

Guidelines for the use of an insulin infusion for the management of hyperglycemia in critically ill patients

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Objective: To evaluate the literature and identify important aspects of insulin therapy that facilitate safe and effective infusion therapy for a defined glycemic end point.

Methods: Where available, the literature was evaluated using Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) methodology to assess the impact of insulin infusions on outcome for general intensive care unit patients and those in specific subsets of neurologic injury, traumatic injury, and cardiovascular surgery. Elements that contribute to safe and effective insulin infusion therapy were determined through literature review and expert opinion. The majority of the literature supporting the use of insulin infusion therapy for critically ill patients lacks adequate strength to support more than weak recommendations, termed suggestions, such that the difference between desirable and undesirable effect of a given intervention is not always clear.

Recommendations: The article is focused on a suggested glycemic control end point such that a blood glucose ≥ 150 mg/dL triggers interventions to maintain blood glucose below that level and absolutely < 180 mg/dL. There is a slight reduction in mortality with this treatment end point for general intensive care unit patients and reductions in morbidity for perioperative patients, postoperative cardiac surgery patients, post-traumatic injury patients, and neurologic injury patients. We suggest that the insulin regimen and

monitoring system be designed to avoid and detect hypoglycemia (blood glucose ≤ 70 mg/dL) and to minimize glycemic variability.

Important processes of care for insulin therapy include use of a reliable insulin infusion protocol, frequent blood glucose monitoring, and avoidance of finger-stick glucose testing through the use of arterial or venous glucose samples. The essential components of an insulin infusion system include use of a validated insulin titration program, availability of appropriate staffing resources, accurate monitoring technology, and standardized approaches to infusion preparation, provision of consistent carbohydrate calories and nutritional support, and dextrose replacement for hypoglycemia prevention and treatment. Quality improvement of glycemic management programs should include analysis of hypoglycemia rates, run charts of glucose values < 150 and 180 mg/dL. The literature is inadequate to support recommendations regarding glycemic control in pediatric patients.

Conclusions: While the benefits of tight glycemic control have not been definitive, there are patients who will receive insulin infusion therapy, and the suggestions in this article provide the structure for safe and effective use of this therapy. (Crit Care Med 2012; 40:3251–3276)

KEY WORDS: critical care; glycemic control; glucose meter; glucose monitoring; guideline; hyperglycemia; insulin; protocol; stress hyperglycemia

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Dr. Agus has consulted for the Diabetes Technology Society. He also has a pending patent on an ECMO-based glucose sensor, which is not connected to idea discussed in this article. Dr. Braithwaite has a U.S. patent. Dr. Kohl has received grant support from Amylin and Eli Lilly. Dr. Krinsley has performed consulting work for Medtronic Inc., Edwards Life Sciences, Baxter, Roche Diagnostics, and Optiscan Biomedical and has received speaker's fees from Edwards Life Sciences, Roche Diagnostics and Sanofi-Aventis. Dr. Nasraway has consulted for Optiscan, Echo Therapeutics. Dr. Geehan has received grant support from the Department of Defense Research. Dr. Rigby has received consulting fees from Medtronic. Dr. Schallom has received honoraria/speaking fees from Roche Laboratories Speakers Bureau on

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The American College of Critical Care Medicine (ACCM), which honors individuals for their achievements and contributions to multidisciplinary critical care medicine, is the consultative body of the Society of Critical Care Medicine (SCCM) that possesses recognized expertise in the practice of critical care. The College has developed administrative guidelines and clinical practice parameters for the critical care practitioner. New guidelines and practice parameters are continually developed, and current ones are systematically reviewed and revised.

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The notion of tight glycemic control (GC) became more prominent in the critical care literature in 2001 when a landmark study by Van den Berghe and colleagues (1) demonstrated a significant mortality benefit when maintaining blood glucose (BG) between 80 and 110 mg/dL. Prior to that publication, GC was not a high priority in most intensive care unit (ICU) patients. Data have confirmed the observation that hyperglycemia is associated with an increase in death and infection, seemingly across the board among many case types in the ICU (2, 3). Many centers have attempted to assess the feasibility of maintaining normoglycemia in critically ill patients and to further establish the potential risk or benefit of this approach in a variety of ICU patient subsets. While there have been conflicting results from numerous studies, the question is no longer whether GC is beneficial or not, but rather what is the appropriate degree of GC that can be accomplished safely and with justifiable utilization of resources.

This Clinical Practice Guideline will evaluate the available literature and address aspects of implementation that permit safe and effective insulin infusion therapy. Methodology and assessment will be emphasized to help clinicians achieve the BG goal that is considered to have the greatest benefit and safety for their patient population while avoiding clinically significant hypoglycemia.

GUIDELINE LIMITATIONS

Guidelines are limited by the available literature and the expertise of the writing panel and reviewers. The recommendations are not absolute requirements, and therapy should be tailored to individual patients and the expertise and equipment available in a particular ICU. The use of an insulin infusion requires an appropriate protocol and point-of-care (POC) monitoring equipment with frequent BG monitoring to avoid hypoglycemia. Recommendations may not be applicable to all ICU populations, and limitations will be discussed when applicable. Future literature may alter the recommendations and should be considered when applying the recommendations within this article.

Intravenous (IV) insulin will be the primary therapy discussed, but subcutaneous (SQ) administration may also have a role for GC in stable ICU patients. Other agents and approaches, including oral

hypoglycemic drugs, and other antidiabetic agents may be continued or restarted in selected patients, but will not be discussed in this article. Studies evaluating insulin as a component of other therapies (such as glucose–insulin–potassium) were not evaluated.

TARGET PATIENT POPULATION FOR GUIDELINE

These guidelines are targeted to adult medical and surgical ICU patients as a group, but individual population differences regarding therapy or monitoring will be discussed. Data on the glycemic management of pediatric ICU patients are limited, but will be described where available.

METHODOLOGY

The Guideline Task Force was composed of volunteers from the Society of Critical Care Medicine with a specific interest in the topic and the guideline process. The Task Force members developed a list of clinical questions regarding the appropriate utilization of insulin infusions to achieve GC, considering patient/populations, interventions, comparisons, and outcomes. Applicable literature was compiled using a variety of search engines (PubMed, OVID, Google Scholar, reference lists from other publications, search of Clinicaltrials.gov, and the expertise and experience of the authors). Searches were performed periodically until the end of 2010 using the following terms: acute stroke, BG, cardiac surgery, critical care, critical illness, critically ill patients, dextrose, glucose, glucose control, glucose metabolism, glucose meters, glucose toxicity, glycemic control, glycemic variability, hyperglycemia, hypoglycemia, ICU, insulin, insulin infusion, insulin protocols, insulin resistance, insulin therapy, intensive care, intensive insulin therapy, mortality, myocardial infarction, neurocognitive function, neuroprotection, outcomes, pediatric, pediatric intensive care, point-of-care, point-of-care testing, sepsis, sternal wound infection, stress hyperglycemia, stress, stress hormones, stroke, subarachnoid hemorrhage, surgery, tight glycemic control protocols, and traumatic brain injury (TBI).

Published clinical trials were used as the primary support for guideline statements, with each study evaluated and given a level of evidence. Abstracts and

unpublished studies or data were not included in the analysis. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) system was used to rate the quality of evidence and strength of the recommendation for each clinical practice question (4). A member of the GRADE group was available to provide input and answer methodologic questions.

Meta-analyses using RevMan and GRADEPro software were applied to organize evidence tables, create forest and funnel plots, and draw conclusions about the overall treatment effects or specific outcomes applicable to a particular recommendation (5, 6).

Recommendations are classified as strong (Grade 1) or weak (Grade 2) and are focused on specific populations where possible. Strong recommendations are listed as “recommendations” and weak recommendations as “suggestions.” Throughout the development of the guidelines, there was an emphasis on patient safety and whether the benefit of adherence to the recommendation would outweigh the potential risk, the burden on staff, and when possible, the cost. If the risk associated with an intervention limited the potential for benefit, or if the literature was not strong, the statement was weakened to a suggestion. Individual patient or ICU circumstances may influence the applicability of a recommendation. It is important to recognize that strong recommendations do not necessarily represent standards of care.

Numerous discussions among the authors led to consensus regarding the recommendations. Individual members or subgroups drafted the recommendations and justifications. Subsequently, each recommendation was reviewed by the Task Force members who were provided the opportunity to comment, propose changes, and approve or disapprove each statement. Once compiled, each member was again asked to review the article and provide input. Consensus was sought for recommendation statements, and controversial statements were repeatedly edited and feedback provided through secret ballots until there was consensus. Actual or potential conflicts of interest were disclosed annually, and transparency of discussion was essential. External peer review was provided through the *Critical Care Medicine* editorial process, and approval was obtained by the governing board of the Society of Critical Care Medicine.

RECOMMENDATIONS

While the initial goal was to suggest glycemic targets for critically ill patients, the limited available literature has narrowed the scope of this article and the ability to make recommendations for specific populations. An overriding focus is on the safe use of insulin infusions. The glycemic goal range of 100–150 mg/dL is a consensus goal, and while it differs slightly from the more stringent goal of 110–140 mg/dL for selected populations, recently published by the American Diabetes Association, and the overall glucose goal of 140–180 mg/dL, this difference is not likely to be clinically significant (7).

1. In adult critically ill patients, does achievement of a BG < 150 mg/dL with an insulin infusion reduce mortality, compared with the use of an insulin infusion targeting higher BG ranges?

We suggest that a BG \geq 150 mg/dL should trigger initiation of insulin therapy, titrated to keep BG < 150 mg/dL for most adult ICU patients and to maintain BG values absolutely <180 mg/dL using a protocol that achieves a low rate of hypoglycemia (BG \leq 70 mg/dL) despite limited impact on patient mortality.

[Quality of evidence: very low]

Numerous reports have associated hyperglycemia with a poor patient outcome (1–3, 8–11). Retrospective analysis of 259,040 admissions demonstrated a significant association between hyperglycemia and higher adjusted mortality in unstable angina, acute myocardial infarction, congestive heart failure, arrhythmia, ischemic and hemorrhagic stroke, gastrointestinal bleeding, acute renal failure, pneumonia, pulmonary embolism, and sepsis (3). The mortality risk was significantly greater at each higher BG range in patients without a history of diabetes in this large Veterans Affairs database. The intensity of the stress response, preexisting diabetes, and concurrent treatment will influence the degree of hyperglycemia. The impact of hyperglycemia on outcome may be related to the presence of preexisting diabetes, the intensity of the hyperglycemic response, the diagnosis, and the risk for infection.

A simple intervention for slightly elevated BG values is to avoid or minimize dextrose infusions when patients are receiving other sources of nutritional support; however, the majority of critically ill patients will require insulin

when BG >150 mg/dL (12). Insulin infusion therapy is recommended for most critically ill patients, although selected patients may be managed on SQ therapy as discussed later in the article.

Several large randomized controlled trials (RCTs) have addressed the impact of GC on mortality with variable results, although the ability to compare results is hampered by differing populations, methodology, and end points (Table 1) (1, 13–16). Small randomized trials, defined as <1,000 patients, are also included (17–22). Several large cohort trials have also been reported, although use of remote historical controls, inconsistent or voluntary utilization of insulin therapy and protocols, and concurrent changes in clinical practice complicate the interpretation of outcome (23–28). One small cohort trial was also evaluated for the impact of insulin therapy on patient outcome (29).

Limitations in these trials are significant. Many are single-center trials, and the influence of local practices (e.g., nutrition, fluid therapy, available technology, nursing expertise with insulin titration) cannot be adequately factored into the results. Several trials failed to achieve the glycemic target or had protocol violations, or voluntary use of an insulin infusion protocol in the cohort studies might have biased the results. The small RCTs were inadequately powered to assess mortality. Most studies used glucose meters, and BG values were checked at varying frequencies (30 mins–4 hrs), influencing the risk for hypoglycemia detection. The data provided on actual BG values are variable, ranging from inclusion of one daily BG to a mean daily BG, or a time-weighted mean. Thus, effectiveness of the protocols at minimizing glucose variability and hypoglycemia cannot be thoroughly assessed. Nursing compliance with intensive insulin protocols is typically unmeasured and unquantified. Cohort studies could not control for practice changes that occurred during the course of data collection or inconsistent protocol utilization. Importantly, the standard of care likely influenced the control population in several studies, as mean BG in the control group has fallen throughout the last decade (30).

Our meta-analysis included the largest clinical trials and large and small cohort trials. indicates a small but significant, 16% reduction in the odds ratio (OR) for hospital mortality with the use of insulin infusion therapy, targeting BG < 150 mg/dL, OR 0.84, 95% confidence

interval (CI) [0.71, 0.99] ($p = .04$), but does not suggest an impact on ICU mortality OR 0.99, 95% CI [0.86, 1.15]; ($p = .92$) (Fig. 1A and B). The data demonstrate a high level of heterogeneity, $I^2 = 80\%$, that led to selection of the random-effects model for analysis. Sensitivity testing was performed excluding each of the large randomized trials (1, 16), but this did not substantially change the results (see Supplemental Digital Content 1, <http://links.lww.com/CCM/A589>).

Our selection of 150 mg/dL as a trigger for intervention is a consensus decision to reflect the various treatment goals reported in the literature. Using a higher trigger value could allow excursion of BG >180 mg/dL, which is undesirable with respect to the immunosuppressive effects and potential to exceed the renal threshold for glucosuria. Our recommendation is similar to the American Diabetes Association guidelines for initiation of insulin for a glucose threshold no higher than 180 mg/dL, and that a more stringent goal of 110–140 mg/dL may be used if there is a documented low rate of severe hypoglycemia (7).

In contrast, there are at least three published meta-analysis reviews published in the peer-review literature that have suggested no significant mortality benefits from insulin infusion therapy to maintain “tight” GC (BG <150 mg/dL). The first review from Wiener et al (31) included abstracts and unpublished data, which we have excluded from our analysis, but did not include cohort studies. These authors concluded that there was no significant impact on mortality when comparing insulin infusions to achieve tight GC compared with usual care, OR 0.93, 95% CI [0.85, 1.03]. A more recent review following the completion of the largest multicenter trial found similar results with a mortality OR 0.93, 95% CI [0.83, 1.04] (32). A third meta-analysis evaluated only the seven largest trials and had a similar conclusion with a mortality OR 0.95, 95% CI [0.87, 1.05] (33). The different methodologies employed and inclusion of different literature likely explain results that are slightly different from the findings in this article. Further analysis of our data is available in the supplemental materials (see Supplemental Digital Content 1, <http://links.lww.com/CCM/A589>), with a subset analysis that separates observational trials from RCTs.

2. In adult critically ill patients, what are the morbidity benefits of maintaining BG < 150 mg/dL?

Table 1. Summary of key clinical trials used to evaluate the impact of glycemic control^a

Author	Intensive Care Unit Population	Study Quality	
		Design/End Point	Design Assessment
Large randomized controlled trials			
Van den Berghe et al (1)	Surgical, mechanical ventilation	Randomized 80–110 mg/dL vs. 180–200 mg/dL Research RN titrated insulin per protocol	Single center, Evaluated mean morning glucose
Van den Berghe et al (14)	Medical, expected intensive care unit stay >72 hrs	Randomized Bedside RN titrated per paper protocol	Single center Evaluated mean morning glucose
Preiser et al (15)	Medical and surgical	Randomized 80–110 mg/dL vs. 140–180 mg/dL Bedside RN titrated per protocol	Multicenter, Evaluated all glucose values, also median morning value
The NICE-SUGAR Investigators (16)	Medical and surgical	Randomized 80–110 mg/dL vs. 140–180 mg/dL Adjusted via computerized algorithm	Multicenter Evaluated mean time-weighted glucose Outcome based on 90-day mortality
Small randomized controlled trials			
Brunkhorst et al (17)	Sepsis	Randomized 80–110 mg/dL vs. 180–200 mg/dL Bedside RN titrated per Van den Berghe protocol	Multicenter, Evaluated mean morning glucose
De La Rosa et al (18)	Medical and surgical	Randomized 80–110 vs. 180–200 mg/dL Bedside RN titrated per protocol	Single center Evaluated mean morning glucose, also daily minimum and maximum values
Arabi et al (19)	Medical and surgical	Randomized 80–110 mg/dL vs. 180–200 mg/dL Bedside RN titrated per paper protocol	Single center, Evaluated daily average glucose
Farah et al (20)	Medical with >3- day length of stay	Randomized 110–140 mg/dL vs. 140–200 mg/dL	Single center, reported overall average glucose
Grey and Perdrizet (21)	Surgical, excluded patients with diabetes	Randomized 80–120 mg/dL vs. 180–220 mg/dL	Single center, reported daily average and overall average glucose
Mackenzie et al (22)	Medical and surgical	Randomized 72– 108 mg/dL vs. 180–198 mg/dL	Two centers, multiple glucose end points reported
Large cohort			
Krinsley (23)	Medical and surgical	Observational cohort <140 mg/dL vs. historical control Bedside RN titrated	Single center Evaluated all glucose values
Furnary et al (24)	CV surgical, diabetic patients	Observational IV-various goals (final <150 mg/dL) vs. SQ control Bedside RN titrated per protocol	Single center Historical control Variable end points Long study timeline Evaluated average daily glucose for three postoperative days
Treggiari et al (25)	Medical, surgical, and trauma	Observational cohort 80–110 mg/dL vs. 80–130 mg/dL vs. historical control Bedside RN titrated per protocol	Single center Protocol utilization was optional Evaluated all glucose values
Krinsley (26)	Medical, surgical, and trauma	Observational cohort <140 or <125 mg/dL vs. historical control Bedside RN titrated	Single center, includes patients in reference 12
Scalea et al (27)	Trauma	Prospective cohort, post-protocol goal <150 mg/dL Bedside RN titrated, no dosing guidelines	Single center, Evaluated highest single daily glucose and pattern of response
Furnary and Wu (28)	CV surgical, diabetics	Observational IV-various goals (final <110 mg/dL) vs. SQ control Bedside RN titrated per protocol	Single center Historical control Variable end points Long study timeline Evaluated average daily glucose for three postoperative days
Small cohort			
Toft et al (29)	Medical-surgical and no CV surgical	Prospective cohort, post-protocol goal 80–110 mg/dL Bedside RN titrated per Van den Berghe protocol	Single center, Evaluated mean morning glucose

IV, intravenous; IQR, interquartile range; CV, cardiovascular; SQ, subcutaneous; 3-blood glucose = 3-day average postoperative blood glucose.

^aSmall trials included <1,000 patients; ^bhospital mortality unless otherwise specified; ^ctreatment not blinded.

No. of Patients		Findings			
		Actual Glycemic End Points Mean ± SD (mg/dL)		Hospital Mortality Odds Ratio [95% Confidence Interval] ^b	Comment ^c
Control	Glycemic Control	Control	Glycemic Control		
783	765	Daily 153 ± 33	Daily 103 ± 19	0.64 [0.45, 0.91]	Control glucose elevated with IV dextrose, stopped early for benefit
605	595	Daily 153 ± 31	Daily 111 ± 29	0.89 [0.71, 1.13]	Control glucose elevated with IV dextrose
542	536	144 (IQR 128–162) median–all values	117 (IQR 108–130) median–all values	1.27 [0.94, 1.7]	Stopped early for hypoglycemia, many protocol violations
3050	3054	144 ± 23	115 ± 18	28-day 1.09 [0.96, 1.23] 90-day 1.14 [1.02, 1.28]	Glycemic control group did not achieve target
290	247	Median daily 138 (IQR 111–184)	Median daily 130 (IQR 108–167)	28-day mortality 0.94 [0.63, 1.38]	Control target artificially elevated with IV dextrose. Study stopped early for hypoglycemia risk. Inadequate size to detect difference in mortality
250	254	Median–all values 149 (IQR 124–180)	Median–all values 120 (IQR 110–134)	28-day mortality 1.08 [0.75, 1.54]	Did not achieve target glucose, inadequate sample to detect mortality difference
257	266	171 ± 34	115 ± 18	0.78 [0.53, 1.13]	Small trial, inadequate size to show mortality impact
48	41	174 ± 20	142 ± 14	1.37 [0.59, 3.16]	Baseline imbalance in diabetes incidence and admission glucose
27	34	179 ± 61	125 ± 36 mg/dL, Daily mean value lower on each day	0.47 [0.12, 1.86]	Lower nosocomial infection incidence with glycemic control
119	121	8.4 ± 2.4	7.0 ± 2.4	0.73 [0.43, 1.24]	Inadequate size to show mortality impact
800	800	152 ± 93	131 ± 55	0.45 [0.34, 0.60]	High protocol adherence, subcutaneous and IV insulin
942	2612	214 ± 41	177 ± 30	0.27 [0.19, 0.39] <i>p</i> < .001	Remote historical controls on SQ insulin only
2366	<130 mg/dL, n = 3322 <110 mg/dL n = 4786	Mean all values 147 ± 42	Mean all values Goal < 130: 142 ± 37 Goal < 110: 133 ± 31	1.07 [0.9, –1.21]	Low protocol utilization, overlap in glucose values actually achieved
2666	2699	Mean overall 154 ± 88	Mean overall 124 ± 51	0.72 [0.62, 0.83]	Includes patients in Krinsky above
1021	1108	Data not provided	Data not provided	0.68 [0.52, 0.89]	Changes in standard of care likely during trial
1065	4469	Data not provided	Data not provided	0.39 [0.28, 0.54]	Includes patients in Furnary above
135	136	Median daily 133 (IQR 121–150)	Median daily 110 (IQR 104–117)	0.77 [0.38, 1.55]	Small trial, but trend to benefit with glycemic control

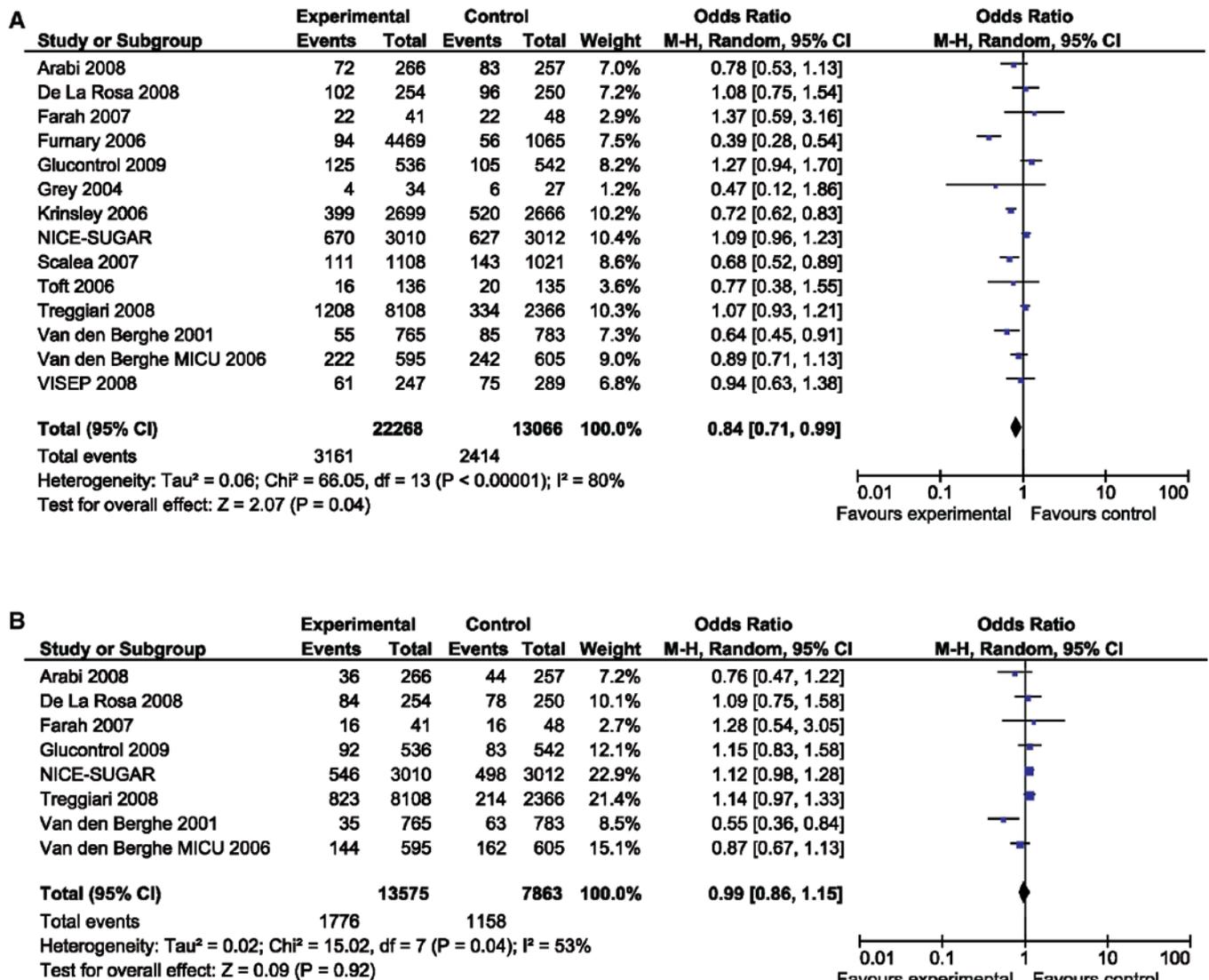


Figure 1. Forest plots of (A) hospital or 28-day mortality and (B) intensive care unit mortality (1, 14–21, 25–29). CI, confidence interval; MH, Mantel-Haenszel.

A. We suggest that there is no consistently demonstrated difference in several morbidity measures (renal failure, transfusion, bacteremia, polyneuropathy, and ICU length of stay [LOS]) when evaluated in the general adult ICU population.

[Quality of evidence: very low]

The following were considered as morbidity outcomes for evaluation, acute renal replacement therapy, incidence of transfusion, bacteremia, critical illness polyneuropathy, and ICU LOS. To analyze ICU LOS in those studies in which data were reported nonparametrically, the median value was used and interquartile range (IQR, 1.35) was used as an estimate of sample standard deviation (SD). Duration of mechanical ventilation was not analyzed as there

was consensus that too many confounding variables existed for this outcome. A reduction in critical illness polyneuropathy was not analyzed as this potential benefit was reported in only one study. Our analysis suggests that no evidence of benefit was found in ICU LOS with OR -0.05 , 95% CI $[-0.14, 0.05]$; prevention of bacteremia OR 0.81, 95% CI $[0.58, 1.11]$; need for transfusion OR 1.06, 95% CI $[0.90, 1.26]$; or need for renal replacement therapy OR 0.90, 95% CI $[0.7, 1.16]$, but variable study design, populations, and end points limit the analysis. The forest and funnel plots are available in Supplemental Digital Content 1 (<http://links.lww.com/CCM/A589>).

B. We suggest implementation of moderate GC (BG < 150 mg/dL) in the postoperative period following cardiac

surgery to achieve a reduced risk of deep sternal wound infection and mortality.

[Quality of evidence: very low]

The only large-scale RCT to date evaluating the impact of tight GC on morbidity and mortality in a population weighted with postoperative cardiac surgical patients was published in 2001 (1). Almost two thirds of this study population underwent cardiac surgery. Patients in the GC group (80–110 mg/dL) had lower ICU and hospital mortality rates compared with conventional therapy (BG 180–200 mg/dL). Morbidity benefits for the GC group included a reduced need for renal replacement therapy, less chance of hyperbilirubinemia, earlier cumulative likelihood of weaning from mechanical ventilation, and ICU and hospital discharge. A follow-up

preplanned subanalysis of the 970 high-risk cardiac surgery patients from the original study confirmed a survival benefit due to GC up to 2 yrs after hospital discharge and longer for the subset treated for at least 3 days (34). Additionally, a series of reports from a clinical database of diabetic cardiac surgery patients suggested that maintenance of BG < 150 mg/dL is associated with a reduction of sternal wound infection and an incremental decrease in hospital mortality compared with remote historical control patients treated with sliding-scale insulin (24, 35–37). Another retrospective review of patients treated with a combination of IV and SQ insulin in the postoperative period showed a strong association between GC and reduction in morbidity and mortality (38).

C. In the population of critically ill injured (trauma) ICU patients, we suggest that BG \geq 150 mg/dL should trigger initiation of insulin therapy, titrated to keep BG < 150 mg/dL for most adult trauma patients and to maintain BG values absolutely < 180 mg/dL, using a protocol that achieves a low rate of hypoglycemia (BG \leq 70 mg/dL) to achieve lower rates of infection and shorter ICU stays in trauma patients.

[Quality of evidence: very low]

A hypermetabolic stress response resulting in hyperglycemia is common in the trauma population (39). Hyperglycemia on admission or within the first 2 ICU days may be predictive of poor outcome (longer LOS, more infection) and higher mortality (40–42). Additionally, persistence of hyperglycemia is associated with poor outcome (43–45). A pre-trauma diagnosis of insulin-dependent diabetes was not associated with higher mortality or hospital LOS (46).

The benefit of insulin therapy on improving trauma patient outcome has not been clearly demonstrated (Table 2) (16, 27, 47, 48). In the Normoglycemia in Intensive Care Evaluation–Survival Using Glucose Algorithm Regulation (NICE-SUGAR) multicenter trial of 6,104 patients, trauma patients represented 15.5% of the conventional therapy group (BG goal 140–180 mg/dL) and 14% of the GC group (goal 80–110 mg/dL) (16). Subset analysis indicated a trend toward lower mortality in the GC group (OR 0.77, 95% CI [0.5, 1.18]; $p = .07$). Although these data are hypothesis-generating and that trauma patients may benefit more from GC than the other ICU patients, additional prospective trials

are needed to confirm this finding. Thus, at this time we recommend that trauma ICU patients should be managed in the same fashion as other ICU patients.

D. We suggest that a BG \geq 150 mg/dL triggers initiation of insulin therapy for most patients admitted to an ICU with the diagnoses of ischemic stroke, intraparenchymal hemorrhage, aneurysmal subarachnoid hemorrhage, or TBI, titrated to achieve BG values absolutely < 180 mg/dL with minimal BG excursions < 100 mg/dL, to minimize the adverse effects of hyperglycemia.

[Quality of evidence: very low]

There is abundant experimental and observational evidence to show that hyperglycemia at the time of the neurologic event is associated with adverse outcomes in stroke and TBI, but no prospective interventional trial has shown that control of hyperglycemia with insulin reduces mortality, as demonstrated by our meta-analysis OR 0.97, 95% CI [0.81, 1.16] (Fig. 2). Hyperglycemia is both a common problem (49–53) and strongly associated with greater mortality and worse functional outcome following ischemic stroke (54–57), intraparenchymal hemorrhage (58, 59), aneurysmal subarachnoid hemorrhage (60–62), and TBI (63–65). Patients who are responsive to insulin therapy have a better prognosis than those with persistent hyperglycemia (66, 67). Four small feasibility trials of insulin infusion have been undertaken (68–71), but none was designed to evaluate outcome, and none is sufficiently powerful to guarantee safety (Table 3). The Glucose Insulin in Stroke Trial was stopped prematurely due to slow enrollment (72). Three more recent studies all failed to demonstrate decreased mortality with tight GC but confirmed substantial increases in the rate of hypoglycemia with tight control (73–75). Thiele et al (75) demonstrated that hypoglycemia was an independent risk factor for mortality in multivariate analysis (OR 3.818). The NICE-SUGAR study has a TBI subgroup, the results of which have yet to be reported.

E. We further suggest that BG < 100 mg/dL be avoided during insulin infusion for patients with brain injury.

[Quality of evidence: very low]

Hypoglycemia carries specific risks for the normal brain and a greater risk for

the injured brain (76). Severe hypoglycemia (SH) can produce or exacerbate focal neurological deficits, encephalopathy, seizures or status epilepticus, permanent cognitive dysfunction, and death. Further, tight GC may induce regional neuroglycopenia in TBI (77). Clinical trials are urgently needed to determine the optimum degree of GC and a safe minimum BG goal in neurologic injury populations with respect to mortality and morbidity. Trials will require careful design as a result of the following three confounders: 1) extreme hypoglycemia and hyperglycemia on admission are associated with increased severity of underlying disease (i.e., a U-shaped mortality curve independent of therapy); 2) current therapeutic interventions carry risks of both creating hypoglycemia (both global and regional) and allowing hyperglycemia to persist (i.e., a U-shaped mortality curve as a direct consequence of therapy); and 3) response to therapy may also be determined in part by the severity of the underlying injury. Case reports of neuroglycopenia and cerebral distress (altered lactate/pyruvate ratios) during insulin infusion therapy have been reported independent of low BG (77). The clinical significance of this finding remains unknown and is further complicated by data suggesting that the rate of glucose change may be more important than the hypoglycemic event itself (78).

3. What is the impact of hypoglycemia in the general ICU population?

We suggest that BG \leq 70 mg/dL are associated with an increase in mortality, and that even brief SH (BG \leq 40 mg/dL) is independently associated with a greater risk of mortality and that the risk increases with prolonged or frequent episodes.

[Quality of evidence: low]

The practice of GC in critically ill patients is associated with a higher incidence of hypoglycemia (BG < 70 mg/dL) and a five-fold increase in the risk of SH (BG < 40 mg/dL) OR 5.18, 95% CI [2.91, 9.22] (Fig. 3). The percentage of adult patients sustaining one or more episodes of SH in the interventional arms of three major prospective randomized trials of intensive insulin therapy has ranged from 5.1% to 18.7% (1, 14, 16). Attempts to achieve tight GC (goal 80–110 mg/L) have not uniformly created the highest risk of severe hypoglycemia, suggesting that the protocol employed or the population studied might have influenced the risk.

Table 2. Summary of clinical trials evaluating impact of insulin therapy on patient outcome after trauma

Author	Study Quality		No. of Patients		Findings				Comments
	Intensive Care Unit Population	Design/Glucose End Point	Design Assessment	Control	Glycemic Control	Actual Glycemic Mean \pm SD (mg/dL)	Glycemic End Points	Hospital Mortality Odds Ratio [95% Confidence Interval]	
Scalea et al (27)	Trauma intensive care unit	Prospective data collection, two patient series before and after protocol 100–150 mg/dL	Single center, reported patterns of glucose control in week 1. Over 51% had glucose >150 mg/dL in first week (poor protocol effect)	1021	1108	NA	NA	Adjusted outcomes: Pre vs. post; mortality 1.4 [1.1, 10]	Reduced vent days and length of stay with improved pattern of glucose control
Reed et al (47)	Surgical and trauma ICU, n = 7261	Retrospective query of prospective database, pre- and post-protocol implementation	Single center, uncontrolled protocol compliance. Measured glucose control by year. End point was estimated mortality ratio measured as actual/estimated mortality	Not reported by group	Not reported by group	Reported by study year 2003: 141 2004: 134	Reported by study year 2005: 129 2006: 125 $p < 0.01$	Estimated mortality ratio measured as actual/estimated mortality unchanged	Lower mean glucose not correlated with estimated mortality risk reduction. Other factors changed during observational period (key personnel, population, quality emphasis)
Collier et al (48)	Trauma, on mechanical ventilation	Prospective postprotocol (80–110 mg/dL) vs. historical control	Single center, Reported mean glucose Pre- vs. post-mortality not reported	383	435	130 \pm 11	124 \pm 13	≥ 1 Glucose days above 150 mg/dL: 2.16 [1.0, 4.6] $p = .049$	Preprotocol, historical control, no significant reduction in mean glucose pre to post, did not achieve glucose target
The NICE-SUGAR Investigators (16)	Trauma subset	Randomized, Tight 81–108 mg/dL vs. control < 180 mg/dL	Multicenter, Reported mean glucose and time-weighted mean overall	465	421	Not reported for trauma subset	Not reported for trauma subset	0.77 [0.5, 1.18] $p = .07$ for heterogeneity 90-day mortality	Hypothesis-generating subset analysis

NA, not applicable, not available.

The impact of insulin-induced hypoglycemia has varied among populations, and in some reports, hypoglycemia was thought to be a marker for more serious underlying illness (79, 80). Risk factors for SH include renal failure, interruption of caloric intake without adjustments in the insulin infusion, sepsis with the use

of vasoactive infusions, insulin therapy, and the use of continuous renal replacement therapy with a bicarbonate-based replacement fluid (81). Some authors also found that diabetes, mechanical ventilation, female sex, greater severity of illness, and longer ICU stays are associated with increased risk of SH (80, 82). Additionally,

liver disease, immune compromise, and medical or nonelective admissions are noted as potential risk factors for the occurrence of low BG (79). Physiologic changes increase the effect of insulin as renal failure prolongs the half-life of insulin, leading to insulin accumulation, while also attenuating renal gluconeogenesis.

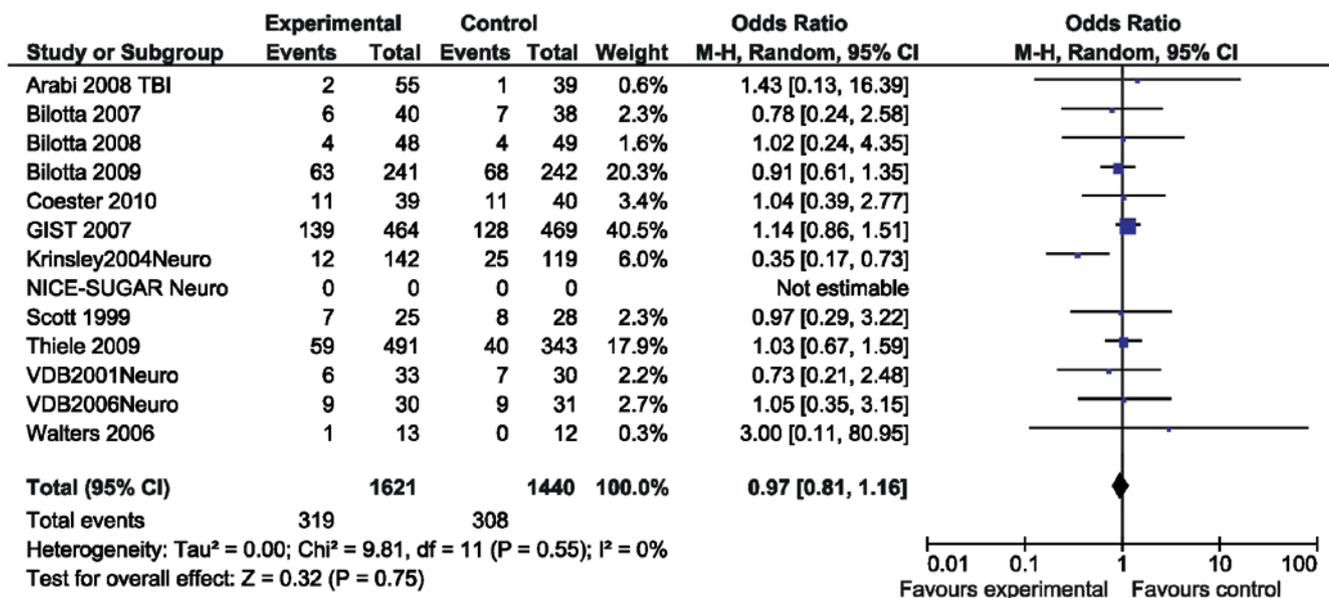


Figure 2. Forest plot of neurological mortality (hospital or 28-day) (1, 14, 16, 19, 23, 60, 65, 68, 71–75). *CI*, confidence interval; *MH*, Mantel-Haenszel.

Hepatic failure can also lead to reduced hepatic gluconeogenesis. The reliability of the insulin infusion therapy protocol and frequency of BG monitoring also appear to influence the frequency of hypoglycemia.

Multivariate regression models demonstrate that even a single episode of SH is independently associated with higher risk of mortality (80–85). The OR for mortality associated with one or more episodes was 2.28, 95% CI [1.41, 3.70]; ($p = .0008$) among a cohort of 5,365 patients admitted to a single mixed medical–surgical ICU (82). Most other reports similarly indicate a higher risk of mortality with hypoglycemia of varying severity (Table 4). Early hypoglycemia has been associated with longer adjusted ICU LOS and greater hospital mortality, especially with recurrent episodes (86). Furthermore, patients with more severe degrees of hypoglycemia sustained higher ICU and hospital mortality (85, 86). A greater risk of mortality (RR 2.18, 95% CI [1.87, 2.53]; $p < .0001$) was similarly reported with mild to moderate hypoglycemia (BG 55–69 mg/dL) in a *post hoc* analysis of prospective data collected in a randomized trial and two large cohorts (87). These data confirmed the results of another cohort study that demonstrated that mild–moderate hypoglycemia, BG 54–63 mg/dL, was independently associated with increased risk of mortality (85). In each of these studies, the mortality risk was greater with more severe hypoglycemia (85, 87). Finally, the Leuven investigators have recently published data pooling the two interventional adult

trials to analyze the independent effects of hypoglycemia and glycemic variability (GV) on the risk of mortality (88). The occurrence of one or more episodes of SH was independently associated with a higher risk of mortality (OR 3.233, 95% CI [2.251, 4.644]; $p < .0001$).

Morbidity impact of SH is difficult to quantitate on critically ill patients as concurrent illness and sepsis may increase the risk of cognitive impairment, and it is unknown how hypoglycemia may interact with other risk factors. Low BG levels lead to nonspecific neurologic symptoms, although severe or prolonged hypoglycemia may produce neurocognitive impairment, seizures, loss of consciousness, permanent brain damage, depression, and death (89–91). A number of factors including sedation, medication, or underlying disease may mask symptoms of neuroglycopenia. To further complicate the analysis, hyperglycemia has also been associated with adverse effects on the brain (92). Further, the risk for neurologic injury may be compounded by additional oxidative stress associated with rapid correction of hypoglycemia with IV dextrose (93).

4. How should insulin-induced hypoglycemia be treated in adult ICU patients?

We suggest that BG < 70 mg/dL (<100 mg/dL in neurologic injury patients) be treated immediately by stopping the insulin infusion and administering 10–20 g of hypertonic (50%) dextrose, titrated based on the initial hypoglycemic

value to avoid overcorrection. The BG should be repeated in 15 mins with further dextrose administration as needed to achieve BG > 70 mg/dL with a goal to avoid iatrogenic hyperglycemia.

[Quality of data: very low]

Although prevention of hypoglycemia is important during insulin therapy, episodes of low BG may occur despite reasonable precautions, and steps should be taken to recognize and treat it promptly. With severe hypoglycemia, interruption of the insulin infusion is a prudent first step. This interruption may be adequate for a patient receiving exogenous dextrose, but treatment with additional IV dextrose is typical, although there is no adequate data to dictate the optimal dose. While the first priority is patient safety through restoration of normoglycemia, rebound hyperglycemia due to excessive replacement should also be avoided, especially because the resulting increase in GV may contribute to adverse outcomes (82, 83, 88, 93).

An IV dextrose dose of 15–20 g has been recommended by the American Diabetes Association, with instructions to recheck BG in 5–15 mins and repeat as needed (7). A dose of 25-g IV dextrose administered to nondiabetic volunteers produced significant but variable BG increases of 162 ± 31 mg/dL and 63.5 ± 38.8 mg/dL when measured 5 and 15 mins postinjection, respectively (94). BG returned to baseline by 30 mins, but the duration may be different in patients receiving exogenous insulin.

A formula to calculate a patient-specific dose of dextrose has been used

Table 3. Summary of clinical trials in neurological patients

Author	Study Quality			No of Patients		Findings	
	Neuro-intensive Care Unit Population	Design/End Point	Design Assessment	Control	Tight Glycemic Control	Hospital Mortality ^a Odds Ratio [95% Confidence Interval]	Comments
Subsets of RCT							
Van den Berghe et al (1)	Mixed, surgical, mechanical ventilation	Randomized 80–110 mg/dL vs. 180–200 mg/dL Research RN titrated insulin per protocol	Single center Evaluated mean morning glucose	30	33	0.73 [0.21, 2.48]	Control glucose elevated with IV dextrose, stopped early for benefit
Van den Berghe et al (14)	Mixed, medical	Randomized Bedside RN titrated per paper protocol	Single center Evaluated mean morning glucose	31	30	1.05 [0.35, 3.15]	Control glucose elevated with IV dextrose
Small RCT or subset of small RCT ^b							
Scott et al (68)	CVA	Randomized Fixed dose glucose-potassium-insulin vs. saline infusion for 24 hrs	Single center, Evaluated glucose trajectory over treatment period	28	25	28-day mortality 0.97 [0.29, 3.22]	No difference in serum glucose at any point studied
Walters et al (71)	CVA	Randomized Target 90–140 mg/dL vs. standard management	Single center Evaluated glucose–time curve AUC	12	13	3.00 [0.11, 80.95]	AUC reduced
Bilotta et al (60)	Aneurysmal subarachnoid hemorrhage	Randomized Target 80–120 mg/dL vs. 80–220 mg/dL	Single center, evaluated percentage of glucose values in target range	38	40	Six-month mortality 0.78 [0.24, 2.58]	83% of control and 69% of intensive therapy in target range
Gray et al (72)	CVA	Randomized, glucose-potassium-insulin infused to target 72–126 mg/dL vs. saline control	Multicenter, evaluated glucose every 8 hrs using repeated measures analysis of variance	469	464	90-day mortality 1.14 [0.86, 1.51]	Average difference in glucose 10 mg/dL ($p < .001$)
Arabi et al (19)	Traumatic brain injury	Randomized 80–110 mg/dL vs. 180–200 mg/dL Bedside RN titrated per paper protocol	Single center, Evaluated average glucose level	39	55	1.43 [0.13, 16.39]	
Bilotta et al (73)	Traumatic brain injury	Randomized, Target 80–120 mg/dL vs. 80–220 mg/dL	Single center, evaluated mean glucose values	49	48	1.02 [0.24, 4.35]	Mean glucose values 97 vs. 147 mg/dL ($p < .0001$)
Bilotta et al (74)	Mixed, neuro-surgical	Randomized, Target 80–110 mg/dL vs. <215 mg/dL	Single center, evaluated mean daily glucose values	242	241	0.91 [0.61, 1.35]	Difference in day 1 to day 14 mean glucoses: 92 mg/dL vs. 143 mg/dL ($p < .0001$)
Cohort Studies							
Krinsley (23)	Mixed	Observational cohort <140 mg/dL vs. historical control. Bedside RN titrated	Single center, evaluated all glucose values	119	142	0.35 [0.17, 0.73]	High protocol adherence, subcutaneous and IV insulin
Thiele et al (75)	Aneurysmal subarachnoid hemorrhage	Retrospective postprotocol target 90–120 mg/dL. Bedside RN titrated protocol	Single center, Evaluated median average glucose	343	491	1.03 [0.67, 1.59]	Median average glucose 121 vs. 116 mg/dL ($p < .001$)

RCT, randomized clinical trial; CVA, acute ischemic stroke; AUC, area under the curve.

^aHospital mortality unless otherwise specified; ^bsmall trials included <1,000 patients.

Aside from Krinsley (23), every trial had an inadequate sample size to detect mortality differences. Treatment was not blinded in any study.

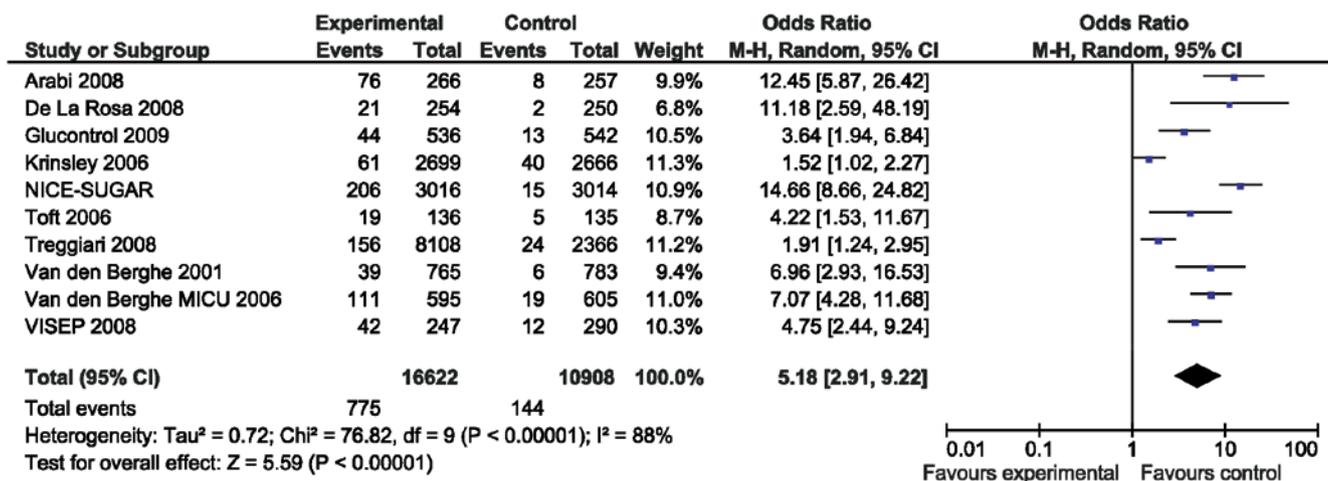


Figure 3. Forest plot of severe hypoglycemia (1, 14–19, 25, 26, 29). *CI*, confidence interval; *MH*, Mantel-Haenszel.

in several reports (50% dextrose dose in grams = $[100 - BG] \times 0.2g$), and it typically advises administration of 10–20 g of IV dextrose, an amount lower than that in traditional dosing methods (95, 96). This approach corrected the BG into the target range in 98% within 30 mins for patients who had received IV insulin infusions (95, 97). Similarly, titrated replacement has been advocated for treatment of adults in the prehospital setting. Administration of 5-g aliquots of dextrose repeated every minute, using either 10% (50 mL) or 50% (10 mL) dextrose, restored mental status to normal in approximately 8 mins with both agents (IQR 5–15 and 4–11, respectively), but the 50% dextrose group received a larger median dose of dextrose, 25 g (IQR 15–25) vs. 10 g (IQR 10–15), and developed a higher median posttreatment BG (169 mg/dL vs. 112 mg/dL [$p = 0.03$]), respectively (98). The authors recommended titrating 10% dextrose in 50-mL IV (5-g) aliquots to treat the symptoms of hypoglycemia and to avoid overcorrection of BG. The rate of administration of concentrated dextrose solutions may also be important, as a report of cardiac arrest and hyperkalemia was associated with rapid and repeated administration of 50% dextrose (99).

A prehospital study comparing an intramuscular 1-mg injection of glucagon to a 25-g IV dose of dextrose demonstrated a rapid and potentially excessive BG response with dextrose, achieving 14–170 mg/dL increase in BG in the first 10 mins (100). The glucagon response was slower, achieving a final BG concentration of 167 mg/dL after 140 mins. Because virtually all ICU patients have venous access, IV dextrose is preferred over glucagon, due to the delay in glucagon response,

although additional testing of this intervention appears warranted.

Oral dextrose replacement (15g) is used in ambulatory patients with hypoglycemia, but is not tested for ICU patients. Fifteen grams of oral carbohydrate produced a BG increase of approximately 38 g/dL within 20 mins and provided adequate symptom relief in 14 ± 0.8 mins in hypoglycemic adult outpatients (101). If oral replacement is used, dextrose or sucrose tablets or solutions are preferred for a more rapid or consistent response compared with viscous gels or orange juice due to variable carbohydrate content in commercial juice (101). The impact of abnormal gastric emptying has not been studied but may alter the response to therapy, especially in an ICU population.

5. How often should BG be monitored in adult ICU patients?

We suggest that BG be monitored every 1–2 hrs for most patients receiving an insulin infusion.

[Quality of evidence: very low]

This is a consensus recommendation based on limited data, as this question has not been tested in a prospective fashion. The optimal frequency of BG testing has not been established. Published protocols generally initiate insulin therapy with hourly BG testing, and then may liberalize the testing to every 4 hrs based on the stability of the BG values within the desired range, as well as an assessment of patient clinical stability. The personnel time required for BG monitoring is the primary barrier to more frequent monitoring. We suggest that unstable patients (e.g., titrating catecholamines, steroids, changing dextrose intake) should have

BG monitored at least every hour to allow rapid recognition of BG outside the goal range. More frequent reassessment is needed after treatment of hypoglycemia, every 15 mins until stable.

A retrospective evaluation of data from 6,069 insulin infusion episodes in 4,588 ICU patients suggested that delays in measuring BG contributed to the risk of severe hypoglycemia. When a hypoglycemic episode occurred, the median delay past the next hourly measurement was 21.8 mins (IQR 12.2–29 mins) (97). Modeling suggested SH was likely with as little as a 12-min delay in the majority of patients who developed hypoglycemia.

Glucose checks every 4 hrs have been used in some protocols; however, there is a risk of unrecognized hypoglycemia with prolonged measurement intervals; so these intervals are not recommended as a routine component of insulin infusion protocols. The rates of hypoglycemia are above 10% for many protocols using BG checks every 4 hrs (1, 14, 15, 17). One exception was reported with a computerized protocol that tested an average of approximately six BG values per day but produced SH in only 1% of patients (102). With the higher rate of hypoglycemia reported with every 4-hourly BG testing, this frequency is not suggested unless a low hypoglycemia rate is demonstrated with the insulin protocol in use.

6. Are POC glucose meters accurate for BG testing during insulin infusion therapy in adult ICU patients?

We suggest that most POC glucose meters are acceptable but not optimal for routine BG testing during insulin infusion

Table 4. Clinical trials reporting rate and impact of hypoglycemia on outcome of critically ill patients

Author/Reference	Design	n	Population	Results
Vriesendorp et al (81)	Retrospective cohort	156 (245 events) 155 control	Glucose <45 mg/dL, closed med-surg ICU, University, teaching	<i>Risk factors:</i> OR [95% CI] Nutrition interruption 6.6 [1.9, 23] Diabetes mellitus 2.6 [1.5, 4.] Sepsis 2.2 [1.2, 4.1] Shock 1.8 [1.1, 2.9] Renal replacement therapy with bicarbonate fluids 14 [1.8, 106] Insulin 5.4 [2.8, 10]
Vriesendorp et al (83) Van den Berghe et al (84)	Retrospective cohort <i>Post hoc</i> analysis of two RCTs	156 146 control 154 intensive 25 control (2,748 total n)	Glucose <45 mg/dL, closed med-surg ICU, University, teaching Glucose ≤40 mg/dL, single center, med-surg ICU	<i>Cumulative in-hospital mortality:</i> hazard ratio 1.03 [0.68, 1.56]; <i>p</i> = .88 <i>Hypoglycemia frequency:</i> control 1.8%, intensive 11.3% (<i>p</i> < .0001) <i>Hospital mortality:</i> control 13 (52%), intensive 78 (50.6%) (<i>p</i> = .9) <i>Mortality in 24 hrs:</i> control 3 (12%), intensive 6 (3.9%) (<i>p</i> < .0004) <i>Hospital mortality:</i> 55.9% vs. 39.5% (cases vs. controls) (<i>p</i> = .0057) For the entire cohort, a single episode of severe hypoglycemia OR 2.28 [1.41–3.7]; <i>p</i> = .0008 (risk of hospital mortality) <i>Risk factors:</i> OR [95% CI] Diabetes 3.07 [2.03, 4.63] Septic shock 2.03 [1.19, 3.48] Mechanical ventilation 2.11 [1.28, 3.48] Acute Physiology, Age and Chronic Health Evaluation system II 1.07 [1.05, 1.10] Treatment in intensive insulin era 1.59 [1.05, 2.41] <i>Hypoglycemia relative risk:</i> 5.13 (4.09, 6.43)
Krinsley and Grover (82)	Retrospective case-control cohort	102 cases 306 control (5,365 total in database)	Glucose <40 mg/dL, single-center. Community med-surg ICU. Insulin given to 72.5% of patients	<i>Hypoglycemia relative risk:</i> 5.13 (4.09, 6.43)
Wiener et al (31)	Meta-analysis	14 of 34 trials Tight glycemic control vs. control n = 7820, 482 hypoglycemia	Intensive care patients, International, glucose ≤40 mg/dL	<i>Higher mortality</i> seen in patients with spontaneous hypoglycemia (OR 2.32 [CI 1.31, 4.12]), but not in patients with insulin-related hypoglycemia (OR 0.92 [CI 0.58, 1.45]) <i>Adjusted mortality</i> hazard ratio, 1.31; 95% CI [0.70, 2.46]; <i>p</i> =.40 <i>Hypoglycemia rate</i> 3.6 per 100 treatment days <i>Risk factors:</i> older age, higher Acute Physiology, Age and Chronic Health Evaluation system II score, longer LOS, females, admitted for nonoperative reasons, diabetics with higher admission blood glucose, septic, mechanically ventilated, had received renal replacement therapy intensive insulin protocol <i>Relative risk for hypoglycemia:</i> 5.99 (4.47, 8.03)
Kosiborod et al (79)	Retrospective cohort	n = 523, 84 hypoglycemia	Study of patients admitted with acute myocardial infarction; database from 40 U.S. medical centers; hypoglycemia defined as glucose <60 mg/dL Med-surg ICU, RCT insulin infusion 80–110 mg/dL vs. conventional 180–200 mg/dL	<i>Relative risk for hypoglycemia:</i> 5.99 (4.47, 8.03)
Arabi et al (80)	Nested cohort in RCT	n = 523, 84 hypoglycemia	Intensive care patients, International, glucose ≤40 mg/dL, including NICE-SUGAR	<i>Higher unadjusted mortality:</i> seen in patients even with mild hypoglycemia, 54–80 mg/dL
Griesdale et al (32)	Meta-analysis	14 of 26 trials; tight glycemic control vs. control n = 4946, 1,109 hypoglycemia	Intensive care patients, two hospitals, 2000–2004	
Egi et al (85)	Retrospective cohort	n = 4946, 1,109 hypoglycemia	Intensive care patients, two hospitals, 2000–2004	

CI, confidence interval; ICU, intensive care unit; med-surg, medical–surgical unit; OR, odds ratio; RCT, randomized controlled trial.

therapy. Clinicians must be aware of potential limitations in accuracy of glucose meters for patients with concurrent anemia, hypoxia, and interfering drugs.

[Quality of evidence: very low]

The use of glucose meters has become common in hospitals due to their ease of use, availability, and ability to provide rapid results. Unfortunately, in the limited testing that has been reported, many of these devices lack accuracy when used in critically ill patients. However, insulin infusion therapy would be impossible without some type of POC testing methodology. The initial study by Van den Berghe et al (1) on intensive insulin therapy used a precise arterial blood gas instrument for BG testing. Later trials have used a variety of POC devices. One possible explanation for the generally unfavorable results in subsequent trials may be due to inappropriate insulin dosing in response to inaccurate BG results.

Studies examining the accuracy of POC glucose meters compared with a reference laboratory methodology of plasma glucose measurement reported significant variability and bias between these testing methods (103). Clinicians must be aware of the limitations with the specific device used. Comparing data on specific meters may be confounded by a lack of consensus on the limits of acceptable error between the Food and Drug Administration (allows up to 20% error) and the American Diabetes Association (up to 5% error) standards. The Clinical and Laboratory Standards Institute and International Organization for Standardization 15197 guidelines allow up to 15 mg/dL variance for BG < 75 mg/dL and up to 20% of the laboratory analyzer value for BG ≥ 75 mg/dL (104). The Clinical and Laboratory Standards Institute suggests that a correlation above .9751 is indicative of equivalence to the laboratory standard (105). Simulation has suggested that meter error exceeding 17% may double the number of potentially significant errors in insulin administration and result in a higher risk of hypoglycemia (106). While meters have generally been considered acceptable within the usual ranges of BG testing (80–200 mg/dL), additional laboratory testing of blood samples at the extremes of BG concentration is needed to detect potential errors and avoid over- or under-treatment with insulin. The logistics of obtaining timely central laboratory measurement and reporting can be overwhelming—leading

to delays that could add significant risk to efficient insulin titration.

The methodology used by a POC meter (glucose oxidase vs. glucose-1-dehydrogenase) will impact the accuracy and the potential for interference by patient physiology, other circulating substances, and sample source. These have been reviewed elsewhere, but some specific factors are pertinent to the ICU (107). For example, high P_{O_2} (>100 mm Hg) can falsely lower BG readings on POC meters that use glucose oxidase methods (108, 109).

Hematocrit (Hct) is an important variable for POC glucose testing in critically ill patients. Most POC meters are approved for BG measurement within a Hct range of 25%–55%, but low Hct has repeatedly been shown to alter the accuracy of BG results with a POC meter. Lower Hct values generally allow meters to overestimate BG values, potentially masking hypoglycemia (110–114). There are no real-time alerts on meters to direct clinicians to use other methodologies in the face of low Hct, although newer meters minimize Hct interference by correcting abnormal values (115, 116). A formula may be applied to correct a meter BG value with low Hct (117). Newer glucose meters appear to have addressed the limitations of older meters (118).

Drugs such as acetaminophen, ascorbic acid, dopamine, or mannitol, along with endogenous substances such as uric acid or bilirubin, may interfere with the accuracy of POC meters, especially those meters using glucose oxidase methodology (119). The direction of interference on BG values depends on the device and the interfering substance. Glucose–dehydrogenase-based assays are sensitive to interference and false elevation of results if the patient receives medications containing maltose (e.g., immune globulins) or icodextrin (e.g., peritoneal dialysis solutions).

An alternative POC method with a cartridge-based amperometric method is available for whole blood testing and has been tested in critically ill populations (120). There are few limitations to these cartridge-type devices using glucose oxidase technology with the exception of known interference from hydroxyurea and thiocyanate (121). A checklist for evaluation of POC glucose devices has been published to improve the quality of device evaluation (122).

7. When should alternatives to finger-stick capillary sampling be used in adult ICU patients?

We suggest arterial or venous whole blood sampling instead of finger-stick capillary BG testing for patients in shock, on vasopressor therapy, or with severe peripheral edema, and for any patient on a prolonged insulin infusion.

[Quality of evidence: moderate]

Finger-stick capillary BG measurement is typical when using a meter, although as discussed, meters may introduce error and bias in the BG value. Studies (Table 5) have compared BG in simultaneous samples drawn from different sites in critically ill patients (105, 123–135). These are difficult to compare due to the differences in reporting, testing methodology, and comparators. Of importance to clinicians is that meter performance deviated from laboratory control by >20% in some reports, regardless of the blood source (130).

Samples from an arterial site are most similar to laboratory plasma or blood gas analyzer BG values in paired samples. Venous specimens are also generally acceptable, as long as care is taken to avoid contamination of the specimen from IV fluid infusing through a multilumen catheter.

Finger-stick capillary glucose levels may provide significantly different results compared with arterial or venous specimens when patients have low perfusion with hypotension, edema, vasopressor infusion, or mottled appearance of the skin (105, 124, 127–130, 132). Hypoperfusion may increase glucose extraction and increase the difference between capillary whole blood and venous or arterial plasma glucose. Unfortunately, there is no consistent pattern to the variability, as finger-stick testing BG results might be lower or higher than arterial or venous samples. Each institution should evaluate the performance of their selected meter in a variety of patient groups.

A sampling site hierarchy that prioritizes arterial or venous sampling should be established for BG monitoring of critically ill patients. Devices that minimize blood waste with catheter sampling are important to minimize the risk of anemia induced by frequent phlebotomy. Finger-stick testing is invasive and often painful for patients who need frequent BG measurements, and thus it should be the site of last resort or avoided completely if the patient is on vasopressors or exhibits hypoperfusion.

8. Can continuous glucose monitoring replace POC methods for critically ill patients?

Table 5. Summary of clinical trials evaluating the use of glucose meters on blood from multiple sites for comparison of accuracy in various patient populations

Author	Device Methodology	Population	Arterial POC vs. Laboratory
Cook et al (124)	SureStepFlexx ^a Single channel GO vs. serum in laboratory	67 ICU patients 67 samples Glucose 62–218 mg/dL Hct 22%–46.2% Peripheral edema rated	NA
Finkielman et al (125)	SureStepFlexx ^a Single channel GO vs. plasma in laboratory	197 ICU patients 816 samples Retrospective data analysis	Arterial and venous POC Mean difference 7.9 ± 17.6 mg/dL LOA +43.1, -27.2
Lacara et al (126)	SureStepPro ^a GO vs. laboratory (plasma or whole blood not specified)	49 ICU patients 49 samples Glucose 58–265 Hct 31.7 ± 0.8 SEM	Arterial and venous POC Bias 0.6 Precision 11.0 (<i>p</i> = .69)
Atkin et al (127)	Accu-Chek II GD vs. serum in laboratory	25 hypotensive patients 39 normotensive patients Glucose 52–485	NA
Desachy et al (135)	Accu-Chek GD vs. laboratory assay (plasma or whole blood not specified)	103 patients 273 samples Glucose 56–675 mg/dL	Arterial and venous POC 7% different from laboratory by >20% LOA 42.4, -39.5
Kulkarni et al (128)	Accu-Chek Advantage GD vs. arterial whole blood gas analyzer	54 ICU patients 493 samples Glucose 37.7–42.5 mg/dL Capillary vs. arterial blood gas analyzer	NA
Karon et al (129)	Accu-Chek ^a comfort curve GD Result is factored to agree with plasma results vs. plasma in laboratory	20 coronary artery bypass grafts patients 14 on pressors, none with systolic blood pressure <80 mm Hg No temperatures recorded	Bias 14 mg/dL (<i>p</i> = .02) 56% of POC samples were within 10% of laboratory
Kanji et al (130)	Accu-Chek ^a Inform GD Result is factored to agree with plasma results vs. plasma in laboratory	30 ICU patients 36 samples Poor peripheral perfusion or vasopressor, significant peripheral edema, postoperative	<i>Overall:</i> 69.9% agreement <i>Vasopressor:</i> 67.6% agreement overall, 50% with glucose <80 mg/dL <i>Edema:</i> 71.4% agreement, 55% with glucose <80 mg/dL
Meex et al (131)	Accu-Chek ^a Inform GD (plasma strips) vs. whole blood gas analyzer	20 ICU samples	Arterial and venous: ICU subset, no difference between POC and blood gas analyzer (<i>p</i> > .05; <i>r</i> = .98)
Critchell et al (105)	Accu-Chek ^a Inform GD by trained technician vs. plasma in laboratory	80 consecutive ICU patients Pressors 25% Edema 42% Pressors and edema 48% 277 samples	NA
Meynaar et al (123)	Accu-Chek Inform GD vs. serum in laboratory	32 ICU patients 239 samples Glucose 25–288 mg/dL	Bias 11 mg/dL 90% of samples <75 mg/dL were within 15 mg/dL of laboratory 90.4% of samples >75 mg/dL were within 20% of laboratory
Ray et al (132)	One Touch Profile, LifeScan GO vs. plasma in laboratory	10 ICU patients Three in shock 105 samples Glucose 86–256 mg/dL	Bias 0.7 mg/dL (95% confidence interval [-41, 40]), intraclass correlation coefficient = 0.86, <i>p</i> < .0001
Corstjens et al (133)	Precision PCx GO vs. blood gas analyzer	19 ICU patients 145 samples	93.7% values within the 95% confidence interval (values not reported)
Boyd et al (134)	Medisense Precision Plus GO vs. whole blood in laboratory	20 ED patients 20 samples	Few hypoglycemic values NA

POC, point-of-care; GO, glucose oxidase; ICU, intensive care unit; Hct, hematocrit; NA, not applicable/not available; LOA, limits of agreement (2 SD); GD, glucose dehydrogenase.

Studies illustrate the variability of glucose meters in clinical use when measuring arterial or venous blood specimens compared with capillary specimens. Error is increased in patients with peripheral edema, poor skin perfusion, or receiving vasopressors. Trials with exogenously spiked blood samples were excluded.

^aMeters display plasma-equivalent glucose results.

Venous POC vs. Laboratory	Capillary POC vs. Laboratory	Venous POC vs. Capillary POC	Confounders
Bias 9.51 mg/dL Precision 8.44 mg/dL 21% samples >20 mg/dL difference LOA +26.5, -10.3 $R^2 = .288, p < .001$ NA	Bias 9.54 mg/dL Precision 11.96 mg/dL 15% samples >20 mg/dL difference LOA +31.5, -12.5 $R^2 = .280, p = .02$ NA	Bias 0.03 mg/dL No significant difference between samples LOA +24.1, -24.0 NA	Venous vs. finger stick No significant difference Low Hct contributed to difference between POC and laboratory Overall agreement, but potential error for individual samples
NA	Bias 2.1 mg/dL Precision 12.3 mg/dL $p = .23$	NA	Low Hct and P_{CO_2} contributed to glucose over prediction
<i>Control</i> : mean value $95.8\% \pm 1.1\%$ of laboratory value <i>Hypotension</i> : $99.2\% \pm 2.5\%$ $p < .05$ vs. laboratory value NA	<i>Control</i> : mean value $91.8\% \pm 1.6\%$ of laboratory <i>Hypotension</i> : $67.5\% \pm 5.7\%$, $p < .001$ vs. laboratory 32% incorrectly diagnosed as hypoglycemic 15% different from laboratory by >20% LOA 58.3, -55.3	NA	Mean value from different methods were different ($p < .05$)
NA	Bias 2.15 mg/dL Precision 13.8 mg/dL LOA 29.8, -2.5 <i>Hypoperfusion</i> : subset 75 samples Bias 4.0 Precision 16.2 mg/dL LOA -36.9, 28.4 Bias -1 mg/dL 74% of samples within 10% of laboratory	NA	Perfusion index from Phillips monitor identified patients with poor correlation
Bias 12 mg/dL ($p = .001$) 63% of samples within 10% of laboratory More potential insulin dosing discrepancies NA	<i>Overall</i> : 56.8% agreement <i>Vasopressor</i> : 61.1% agreement overall, 25% with glucose < 80 mg/dL <i>Edema</i> : 55.8% agreement, 23.8% with glucose < 80 mg/dL NA	NA	Adequate agreement unless patient has systolic blood pressure < 90 mm Hg or on vasopressors
NA	NA	NA	Bias became greater at glucose > 160 mg/dL with all methods ($p < .001$). No report on vasopressor effect Agreement = same insulin dose based on glucose Agreement significantly lower when glucose < 80 mg/dL vs. > 80 mg/dL in all Overall POC results higher (-3% to 24%) but correlation with laboratory good Finger-stick overestimated glucose more than underestimated. Vasopressor predicted disagreement in results Correction Art Accu-chek $\times 1.086 =$ plasma glucose
Bias 8.6 ± 18.6 mg/dL LOA: 45.8, -28.6 mg/dL NA	NA	NA	Did not assess impact of pH or Hct
NA	Hct 20%–44% did not influence results	NA	ABL715 blood gas analyzer highly correlated with laboratory plasma assay
NA	NA	NA	10 samples outside 95% CI Significant difference between mean values ($p < .001$)
Peripheral cannula Bias 18 mg/dL (95% CI [11, 25] mg/dL)	NA	NA	

In the absence of compelling data, no recommendation can be made for or against the use of continuous glucose sensors in critical care patients.

[Quality of evidence: very low]

The safety and potentially the effectiveness of insulin infusion therapy could be improved with more frequent or continuous glucose measurement. Ultimately, a closed-loop system (artificial pancreas) could be used to titrate insulin infusion therapy and minimize glucose variability, as it has been demonstrated to be feasible (136). Continuous glucose sensors have been developed to measure interstitial and intravascular glucose concentrations, and this technology has been reviewed (137–139). However, intravascular devices remain in preclinical and limited clinical testing (136).

Interstitial measurement devices may be subject to the same limitations as finger-stick BG testing, related to variable tissue perfusion, temperature, and local humoral factors in addition to delays related to glucose equilibration, and need for calibration. Initial reports of continuous interstitial glucose sensors have demonstrated acceptable accuracy in select patients (133, 140–143). Concurrent norepinephrine infusion did not alter the accuracy of continuous SQ glucose monitoring (140). Additional evaluation of accuracy and utility of continuous monitoring in broad patient populations is needed before these devices can be recommended for routine use. In studies of pediatric postoperative cardiac surgical patients and pediatric medical/surgical ICU patients, correlation of continuous interstitial glucose monitors with BG readings is acceptable (i.e., mean absolute relative difference of 17.6% and 15.2%) and unaffected by inotrope use, body temperature, body wall edema, patient size, or insulin use (144, 145).

9. How should IV insulin be prepared and administered?

We suggest continuous insulin infusion (1 unit/mL) therapy be initiated after priming new tubing with a 20-mL waste volume.

[Quality of evidence: moderate]

Titration of insulin therapy to an end point of tight GC requires the rapid response and immediate flexibility of a continuous infusion. These infusions should be prepared in a standardized concentration, with most protocols reporting use of a 1 unit/mL solution of human

regular insulin, although 0.5 unit/mL solutions may also be found in the literature. Insulin may be mixed with 0.9% sodium chloride, lactated Ringer's injection, Ringer's injection, or 5% dextrose. Insulin may be prepared in glass or plastic containers (polyvinyl chloride [PVC], ethylene vinyl acetate, polyethylene, and other polyolefin plastics), although loss will occur through adsorption to containers and to IV tubing and filters. Adsorption is immediate upon contact, producing a bioavailability of approximately 50–60% in PVC with sustained stability for 168 hrs (146). Factors such as storage temperature, concentration, and infusion rate influence the extent of adsorption. A trial of various priming volumes of 10–50 mL concluded that a 20-mL prime from a 100-mL polyvinyl chloride bag containing regular insulin, 1 unit/mL, produced insulin delivery through a 100-inch latex-free polypropylene IV infusion set that was not statistically different from a 50-mL priming volume (147). This maneuver should be repeated each time new tubing is initiated to maintain consistent insulin delivery rates. The optimal priming volume for syringe pump systems has not been reported.

Accurate insulin administration strategies include use of a reliable infusion pump for insulin administration, ideally with safety software that prevents inadvertent overdosing. The pump must be able to deliver insulin dose increments of <1 unit/hr for insulin-sensitive patients (148). While most insulin infusion protocols employ regular human insulin, rapid-acting insulin aspart and glulisine are also compatible with 0.9% sodium chloride in IV admixture and are labeled and studied for IV use (149–151).

10. What is the role for SQ insulin in adult ICU patients?

Subcutaneous insulin may be an alternative treatment for selected ICU patients.

[Quality of evidence: very low]

Intravenous insulin infusion is preferred for patients with type 1 diabetes mellitus, hemodynamically unstable patients with hyperglycemia, and also patients in whom long-acting basal insulin should not be initiated due to changing clinical status (hypothermia, edema, frequent interruption of dextrose intake, etc.). Subcutaneous insulin regimens with basal and rapid-acting insulin are frequently initiated after stabilization of BG with IV insulin. However, initiating

treatment with SQ insulin therapy may be adequate to maintain BG < 180 mg/dL in select patients with low insulin requirements who are clinically stable. Krinsley (26) reported a mean BG level of approximately 122 mg/dL using a protocol that used titrated doses of short-acting insulin given via SQ injection every 3 hrs. However, patients with significant hyperglycemia at baseline, type 1 diabetes mellitus, or two consecutive BG > 200 mg/dL triggered initiation of an insulin infusion according to the nurse-managed protocol. Long-acting insulin was added to the SQ regimen when feasible and appropriate. The patient-specific treatment protocol combining SQ and IV insulin regimens demonstrated safety and efficacy in maintaining the BG concentration predominately within the goal range with excursions of BG > 180 mg/dL in <10% and BG < 40 mg/dL in only 1.9% of patients. While this approach may not be feasible in all settings, and patient outcome has not been compared with insulin-infusion-only protocols, it has the potential to reduce the number of BG measurements and associated workload.

11. How should adult ICU patients be transitioned off IV insulin infusions?

- A. We suggest that stable ICU patients should be transitioned to a protocol-driven basal/bolus insulin regimen before the insulin infusion is stopped to avoid a significant loss of GC.

[Quality of evidence: very low]

Specific patient groups have been shown to benefit from transition to a scheduled SQ insulin regimen, including type 1 diabetes patients, type 2 diabetes patients on insulin as outpatients, type 2 diabetes patients receiving insulin infusion at a rate of >0.5 unit/hr, or stress hyperglycemia patients receiving insulin infusion at a rate of >1 unit/hr (152–156).

However, transition to SQ insulin should be delayed until there are no planned interruptions of nutrition for procedures, until peripheral edema has resolved, and until off vasopressors. A protocol for transition leads to better glucose control than nonprotocol therapy (157). Failure of SQ regimens to produce or maintain GC (BG < 180 mg/dL) should trigger redesign of the regimen or resumption of insulin infusion therapy.

A retrospective review of 614 cardiothoracic patients determined the effectiveness of an IV (in the ICU) followed by

SQ (outside the ICU) regimen on morbidity and mortality (158). The authors found the SQ regimen to be less nursing-intensive and less costly in all patients, but only those with a preexisting diagnosis of diabetes demonstrated significantly lower rates of postoperative mortality. Protocolized transition to an SQ regimen has been shown to decrease rebound hyperglycemia after infusion discontinuation (159).

- B. We suggest that calculation of basal and bolus insulin dosing requirements should be based on the patient's IV insulin infusion history and carbohydrate intake.

[Quality of evidence: very low]

Several models have been proposed for transition from insulin infusion to SQ insulin therapy (156, 158–161). The majority of these models include a three-component approach to insulin replacement: basal insulin, nutritional insulin, and correction insulin. Basal insulin is provided as an injection of long-acting insulin given every 24 hrs (e.g., glargine) or intermediate-acting insulin given every 6–12 hrs (e.g., NPH). Basal insulin will be needed in many diabetic patients on enteral feedings to achieve the desired BG goal (162). The initial basal insulin dose is recommended at least 2–4 hrs before stopping the insulin infusion when possible to prevent rebound hyperglycemia (28, 163). If this overlap is not feasible, a simultaneous injection of rapid-acting insulin (approximately 10% of the basal dose) may be given with the basal insulin injection when stopping the infusion (156). One group suggests calculating a total daily dose (TDD) of IV insulin from the mean hourly dose for at least the prior 6 hrs as a guide to the basal insulin dose (28). As IV insulin delivery is reduced by adsorption to the container and tubing, the authors reduced the initial basal dose to 80% of the estimated TDD and achieved their target for glucose control more readily than using smaller percentages of the TDD, although others have shown acceptable glucose control using 60%–70% of the TDD (156, 158, 159, 164). It is important to consider concurrent changes in other drug therapy or nutritional regimens when planning a transition regimen.

Mixing insulin in a parenteral nutrition (PN) solution can replace a separate insulin infusion or basal insulin injections once the daily requirements are

stabilized. Additional correction doses can be given to fine-tune GC every 3–6 hrs.

- 12. What are the nutritional considerations with IV insulin therapy in adult ICU patients?

- A. We suggest that the amount and timing of carbohydrate intake should be evaluated when calculating insulin requirements.
- B. We also suggest that GC protocols should include instructions to address unplanned discontinuance of any form of carbohydrate infusion.

[Quality of evidence: low]

Nutritional support requirements of critically ill patients vary and are beyond the scope of this discussion. Guidelines for nutritional support of critically ill patients are available (165).

Consistent intake of nutrition appears to simplify glycemic management during an insulin infusion. Overfeeding may produce hyperglycemia that necessitates insulin infusion therapy, and should be avoided.

Provision of 200–300 g of dextrose per day was a component of the initial trial by Van den Berghe et al (1) in surgical ICU patients. The reduction of mortality reported with achievement of BG values of 80–110 mg/dL has been suggested to reflect minimization of complications from PN, although similar calories were provided in the medical ICU study, without the same impact on outcome (14). While a meta-analysis of clinical trials, stratified by source of calories, suggested that tight GC is potentially more beneficial during PN regimen compared with enteral feeding, this was not confirmed in a prospective trial comparing early vs. late PN (33, 166). Tight GC (mean BG 100–110 mg/dL) was similarly achieved in patients who received 3–4 g/kg/d of carbohydrate (early) compared with 0.5–2 g/kg/d (late) over the first 7 ICU days (166). The patients on early PN required higher total insulin doses per day but fewer patients had SH (2% vs. 3.5%, $p = .001$). Nevertheless, the patients on late PN (who received carbohydrates from enteral nutrition and 5% dextrose infusion for the first week) had better overall outcomes. Thus, insulin infusion appears to be suitable for patients regardless of the source of carbohydrates, and GC alone is not enough to reduce the apparent risks associated with PN. The enteral route is preferred over the parenteral route for nutrition

support in the ICU setting when possible (165). However, due to several factors common to the ICU (e.g., gastric stasis, interruption of enteral nutrition for tests/procedures, and anatomical anomalies), the amount of feeding that can be delivered enterally is generally less than the amount delivered parenterally. Interruption of enteral feeds was found to cause the majority of the hypoglycemic events (62%) in the Leuven MICU trial, and similar results were noted elsewhere (13, 167). Initiation of a 5% dextrose-containing IV solution at the same rate as the discontinued enteral feeding solution appears to prevent hypoglycemia (168). Dextrose (10%) solutions may be used to minimize the volume of free water.

Integration of an insulin protocol with nutritional intervention has been suggested to achieve a high level of GC. The Specialized Relative Insulin Nutrition Tables protocol titrates both feeding and insulin doses to achieve tight glucose control and was more effective at achieving the BG target than a retrospective control (169, 170). Insulin was administered with hourly bolus injections and could be supplemented by an infusion of up to 6 units/hr. The rate of enteral feeding was also adjusted to facilitate GC, but resulted in delivery of only 50% of the predicted caloric requirement, and thus may not be an optimal long-term nutritional strategy.

Bolus doses of IV insulin may be administered for nutritional insulin therapy during an insulin infusion when carbohydrates are delivered intermittently, based on carbohydrate ratio, as previously discussed. Consistent oral intake should trigger transition to SQ insulin therapy and a consistent carbohydrate diet plan. Glucose monitoring should be scheduled to avoid measurement of postprandial BG concentrations.

- 13. What factors should be considered for safe insulin therapy programs in the adult ICU?

We suggest that insulin is a high-risk medication, and that a systems-based approach is needed to reduce errors.

[Quality of evidence: very low]

Insulin is a high-alert, high-risk medication due to the risk of hypoglycemia, complexity of therapeutic regimens, and availability of multiple products in patient-care areas. It is in the top five “high-risk” medications that account for about one third of all major drug-related,

injurious medication errors. One analysis indicated that 33% of errors causing death within 48 hrs involved insulin therapy (171). Strategies to reduce such errors have been suggested and should be applied to the ICU setting (172). These include standardized protocols for insulin dosing and monitoring, computerized provider order entry, minimizing available insulin products, avoidance of abbreviations such as “U” for units, storing insulin away from other medications, and detailed multiprofessional analysis of actual errors and near-miss events. Strategies to improve insulin safety include mandating an independent double-check of doses, frequent BG monitoring, and prominent product labeling.

The limitations of BG monitoring equipment and methodology may also increase the risk of error. For example, factitious elevations in BG occur when icodextrin peritoneal dialysis solutions or maltodextrin-containing medications (selected immune globulin products) are administered and monitored with a glucose dehydrogenase monitoring system (173). Also, a dextrose solution administered via a pressurized flush system produced factitious elevations in BG values drawn through an arterial line, and subsequent inappropriate insulin administration led to fatal neuroglycopenia (174).

Safety in insulin administration methodology is also important, and a systems-based approach is needed to reduce insulin errors. Complex insulin therapy protocols with multiple patient-specific exceptions and the need for a high-level training for accurate use are common. A standardized protocol should be utilized only after adequate education and processes are implemented to monitor outcomes. Routine and frequent assessment of glucose metrics, as will be described, should be performed. Failure to achieve adequate glucose control or frequent episodes of hypoglycemia should trigger rapid reassessment of the protocol and monitoring system.

14. What are the characteristics of an optimal insulin dosing protocol for the adult ICU population?

We suggest that ICUs develop a protocolized approach to manage GC. Components include a validated insulin administration protocol, appropriate staffing resources, use of accurate monitoring technologies, and a robust data platform to monitor protocol performance and clinical outcome measures.

A standard insulin infusion protocol should include a requirement for continuous glucose intake, standardized IV insulin infusion preparation, a dosing format requiring minimal bedside decision-making, frequent BG monitoring, provisions for dextrose replacement if feedings are interrupted, and protocolized dextrose dosing for prompt treatment of hypoglycemia.

[Quality of evidence: very low]

A standard protocol for insulin administration and monitoring is essential for consistency and safety. Comparison of existing protocols is difficult due to significant differences in processes and outcome measures, but key features will be discussed.

Computerized decision-support systems achieved better glucose control than that achieved with paper-based systems using “if-then” decision model (175). Although paper-based systems may be adequate, they may be more complex and time-consuming and lack a reminder system to ensure timely BG measurement. Most of the studies comparing protocols employed pre- and post-intervention cohort design, limiting the ability to conclude if the new protocol was the cause of improved results. However, several RCTs demonstrated favorable features of computerized insulin infusion protocols vs. paper-based systems (148, 176–178). Glycemic control metrics and hypoglycemia rates have been consistently better with computerized protocols. Reminder alerts lead to more consistent and timely BG assessments. Commercial systems have licensing fees that may be a barrier to utilization, although several institutions have developed custom computer-based systems (96, 97). The largest trial, NICE-SUGAR, had a computer-assisted protocol, but dosing was based on a complex decision tree, rather than a specific set of formulas (16). It should be noted that this protocol failed to achieve an average BG level within the goal range of 80–110 mg/dL.

Numerous cohort reports describe the utility and effectiveness of paper-based protocols as they evolve over time, compared with historical controls (23, 151, 152, 179–182). The reports are of low quality due to small study size, single-center experience, use of historical controls, and variable outcome measures (including surrogate measures such as BG results rather than patient outcomes). These protocols vary in insulin dosing intensity and complexity. Some contain insulin bolus

doses, and others require multiple steps to alter insulin dosing, which can lead to markedly different insulin doses in a simulated patient model (183).

The original protocol published by Van den Berghe et al (1) (Leuven protocol) was relatively unstructured, although it was successfully administered in a research setting with trained providers. Subsequent use by bedside providers in other ICU settings has produced hypoglycemia rates that were deemed to be excessive (15, 17).

Advantages of paper-based protocols include easy bedside access, insulin rate changes are made only when outside of goal BG ranges, and sometimes separate scales for differing levels of insulin sensitivity. The major disadvantages of these protocols include their complexity (with multiple recommendations on the same page), a lack of flexibility with major clinical changes, and lag time to respond to BG trends (may recommend a dose increase for a persistently high BG, even if the BG level has actually declined).

A more straightforward approach is to use an algebraic formula to calculate the insulin rate based on the BG and a multiplier (M) that relates to insulin sensitivity (insulin dose [unit/hr] = [BG – 60] × M) (95–97, 184). This calculation can be computerized, assisted by a tabular format, or calculated manually (185, 186). The multiplier increases for BG above the target range and decreases when the BG is below the goal. Advantages to this approach include rapid determination of the new insulin dose without the need for extensive judgment or training of the bedside caregiver and constant titration based on the BG trend. It has resulted in some of the lowest reported rates of severe hypoglycemia (177, 182, 183). Disadvantages include the need for a bedside computer and the potential for exaggerated increases in insulin infusion rate in response to an elevated BG value, especially with a high multiplier. The multiplier may need to be reset to a lower value, especially following a significant change in nutritional intake or change in clinical status. More sophisticated computerized protocols have also been developed and have similarly been shown to perform better than conventional protocols (169, 170, 178, 187, 188). Computerized programs can also collect data on the performance of the program and calculate a variety of metrics.

A source of error with virtually all insulin protocols is incorrect transcription of

BG values into a freestanding computer program, which may occur approximately 5% of the time (189). Similarly, protocol violations are reported with paper-based systems (190). The amount of practitioner latitude in deviating from the protocol recommendations should be predefined and evaluated as a component of quality assurance programs.

With many published protocols available, there is no need to reinvent the wheel to implement an insulin infusion protocol. The local barriers to safe insulin therapy must be identified and addressed, including availability of adequate and appropriate testing equipment, consideration of workforce impact, and a team approach to education and implementation (191). Tight levels of BG control should not be attempted when a new protocol is initiated, to minimize hypoglycemia risk during the initial learning curve. Systematic and frequent assessment of results is needed. Feedback to providers is essential when protocol violations or adverse events occur. In addition, a protocol is only effective if used in a consistent fashion. Automatic triggers for protocol initiation are more efficient than waiting for prescriber recognition of hyperglycemia and appropriate response through patient-specific orders.

Other keys to a successful glycemic management program include the availability of a reliable methodology for BG testing, with an adequate number of devices to minimize delays and wasted time obtaining the device. The data should be recorded in the electronic medical record promptly and be displayed along with insulin dosing adjustments to assess protocol performance and allow evaluation of variances. In addition, the glycemic management program should be coordinated with nutrition support interventions to minimize the risk of hyperglycemia or hypoglycemia with addition or interruption of nutritional intake. Concurrent medications dosed intermittently should be mixed in sodium chloride solutions to reduce glucose variation induced by episodic dextrose administration. While patients should receive a consistent carbohydrate intake, the need for insulin may be minimized by limiting the infusion of excessive quantities of dextrose solutions.

15. What is the impact of GV on outcomes of critically ill patients?

Glycemic variability has been independently associated with mortality in several cohorts of critically ill patients; however, there is no consensus regarding the appropriate metric for mathematically defining GV. We suggest that the simplest tools—*SD* of each patient's mean BG and coefficient of variation (*SD*/mean)—be reported in all published interventional studies.

[Quality of evidence: very low]

Glucose metrics are important to evaluate the overall results of a GC program. In clinical trials, glucose variability has been suggested as a better end point to assess the impact of blood sugar on patient outcome during insulin infusion compared with other measures, such as mean morning BG, mean of all BG values, or time-weighted average value. Higher levels of GV have been independently associated with mortality in adult cohorts of mixed medical-surgical patients (83, 86), surgical ICU patients (192), patients admitted with sepsis (193), as well as in critically ill pediatric patients (194). However, the most appropriate metric to describe GV has not yet been defined. Relatively simple measures to calculate variability include *SD*, coefficient of variation, and mean daily delta (maximum – minimum BG). More complex measures that have been evaluated in different studies include mean amplitude of glycemic excursion, the glycemic lability index, maximal glucose change, and the variability index (195, 196).

A recent review summarized the biologic basis for the deleterious effect of increased GV (196). One purported mechanism is the “oxidative stress” that occurs at the cellular level induced by rapid changes in the BG level (93, 197, 198). Fluctuations in BG levels may lead to changes in serum osmolality that cause injury at the cellular and organ levels (199). Finally, wide excursions may mask occult hypoglycemia, which has been recognized as a risk factor for mortality in the critically ill (82). It is not known yet whether efforts to minimize GV will decrease the mortality rate in critically ill patients, but this remains a promising avenue for future research.

16. What metrics are needed to evaluate the quality and safety of an insulin infusion protocol and GC program in the adult ICU?

Measures of overall glucose control should include mean (*SD*) and median (IQR) BG levels as well as ICU-level run

charts of percentage BG < 150 mg/dL and 180 mg/dL. We suggest that hypoglycemic events should be monitored regularly and reported as events per patient, as a percentage of all BG values, and events per 100 hrs of insulin infusion.

[Quality of evidence: very low]

This is a consensus suggestion to improve the safety and efficacy of GC and insulin therapy. Data on the performance of an insulin infusion protocol should be assessed multiple times throughout the year (e.g., at least quarterly). Potential measures of protocol effectiveness include global measures of BG control, such as mean and median BG per patient, measures of glucose variability, and time to specific end points, including mean and median time required to reach the designated glycemic target as well as mean and median time spent within the desired glycemic range, reported as a percentage of total time in range (200–202). Patients with diabetic ketoacidosis and hyperglycemic hyperosmolar coma should be excluded from this analysis.

Protocol safety should be regularly assessed through metrics relating to hypoglycemia, which should be defined as severe (<40 mg/dL), moderate (40–59 mg/dL), or mild (60–69 mg/dL). A system to evaluate patients with SH should analyze precipitating events and plan for prevention. The hypoglycemia event rate could include patients with hypoglycemia related to other treatments, such as oral hypoglycemic agents or disease states such as hepatic failure or sepsis. There are no existing benchmarks to establish a goal, other than the lowest rate possible.

Although a hypoglycemia rate is important for the overall assessment of a protocol, the impact of a single, severe hypoglycemic event cannot be overlooked or minimized by metrics that compress the GC measure into one global variable or BG averaging method.

Other measures of glycemic performance have been studied in select populations. The percentage of patients with a morning BG <200 mg/dL for the 3 days after cardiovascular surgery is a component of the Surgical Care Improvement Project Measures based on the association of improved glucose control with fewer deep sternal wound infections (203). Time-weighted mean BG, as used in NICE-SUGAR, may provide a more accurate assessment of overall per-patient BG control, but is more complex to calculate than a simple mean BG measurement (16). The Glycemic Penalty Index is another

measure of the consistency of glucose control (88). This tool scores glucose values based on the degree of excursion from the goal, making it a more dynamic measure of the variability of glucose values in a single patient. A higher value indicates fewer values within the goal range. This tool has been used to compare insulin infusion protocols, but not to evaluate patient outcome. The Hyperglycemic Index measures the area under the curve of BG values above the upper limit of the goal range vs. time (204). This method has shown a significant association with mortality when used for retrospective analysis of BG values for surgical ICU patients. This metric is most meaningful when the daily number of BG values is consistent from patient to patient.

17. What are the economic and workforce impacts of a GC program in the adult ICU?

A. We recommend that programs to monitor and treat hyperglycemia in critically ill patients be implemented to reduce hospital costs.

[Quality of evidence: moderate]

B. We suggest implementation of programs to monitor and treat hyperglycemia in diabetic patients following cardiovascular surgery to reduce hospital costs.

[Quality of evidence: low]

The cost implications of implementation of programs to monitor and treat hyperglycemia in hospitalized patients have been studied in a variety of different patient populations. Complications associated with poor GC have the potential to increase total hospital costs. A reduction in sternal wound infections was associated with improved GC and produced lower costs (205). This single-center investigation estimated that each 50 mg/dL increase in mean BG level was associated with an excess of \$2,824 in the cost of hospitalization. Promulgation of a hospital-wide inpatient diabetes management program produced a reduction in LOS that resulted in over \$2 million in savings to another facility (206). However, total cost is not the only important measure of the impact of GC programs. Aragon evaluated the nursing work burden imposed by an IV insulin protocol on four different ICUs within a single academic institution (207). A mean of 4.7 (± 1.1) mins was needed for each hourly analysis of

BG, which extrapolated to nearly 2 hrs of nursing time each day for insulin infusion management. The design of this observational study did not include calculation of total paid nursing hours. Another time-motion study noted a marked difference in the time required for GC activities with a paper protocol, depending on clinical urgency. Malesker et al (208) reported a mean of 2.24 (± 1.67) mins from BG to therapeutic action and 10.55 (± 3.24) mins for hyperglycemia, although multitasking by nurses makes discreet evaluation of this activity more challenging. The complete time from meter acquisition to completion of documentation might have been as long as 33 mins for adjustment of infusion therapy, and longer for infusion initiation.

There are few published studies of the effect of tight GC implementation on ICU costs. Van den Berghe et al (209) performed an analysis of the 1,548-patient cohort from their landmark surgical ICU study. The methodology consisted of a cost accounting of the components of care found to change significantly as a result of intensive insulin therapy: the direct cost of insulin administration, ICU days, mechanical ventilation, and the use of vasopressors, inotropes, IV antibiotics, and blood transfusion. The total savings per patient associated with the intensive insulin protocol was \$2,638 per patient. The mean LOS in the conventional treatment and intensive treatment groups was 8.6 and 6.6 days, respectively, accounting for over 80% of the cost per patient.

The cost implications of a 1,600-patient pre- and post-intervention cohort study of tight GC were implemented in a mixed medical-surgical ICU of a university-affiliated community teaching hospital (210). These investigators attempted to quantify all major components of the cost of care: ICU days, mechanical ventilation time, laboratory testing, pharmacy, diagnostic imaging, and days in the hospital on the regular wards after discharge from the ICU. The net savings per patient was \$1,580. The 17% decrease in ICU mean LOS (from 4.1 to 3.4 days) accounted for 28% of the savings, but there were also substantial savings associated with decreased use of mechanical ventilation, diagnostic imaging, laboratory testing, and days in the hospital after discharge from the ICU.

A third report from Sadhu and colleagues (211) used a difference-in-differences (quasi-experimental) design to measure an association between a

multi-ICU glycemic management program and hospital and patient outcome variables. The participating ICUs demonstrated a reduction in mean BG compared with nonparticipating units in the hospital. Outcomes were compared in the groups to address the impact of secular time trends and patient characteristics that might have altered the results in this before and after study. The glycemic management protocol was associated with an average reduction of 1.19 days of ICU care per admission ($p \leq .05$) and a trend toward lower mortality and resource use including a reduction of \$4,746 in total costs per patient ($-\$10,509$ to \$1,832).

18. What are the implications of hyperglycemia in pediatric critically ill patients?

In the absence of compelling data, no recommendations could be made for or against the use of tight GC in pediatric critical care patients.

Hyperglycemia is highly prevalent in pediatric critical care. While studies show an independent association between hyperglycemia and morbidity and mortality rates, the paucity of data has resulted in practice variability (194). As in adults, children develop critical illness hyperglycemia with no history of premorbid diabetes or insulin resistance related to severity of illness. Although most pediatric intensivists believe that hyperglycemia may cause harm in their patients and support the concept of avoiding hyperglycemia, most are reluctant to practice routine GC (212, 213). An RCT of 700 critically ill pediatric patients was completed in a single center in Leuven, Belgium, which established that insulin infusion titrated to a goal of 50–80 mg/dL in infants and 70–100 mg/dL in children, compared with insulin infusion only to prevent BG >215 mg/dL, improved short-term outcomes (214). The absolute risk of mortality was reduced by 3% (conventional 5.7% vs. interventional 2.6%, $p = .038$), and insulin therapy also reduced the ICU LOS and C-reactive protein (the primary outcome variable). The study was notable for its first proof of principle that tighter levels of GC produce clinical benefit. It was also remarkable for its low target BG ranges in the intervention groups, which were described as “age-adjusted normoglycemia” (50–80 mg/dL in those <1 yr old, 70–100 mg/dL in those >1 yr old). Although several outcomes in this trial

were favorable, there were extremely high rates of SH (<40 mg/dL): 44% in those <1 yr old and 25% overall. In light of this, the protocol is unlikely to be replicated outside Leuven, and the findings of clinical benefit cannot be widely applied. Of note, the importance of the hypoglycemia rates will ultimately need to be reinterpreted in light of the neurocognitive outcomes in these subjects, which is being assessed as a follow-up study.

Despite the inherent flaws of the retrospective pediatric literature and the single prospective RCT, many pediatric intensivists believe hyperglycemia should be avoided, and some pediatric ICUs have implemented GC measures into their standard clinical care. Recent studies have shown that pediatric-specific GC protocols can be implemented in different ICU settings and afford seemingly reasonable control with low rates of hypoglycemia (215–218). However, no formal recommendation can be made in favor of broad implementation of GC to a low range. Regular internal “quality” evaluations of GC in individual practices will likely assist in refining and improving practice.

In recognition of the distinct physiology and pathophysiology of children, more clinical trials evaluating pediatric-specific GC protocols in the different critical care disciplines (i.e., medical, surgical, trauma, and cardiac), with an emphasis on safety, are urgently needed. End points of any pediatric GC study will ideally include safety (hypoglycemia rates) and efficacy (time in goal BG range), length of ICU/hospital stay, ventilator and pressor/inotropes days, rates of nosocomial infection and mortality, as well as rehabilitation and long-term neurodevelopmental outcome. The strongest recommendation that can be made at this time is that it is reasonable to incorporate approaches to control persistent significant hyperglycemia (i.e., BG levels >180–220 mg/dL) into practice. An optimal glycemic range currently cannot be recommended due to lack of pediatric-specific data. Yet, for those opting to practice GC in line with adult efforts, choosing a target BG that is in the range of 100–180 mg/dL may be a reasonable goal. This suggestion should not preclude alternative glycemic targets, depending on the practice group’s comfort and experience. Although children do have lower basal BG levels than adults, levels <60 mg/dL should be minimized, and BG levels <40 mg/dL should be treated emergently.

Due to the sensitivity of the developing central nervous systems of neonates and

infants, meticulous BG monitoring will be crucial in pediatric insulin infusion protocols. Frequent BG monitoring, and ideally continuous glucose monitoring (145, 219), combined with explicit, preferably computer-assisted, algorithms will likely augment the safety and acceptance of these protocols.

Stronger practice recommendations and optimal glycemic targets in pediatric critical care can only come with the publication and confirmation of clinical trials with explicit methodologies in critically ill children (220, 221). An RCT of insulin infusion (target BG 80–110 mg/dL) vs. standard care produced improved glycemic control but did not reduce nosocomial infections, mortality, length of stay, or other morbidity measures (222). Insulin infusion was accomplished safely with SH reported in only 3% of tight GC patients. This study does not alter the recommendation.

FUTURE RESEARCH

Although data have been generated in numerous subpopulations of critically ill patients, not all populations have been adequately studied and a “one size fits all” treatment approach may not be appropriate for different institutions and patients. Furthermore, a critical reading of the published literature indicates that these different populations have variable responses; thus, survival benefit in one population may not be extrapolated to another. As such, more prospective RCTs are needed in populations that have yet to be adequately studied. Trials should be designed to include several key features:

1. Inclusion and exclusion criteria should reasonably define a unique population. In light of the unique benefits to postoperative cardiac surgical patients, for example, trials should not mix cardiac and noncardiac patients unless the study design provides adequate power to measure outcomes in each group.
2. Studies should be adequately powered to detect clinically significant outcomes. In adults, 28-day and in-hospital mortality should be considered primary outcomes in most populations; additionally, in surgical patients (i.e., coronary artery bypass graft) with a low mortality rate, hospital complications and costs may represent important secondary outcomes. Similarly, in pediatrics, with very low ICU mortality, surrogate outcomes may need to be the primary outcomes, such

as ICU LOS, rate of infection, or organ dysfunction score.

3. Methodology in proposed trials should be as safe as possible and replicable in a naïve ICU setting. Study design should target a range that may be safely achieved without excessive (>5%) rates of severe hypoglycemia.

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