mg/dL	Adjustment was performed for age, sex, admission for cardiothoracic surgery, sepsis, the daily sequential organ failure assessment (SOFA) score over time, and ICU days; 20,737 SOFA scores were collected.	Adjusted incidence rate ratio of ICU death (95% CI), according to presence or absence of severe hypoglycemia: 2.1 (1.6–2.8), $p < 0.001$
D'Ancona [17]	Single site cardiac surgery patients treated with IV insulin boli intraoperatively and drips postoperatively; multivariate analysis including mortality	596 patients treated with intraoperative target < 250 mg/dL and postoperative target 80–126 mg/dL, 123 patients with hypoglycemia <70 mg/dL	Diabetes and chronic renal failure were associated with hypoglycemia.	OR for in-hospital mortality, according to presence or absence of hypoglycemia: 20.0 (2.9–136.9), $p = 0.002$
Badawi [23]	Observational study from 344 ICUs; standardized mortality ratio (SMR, actual number of deaths divided by expected number of deaths)	101,877 ICU patients who did not have any evidence of hyperglycemia or hypoglycemia within 1st 24 h of admission, 5369 patients with ICU-acquired hypoglycemia < 60 mg/dL after 24 h in ICU	Of the possible confounders of the relationship between dysglycemia and mortality, ICU-acquired renal injury and respiratory failure were the most strongly associated with mortality.	SMR (95% CI) according to presence or absence of ICU-acquired hypoglycemia: 1.06 (1.00–1.12)
Mahmoodpoor [48]	Two-site observational study; medical-surgical ICU with exclusion of cardiac surgery; stepwise logistic regression analysis to identify predictors of hypoglycemia; multivariate regression model to assess association between hypoglycemia and ICU mortality	450 controls and 50 patients having hypoglycemia < 50 mg/dL	SOFA score, acute kidney injury, and higher HgbA1C were independent risk factors for hypoglycemia.	RR (95% CI) for mortality according to detection of hypoglycemia: 1.2 (0.927–1.58), $p = 0.221$

Mortality and Spontaneous vs. Medication-Induced ICU Hypoglycemia

Reference	Study design	Patients	Factors	Mortality associated with spontaneous hypoglycemia
Kosiborod [12]	40 hospitals; acute myocardial infarction admissions; retrospective cohort study;	482 of 7820 patients who were hyperglycemic on admission and who had random glucose < 60 mg/dL; 346/3045 treated	Septic shock, respiratory failure, acute kidney injury, longer hospital lengths of stay, and higher glucose levels at	For all-cause hospital mortality associated with hypoglycemia, among those receiving vs. not receiving insulin, OR (95% CI):

Table 1 (continued)

Mortality and spontaneous vs. medication-induced ICU hypoglycemia

Reference	Study design	Patients	Factors	Mortality associated with spontaneous hypoglycemia
	logistic regression models; multivariable adjustment	with insulin and 136/4775 not treated with insulin	admission were associated with the development of hypoglycemia.	0.92 (0.58-1.45) vs. 2.32 (1.31-4.12)
Finfer [25••]	Multisite randomized ICU trial of intensive vs. conventional control; multivariate logistic regression analysis	6026 randomized patients, of whom 2714 experienced moderate hypoglycemia 41–70 mg/dL, 223 experienced severe hypoglycemia ≤ 40 mg/dL, and 3089 patients were without hypoglycemia	Risk factors at baseline for subsequent hypoglycemia included age, APACHE II score, higher body mass index, BG elevation, female sex, non-postoperative status, severe sepsis, trauma, diabetes, prior insulin treatment, prior glucocorticoid treatment, cardiovascular failure, and intensive treatment group assignment.	Hazard ratio (95% CI) for death within 90 days after randomization, adjusted for baseline and postrandomization characteristics, for each group when compared to the group without hypoglycemia, for moderate ICU hypoglycemia: 1.41 (1.21 to1.62), $p < 0.001$; for severe hypoglycemia: 2.10 (1.59 to 2.77), $p < 0.001$; for severe hypoglycemia in the absence of insulin treatment: 3.84 (2.37 to 6.23), $p < 0.001$
Saliba [51]	Single center; admissions to medical or surgical ICU; retrospective cohort study; logistic regression analysis	642 patients, 337 with spontaneous hypoglycemia, 305 with hypoglycemia attributed to an antihyperglycemic agent; hypoglycemia classified as severe, moderate, or mild at BG < 40, 40 to 54, and 55 to 69 mg/dL	All-cause hospital mortality was adjusted for the severity and frequency of hypoglycemia, age, sex, APACHE II score without age component, admission location in medical or surgical ICU, diabetes, and chronic pancreatitis.	In the adjusted analysis, OR (95% CI) for hospital mortality for severe vs. mild hypoglycemia: 5.44 (2.91–10.18), $p < 0.001$; for moderate vs. mild hypoglycemia: 2.38 (1.52–3.73), $p < 0.001$; for severe vs. moderate hypoglycemia: 2.29 (1.15–4.56), $p = 0.02$; for medication-induced compared to spontaneous hypoglycemia: 1.22 (0.77–1.93), $p = 0.39$

Confounding factors might predispose both to hypoglycemia and to mortality. However, a number of studies suggest that the association between ICU hypoglycemia and mortality may be partly independent of other predisposing factors

Table 2 Insulin dose and hypoglycemia during glycemic management of critically ill adults

Reference	Population	Comparison	BG targets	BG central tendency and dispersion	Insulin delivered	Hypoglycemia
Barletta [73]	Single site; surgical patients	Observational study: user-interpreted protocol before introduction of computer-guided dosing (145 patients) vs. computer-guided dosing (47 patients)	80–110 mg/dL	Mean ± SD 116 ± 11 vs. 113 ± 11 mg/dL, $p = 0.067$	Daily insulin dosage 80 (14–393) vs. 71 (15–259) units/day, $p = 0.337$	Percentage of BG < 40 mg/dL: 0.1 ± 0.5 vs. 0.04 ± 0.2, $p = 0.518$; percentage of patients having any BG < 40 mg/dL: 4.1 vs. 2.1, $p = 1.00$
Lazar [21]	Single site; cardiac surgery patients during and after anesthesia and for 18 h in ICU	Randomized study, with user-interpreted drip protocols with bolus supplements: aggressive targets (40 patients) vs. moderate targets (42 patients)	90–120 vs. 120–180 mg/dL	Mean ± SD 135 ± 12 vs. 103 ± 17 mg/dL, $p < 0.0001$	Mean ± SD insulin while on drip 118 ± 35 vs. 77 ± 30 units; $p = 0.004$	BG < 80 mg/dL: 75% vs. 10% of patients, $p < 0.0001$

Table 2 (continued)

Reference	Population	Comparison	BG targets	BG central tendency and dispersion	Insulin delivered	Hypoglycemia
Yamashita [74]	Single site; CV surgery patients	Observational study: user-interpreted protocol before introduction of computer-guided dosing (50 patients) vs. after introduction of computer-guided multiplier algorithm (50 patients)	Single target, 5.1–8.0 mmol/L	Mean ±SD 8.7 ± 1.0 vs. 7.9 ± 1.3 mmol/L, $p = 0.002$	Mean ± SD 2.6 ± 1.1 vs. 3.6 ± 2.0 units/h, $p = 0.01$	BG < 4.0 mmol/L: 12 (1.4%) of 875 vs. 36 (3.7%) of 973 measurements, $p = 0.003$
Finfer [25••]	Multi-site	Randomized study, with user-interpreted protocols: intensive target (3013 patients) vs. conventional target (3013 patients)	81–108 vs. ≤ 180 mg/dL	Mean BG ± SD in milligrams per deciliter during treatment according to lowest BG: lowest BG ≤ 40, mean BG 110 ± 17; lowest BG 41–70, mean BG 116 ± 22; lowest BG > 70, mean BG 139 ± 25	Mean ± SD according to the lowest BG: BG ≤ 40 mg/dL, 44.0 ± 28.9 units/day; BG 41–70 mg/dL, 47.9 ± 39.3 units/day; BG > 70 mg/dL, 20.3 ± 31.6 units/day	Hazard ratio (CI) for BG ≤ 70 mg/dL, intensive vs. conventional: 24.19 (20.98, 27.88), $p < 0.001$
Horibe [75]	Single site; postoperative patients	Randomized study: user-interpreted protocol (25 patients) vs. fading memory computer-guided dosing (23 patients)	Single target, 140 ± 20 mg/dL	BG measurements within target during maintenance: 59% vs. 71%, $p = 0.16$; pooled within-patient SD of glucose levels during maintenance: 21.6 mg/dL ($n = 22$) vs. 15.6 mg/dL ($n = 23$ patients), $p < 0.001$	Mean ± SE 4.6 ± 0.4 vs. 3.5 ± 0.4 units/h, $p = 0.043$	BG < 60 mg/dL: 1 vs. 0 patients
Van Herpe [76]	Single site	Randomized study: nurse-directed algorithm (151 patients) vs. LOGIC-C computer-guided dosing (149 patients)	Single target, 80–110 mg/dL	Mean ± SD 107 ± 11 vs. 106 ± 9 mg/dL, $p = 0.36$; percent time in target, mean±SD 60.1 ± 18.8 vs. 68.6 ± 16.7%, $p = 0.00016$	Median (IQR) 21.6 (13.8–37.3) vs. 20.0 (13.7–34.6) units/day, $p = 0.40$	Number (%) of patients having BG < 70 mg/dL: 73 (48.3%) vs. 48 (32.2%), $p = 0.0048$
Kalfon [33]	Multi-site; patients having ≥ 3 days in adult ICU	Randomized study: tight control, computer-guided dosing (1317 patients) vs. conventional control, user-interpreted protocols (1284 patients)	4.4–6.1 vs. < 10.0 mmol/L	Median (IQR) of patient means of BG 6.4 (6.0–7.1) vs. 7.0 (6.3–7.9) mmol/L, $p < 0.001$	For those receiving insulin, median (IQR) 43.1 (24.5–70.0) vs. 34.1 (17.9–58.3) units/day, $p < 0.001$	Number (%) of patients having BG < 2.2 mmol/L: 174 (13.2%) vs. 79 (6.2%), $p < 0.001$
DiMuzio [45]	Single site; patients having diabetes	Observational study, with user-interpreted protocols: before discontinuation of tighter targets (40 patients) vs. after introduction of liberal targets (40 patients)	6–10 vs. 10–14 mmol/L	Median (IQR) of 48-h time-weighted patient means of BG 9.0 (7.5–10) vs. 9.7 (7.3–12) mmol/L, $p = 0.37$	Percent of patients receiving insulin on day 1: 50.0 vs. 16.7%, $p = 0.007$	Number (%) of patients having absolute hypoglycemia: 4 (10.0%) vs. 4 (10.0%), $p = 1.0$; relative hypoglycemia (30% reduction from eAG by A1C): 20 (50.0%) vs. 9 (22.5%), $p = 0.01$
Kar [47]	Single site; patients having type 2 diabetes, with chronic hyperglycemia (A1C ≥ 7%)	Observational study, with user-interpreted protocols: before discontinuation of standard targets for chronic hyperglycemia (52 patients) vs. after introduction of liberal	6–10 vs. 10–14 mmol/L	Mean (SD) of 7-day time-weighted patient mean or median of BG 9.3 (1.8) vs. 10.3 (2.1) mmol/L, $p = 0.02$; coefficient of variability mean ± SD	Rate of insulin administration: similar between groups	Number of patients having BG ≤ 3.9 mmol/L: 18 (35%) vs. 5 (16%); relative risk (95% CI) for episode of BG ≤ 3.9 mmol/L, after vs.

Table 2 (continued)

Reference	Population	Comparison	BG targets	BG central tendency and dispersion	Insulin delivered	Hypoglycemia
	and BG > 10 mmol/L	targets for chronic hyperglycemia (31 patients)		33.2 ± 12.9 vs. 23.8 ± 7.7%, $p < 0.01$		before: 0.47 (0.19–1.13), $p = 0.09$
Marvin [49•]	Multi-site; medical and surgical	Observational study, with computer-guided dosing: before inclusion of mid-protocol bolus feature (2620 protocol use periods) vs. after inclusion of mid-protocol bolus feature (105 protocol use periods)	Single target, 140 mg/dL	Mean after first attaining BG < 180 mg/dL, 143.8 vs. 146.4 mg/dL	Percent of infusions < 5 units/h 44.4 vs. 64.8%, $p < 0.001$	Percent of protocol use periods having BG < 70 mg/dL: 5.8% vs. 0.95% (1/105 protocol use periods having BG 69 mg/dL)
Stewart [77•]	Two-site; medical and surgical	Observational study, with computer-guided dosing: at Gyula (47 patients), vs. at Christchurch, with bolus feature (267 patients)	Single target, 4.4–8.0 mmol/L	Per-episode hourly interpolated BG, median (IQR) in millimoles per liter, 6.7 (6.5–7.1) vs. 6.7 (6.4–7.3), $p = 0.60$	Median (IQR) 3.2 (2.4–4.6) vs. 2.7 (1.9–3.5) units/h, $p < 0.05$	Number (%) of patients having BG < 4.0 mmol/L: 25 (53.2%) vs. 70 (26.3%), $p < 0.05$
Welsh [52]	Single site; liver or liver/kidney transplant	Randomized study, with user-interpreted protocols: lower targets (79 patients) vs. higher targets (76 patients)	140 vs. 180 mg/dL	N/A	Peak insulin drip rates according to hypoglycemia vs. no hypoglycemia 17.4 ± 10.3 vs. 13.1 ± 9.9 units/h, $p = 0.044$	Number of episodes and number (%) of patients having BG < 70 mg/dL while on drip: 20 episodes in 13/79 (16%) of patients vs. 2 episodes in 2/76 (2.6%) of patients
Krinsley [53]	Single site	Observational study, after a practice change, with user-interpreted guidelines embedded in EMR: targeting tighter control for diabetes with A1C < 7% or non-diabetes (104 patients) vs. targeting looser control for diabetes with A1C ≥ 7% (106 patients)	80–140 vs. 110–160 mg/dL	Median (IQR) of the patient means of BG 136 (119–149) vs. 159 (138–177) mg/dL, $p < 0.0001$	Median (IQR) 9.8 (4.7–25.4) vs. 25.0 (10.6–48.3) units/h, $p < 0.0001$	Percent of patients having BG < 70 mg/dL: 20.19 vs. 14.15%, $p = 0.33$

Lower glycemic targets and higher doses of insulin may be accompanied by increased occurrence of hypoglycemia. Insulin resistance and nutritional exposure could alter the relationship. The possibility of identifying "protocol maxima" for insulin delivery, appropriate to patient condition, has not been systematically studied for its potential to achieve target range control while reducing the risk for hypoglycemia

Table 3 Recurring doses of subcutaneous or intravenous bolus insulin to accompany intravenous insulin infusion

Reference	Indication for bolus	Bolus rules
DeSantis [79]	Recommended component of IV therapy under user-interpreted insulin infusion protocol for critically ill patients	Loading bolus according to BG elevation at initiation of protocol, additional recurring doses of bolus insulin to accompany insulin infusion in doses indicated by protocol
Olansky [80]	Recommended component of IV therapy under user-interpreted insulin infusion protocol for postoperative patients in cardiovascular intensive care unit	If BG > 150 mg/dL for 4 consecutive measurements, bolus with 0.05 units/kg (maximum bolus is 5 units)
Dungan [81]	Subcutaneous prandial coverage in conjunction with user-interpreted protocol for postoperative heart patients receiving IV insulin infusion, preparatory to transitioning	Insulin aspart, 1 unit per 10 g carbohydrate, as soon as a diet was ordered. In case of very large basal insulin requirements (> 70 units), 1 unit per 5 g of carbohydrate intake

Table 3 (continued)

Reference	Indication for bolus	Bolus rules
Lazar [21]	Recommended component of IV therapy under user-interpreted insulin infusion protocol for cardiac surgery patients during and after bypass	Recurring doses of bolus insulin to accompany insulin infusion in doses indicated by protocol
Kreider [82]	Subcutaneous prandial coverage in conjunction with user-interpreted insulin infusion protocol for patients who need to continue intravenous insulin while having an oral diet	Give 4 units of rapid-acting insulin analog insulin three times/day before meals only
Marvin [49•]	Recommended component of IV therapy under computer-guided insulin infusion protocol	For BG > 180 mg/dL and not decreasing or for BG 141–180 and increasing, give IV bolus in dosage dependent upon change of BG and recommended change of rate of IV infusion
Stewart [77•]	Recommended component of IV therapy under computer-guided insulin infusion protocol	Hourly bolus IV insulin may be delivered, with added continuous insulin infusions up to 3 units/h when insulin requirements are high and sustained

Protocol subroutines may recommend subcutaneous (SC) or intravenous (IV) bolus therapy as partial substitution for insulin that otherwise might be delivered by continuous IV insulin infusion. Insulin bolus therapy during IV insulin infusion offers a potential advantage of restricting extended duration of higher rates of insulin infusion, thus limiting total insulin delivery and possibly reducing hypoglycemia. Low doses of hourly insulin may be sufficient for many patients. To substitute for part of the insulin dose that otherwise would be given as a continuous IV insulin infusion, recurring bolus therapy may be a promising approach, with theoretical advantages compared to continuous IV infusion alone [49•, 77•]. Insulin resistance may decline early in the course of ICU care. Excessive loading with insulin perhaps should be avoided [106]

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- • Of importance
- •• Of major importance

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