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Glycemic targets in critically ill adults: A mini-review

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Abstract

Illness-induced hyperglycemia impairs neutrophil function, increases pro-inflammatory cytokines, inhibits fibrinolysis, and promotes cellular damage. In turn, these mechanisms lead to pneumonia and surgical site infections, prolonged mechanical ventilation, prolonged hospitalization, and increased mortality. For optimal glucose control, blood glucose measurements need to be done accurately, frequently, and promptly. When choosing glycemic targets, one should keep the glycemic variability < 4 mmol/L and avoid targeting a lower limit of blood glucose < 4.4 mmol/L. The upper limit of blood glucose should be set according to casemix and the quality of glucose control. A lower glycemic target range (*i.e.*, blood glucose 4.5-7.8 mmol/L) would be favored for patients without diabetes mellitus, with traumatic brain injury, or who are at risk of surgical site infection. To avoid harm from hypoglycemia, strict adherence to glycemic control protocols and timely glucose measurements are required. In contrast, a higher glycemic target range (*i.e.*, blood glucose 7.8-10 mmol/L) would be favored as a default choice for medical-surgical patients and patients with diabetes mellitus. These targets may be modified if technical advances for blood glucose measurement and control can be achieved.

Key Words: Brain injuries; Traumatic; Critical care; Diabetes mellitus; Glycemic control; Insulin infusion systems; Sepsis

Core Tip: A lower glycemic target range (*i.e.*, blood glucose 4.5-7.8 mmol/L) would be favored for patients without diabetes mellitus, or with traumatic brain injury, or who are postoperative and at risk of surgical site infection. Requirements for targeting a lower range and avoiding hypoglycemia would be availability of intensive glucose monitoring and management, strict adherence to glycemic control protocols, and strict

adherence to timely glucose measurements. In contrast, a higher glycemic target range (*i.e.*, blood glucose 7.8-10 mmol/L) would be favored as a default choice for medical-surgical patients and patients with diabetes mellitus.

INTRODUCTION

Illness-induced hyperglycemia can be a double-edged sword. On the one hand, it may be an adaptive response to provide extra metabolic substrate to organs like the brain and to blood cells[1]. On the other hand, hyperglycemia impairs neutrophil function and innate immunity, increases pro-inflammatory cytokines and oxidative stress[2,3], inhibits fibrinolysis[4], and promotes cellular damage[1]. In addition, hyperglycemia in brain-injured patients can lead to microcirculatory damage, blood-brain barrier disruption, and cellular swelling[5]. These pathological derangements potentially lead to complications such as pneumonia and surgical site infections, prolonged mechanical ventilation, increased intensive care unit (ICU) and hospital lengths of stay, and increased mortality.

Unlike hyperglycemia, hypoglycemia is always harmful. For example, hypoglycemia was independently associated with respiratory complications and prolonged ICU and hospital lengths of stay after cardiac surgery[6]. These adverse events may be mediated by hypoglycemia-related neuronal damage and cardiac arrhythmia[7]. Apart from the clear need to avoid blood glucose extremes, there is also a need to avoid excessive blood glucose fluctuations[8], which can be measured in various ways (Table 1). The simplest measure of blood glucose fluctuation is glycemic variability, which is the difference between the maximum and minimum blood glucose measured over a defined time interval. At the cellular level, glycemic variability has been associated with oxidative stress, endothelial dysfunction, and apoptosis[7]. Clinically, glycemic variability has been linked to increased ICU and hospital mortality[9,10].

Blood glucose measurements need to be done accurately, frequently, and promptly [11]. Ideally, blood glucose measurements should be done continuously, though continuous glucose monitoring (CGM) for critically ill patients may not be accurate enough, with wide limits of agreement despite small mean bias[12]. CGM appears unreliable when using minimally-invasive subcutaneous devices that assay interstitial glucose measurements[13-15], and does not seem to improve glucose control[16]. Although invasive (intravascular) CGM devices may have an acceptable accuracy, some drawbacks include vascular and infectious complications (thrombosis, catheter occlusion, biofilm formation, or intravascular catheter-related infection)[17,18].

Accuracy and variation of glucose measurement methods influence the feasibility and adherence to glycemic targets[19]. In the real world, a variety of blood samples (arterial, venous, and capillary) are assayed intermittently, using both point-of-care and laboratory methods[20,21], and managed using various protocols. Nonetheless, despite such variation, clinical utility of current glucose measurement systems seems adequate, with little evidence of over or under-treatment[22]. Additionally, to achieve optimal clinical outcomes, blood glucose should be lowered if it were to rise too high, blood glucose should not be allowed to dip too low, and blood glucose variability should be constrained.

To determine clinically optimal glycemic targets for critically ill adult patients, the key questions would therefore be as follows: (1) What should the *hyperglycemic* threshold be; (2) What should the *hypoglycemic* threshold be; and (3) How far apart should these thresholds be? This review aims to integrate empirical evidence to answer these questions, and to suggest practical recommendations for choosing glycemic targets.

Table 1 Types of glycemic targets in intensive care unit

Glycemic target	Unit	Definition
Glucose	mmol/L	Concentration of glucose in blood or plasma. To convert to mg/dL, multiply by 18, *i.e.*, 1 mmol/L = 18 mg/dL
COV	%	Coefficient of variation, a measure of glucose variability. COV = standard deviation divided by mean glucose × 100%
GG	mmol/L	Glycemic gap. GG = blood glucose - [(1.59 × HbA1c) - 2.59], HbA1c being used to estimate average glucose concentration over the prior 3 mo
Glucose variability	mmol/L	Maximum – minimum glucose in a given time period
SHR	Nil	Stress hyperglycemia ratio. SHR = plasma glucose divided by [(1.59 × HbA1c)–2.59], HbA1c being used to estimate average glucose concentration over the prior 3 mo

HbA1c: Glycosylated hemoglobin.

EMPIRICAL EVIDENCE FOR GLYCEMIC THRESHOLDS IN ICU

Several trials are inconclusive with respect to intensive (lower) *vs* conventional (higher) glycemic targets, which may be due to insufficient separation of achieved glucose levels between the intervention and control groups[23-25]. Another reason could be that the impact of glucose control was modified by the main diagnosis (*i.e.*, casemix). In terms of the hyperglycemic threshold, the blood glucose level beyond which clinical complications occur seems to differ by casemix (Table 2). Patients without diabetes mellitus (DM)[26], patients with traumatic brain injury (TBI), and post-surgical patients at risk of wound infection experience adverse effects of hyperglycemia at a relatively low range, with the threshold set at 6.7-8.3 mmol/L[27-30].

The NICE-SUGAR trial showed that undifferentiated medical-surgical ICU patients had decreased 90-d mortality and incident hypoglycemia when the upper limit of blood glucose was set at 10 mmol/L rather than 6.1 mmol/L[31]. Patients who suffered non-TBI-specific injury[32] or who had post-cardiac arrest[33] also experienced better neurological recovery if blood glucose could be kept below 10 mmol/L.

Patients with prior DM were able to tolerate a higher mean blood glucose level (*i.e.*, blood glucose level > 10 mmol/L) without excess complications during critical illness, although these patients benefited from lowering blood glucose below 7.8 mmol/L after coronary artery bypass surgery[34]. Chronic hyperglycemia may have compensatory mechanisms in place that provide protection from acute hyperglycemia-related cellular damage[2]. The upper limit of safety in patients with DM appears to be a blood glucose level of 14 mmol/L[35].

In contrast to the risk of hyperglycemia differing by casemix, the risks of hypoglycemia appear to affect a broad range of patients similarly. Severe hypoglycemia (< 2.2 mmol/L), moderate hypoglycemia (< 3.3 mmol/L), and even mild hypoglycemia (<4 mmol/L) have been associated with ICU and hospital mortality[36-39]. Targeting lower blood glucose levels resulted in higher rates of severe hypoglycemia[40,41], and no clinical trial has targeted a lower limit of blood glucose < 4.4 mmol/L. The NICE-SUGAR trial demonstrated that the risk of hypoglycemia can be mitigated by avoiding targeting blood glucose below 6.1 mmol/L[31]. Nonetheless, if intensive glucose monitoring and management resources are available, and if glycemic control protocols and timely glucose measurements can be strictly adhered to, the Leuven studies demonstrated advantages of targeting blood glucose below 6.1 mmol/L, with surgical patients deriving clearer survival benefit and morbidity reduction compared to medical patients[23,42].

EMPIRICAL EVIDENCE FOR MINIMIZING GLYCEMIC VARIABILITY IN ICU

In a multicenter observational study, Egi *et al*[43] first showed that ICU non-survivors had a wider spread of glucose values compared to ICU survivors. Specifically, the standard deviation of blood glucose values was 2.3 mmol/L in non-survivors compared to 1.3 mmol/L in survivors. The association between spread of blood glucose with hospital mortality persisted after controlling for confounders (hospital

Table 2 Glycemic targets in intensive care unit by casemix and thresholds

Casemix	Blood sample	Method	Glycemic target	Evidence
Burns	Not stated	Not stated	Glucose > 7.8 mmol/L	Increased pneumonia, ventilator-associated pneumonia, and urinary tract infection; Obs[72]
Cardiac	Not stated	Not stated	Glucose 4.4-6.1 mmol/L	Decreased 30-d mortality compared to glucose 5-7.8 mmol/L; Obs[73]
DM	Not stated	Portable glucometer, blood gas analyzer	Glucose < 14 mmol/L	Decreased glycemic variability and incident hypoglycemia; before-and-after study[35]
DM	Arterial, venous	Blood gas analyzer	Glucose 10-14 mmol/L	Decreased incident hypoglycemia; before-and-after study[74]. No increased risk of hospital-acquired infectious, cardiovascular, renal or neurological complications; before-and-after study[75]
DM	Not stated	Portable glucometer	Glucose 5.6-7.8 mmol/L	Decreased complications (infection, cardiac events, respiratory failure, kidney failure) after coronary artery bypass graft surgery compared to glucose 7.8-10 mmol/L; RCT[34]
DM	Not stated	Portable glucometer	Glucose 5-7.8 mmol/L	Decreased 30-day mortality compared to glucose 4.4-6.1 mmol/L; Obs[76]
Medical	Capillary	Portable glucometer	Glucose > 7 mmol/L	Increased ICU mortality; Obs[77]
Medical-surgical	Arterial	Point-of-care or blood gas or laboratory analyzers	Glucose 8-10 mmol/L	Decreased 90-d mortality and incident severe hypoglycemia compared to glucose 4.5-6.0 mmol/L; RCT[31]
Medical-surgical	Not stated	Portable glucometer	Glucose 4.4-6.1 mmol/L	Decreased 30-d mortality compared to glucose 5-7.8 mmol/L in patients without DM; Obs[76]
Medical-surgical	Arterial	Point-of-care or blood gas or laboratory analyzers	Glucose 4.4-6.1 mmol/L	Increased incident severe hypoglycemia compared to more liberal control (95%CI of glucose -7.8-9.4) mmol/L; RCT[78]
Medical-surgical	Arterial, capillary	Glucometer	Glucose 10-11.1 mmol/L	Decreased incident severe hypoglycemia compared to glucose 4.4-6.1 mmol/L; RCT[46]
Medical-surgical	Arterial, capillary, venous	Glucometer or blood gas analyzer	Glucose 7.8-10 mmol/L	Decreased incident severe hypoglycemia compared to glucose 4.4-6.1 mmol/L; RCT[79]
Medical-surgical	Arterial	Portable glucometer	Glucose 7-9 mmol/L	Decreased ICU mortality compared to out-of-range glucose; Obs[80]
Medical-surgical	Arterial, capillary	Glucometer or blood gas analyzer	Glucose < 10 mmol/L	Decreased incident severe hypoglycemia compared to glucose 4.4-6.1 mmol/L; RCT[31,81]
Medical-surgical	Arterial	Glucometer	Glucose < 8 mmol/L	Decreased ICU mortality compared to higher glucose levels; Obs[82]
Medical-surgical	Arterial	Blood gas analyzer	Glucose > 8.3 mmol/L	Increased ICU mortality compared to glucose 6.1-8.3; Obs[83]
Medical-surgical	Arterial, capillary	Glucometer	Glucose < 8.2 mmol/L	Decreased ICU mortality compared to higher glucose levels; Obs[84]
Medical-surgical	Arterial, venous	Glucometer	Glucose 4.4-7.8 mmol/L	Decreased ICU and hospital mortality compared to glucose 7.8-10 mmol/L in patients without DM; Obs[26]
Medical-surgical	Not stated	Glucometer	Glucose 3.9-7.8 mmol/L	Time in range associated with decreased ICU mortality in patients without DM; Obs[85]; Time in range associated with decreased ICU mortality in patients receiving insulin; Obs[86]
Medical-surgical	Venous	Laboratory	Low SHR < 1	Decreased hospital mortality compared to SHR > 1 regardless of baseline HbA1c; Obs[87]
Post-CA	Capillary, venous	Not stated	Glucose 3.9-7.8 mmol/L	Higher survival, compared to higher glucose levels; Obs[88]
Post-CA	Not stated	Not stated	Glucose 4-10 mmol/L	Better neurological recovery, compared to higher glucose levels; Obs[33]
Surgical	Arterial	Blood gas analyzer	Glucose 4.4-6.1 mmol/L	Decreased hospital mortality, blood stream infections, acute renal failure, blood transfusion, critical-illness polyneuropathy, prolonged mechanical ventilation, compared to glucose 10-11.1 mmol/L; RCT[42]
Surgical	Not stated	Not stated	Glucose 4.4-6.1 mmol/L	Decreased post-operative renal failure and 30-d mortality compared to glucose > 8.3 mmol/L; Obs[89]

Surgical	Arterial, capillary, venous	Glucometer or blood gas analyzer	Glucose 4.4-7.8 mmol/L	Decreased hospital mortality compared to glucose >7.8 mmol/L; Obs[27]
Surgical	Not stated	Glucometer	Glucose 4-8 mmol/L	Decreased surgical site infection after coronary artery bypass graft surgery compared to glucose 4-10 mmol/L; before-and-after study[28]
Surgical	Arterial, venous	Continuous sensor, in a closed-loop system	Glucose 4.4-6.1 mmol/L	Decreased surgical site infection post- hepato-biliary-pancreatic surgery, compared to glucose 7.7-10.0 mmol/L; RCT[90]
Surgical	Arterial	Blood gas analyzer	Glucose 6.7-8.9 mmol/L	Decreased mortality compared to glucose 8.9-10 mmol/L; quasi-experimental (alternate allocation of participants)[91]
Surgical	Capillary	Glucometer	Glucose 6.1-8.3 mmol/L	Decreased surgical site infection and atrial fibrillation after coronary artery bypass graft surgery; before-and-after study[29]
TBI	Arterial	Blood gas analyzer	Glucose 3.5-6.5 mmol/L	Reduced intracranial hypertension and decreased rate of pneumonia, bacteremia and urinary tract infections during 2nd week, compared to glucose 5-8 mmol/L; Obs[5]
TBI	Not stated	Not stated	Glucose 4.4-6.7 mmol/L	Decreased risk of poor neurological outcomes but increased risk of hypoglycemia, and no mortality benefit, compared to higher glucose targets; systematic review of RCT[30]
TBI	Arterial	Point-of-care or blood gas or laboratory analyzers	Glucose 8-10 mmol/L	Decreased incident severe hypoglycemia, but no mortality benefit, compared to glucose 4.5-6.0 mmol/L; RCT[92]
TBI	Not stated	Not stated	Glucose < 11.1 mmol/L	Decreased hospital mortality compared to glucose > 11.1 mmol/L; Obs[93]
Trauma	Arterial, capillary, venous	Point-of-care or laboratory analyzers	Glucose < 7.8 mmol/L	Decreased ICU mortality compared to glucose > 7.8 mmol/L; Obs[94]
Trauma	Capillary	Not stated	Glucose < 10 mmol/L	Decreased hospital mortality compared to glucose > 10 mmol/L; Obs[32]

DM: Diabetes mellitus; HbA1c: Glycosylated hemoglobin; ICU: Intensive care unit; Obs: Observational study; RCT: Randomized controlled trial; SHR: Stress hyperglycemia ratio; TBI: Traumatic brain injury.

site, surgical patients, neurologic diseases, mechanical ventilation, acute physiological and chronic health evaluation II score, age, mean blood glucose level, maximum blood glucose level, and admission blood glucose level).

Subsequently, other observational studies have demonstrated that the difference between maximum and minimum blood glucose levels (*i.e.*, glucose variability) should not exceed 4-6 mmol/L, regardless of casemix[10,44,45] (Table 3). In other words, glycemic target ranges should ideally be < 4 mmol/L in width. Such a narrow range seems to be achievable, given that both single-center and multi-center randomized trials using a variety of protocols have successfully constrained glucose levels within standard deviations of < 2 mmol/L[23,31,42,46].

CHOOSING LOWER *VS* HIGHER GLYCEMIC TARGET RANGES

To minimize patient harm, empirical evidence suggests that when choosing glycemic targets, one should keep the glycemic variability < 4 mmol/L and avoid targeting a lower limit of blood glucose < 4.4 mmol/L. The upper limit of blood glucose should then be set according to casemix and the quality of glucose control.

A lower glycemic target range (*i.e.*, blood glucose 4.5-7.8 mmol/L) would be favored for patients without DM, with TBI, or who are postoperative and at risk of surgical site infection. Requirements for targeting a lower range and avoiding harm from hypoglycemia would be availability of intensive glucose monitoring and management, strict adherence to glycemic control protocols, and strict adherence to timely glucose measurements (Table 4).

In contrast, a higher glycemic target range (*i.e.*, blood glucose 7.8-10 mmol/L) would be favored as a default choice for medical-surgical patients and patients with DM. Additionally, a higher range would be favored if conditions to avoid hypoglycemia cannot be strictly met, *i.e.*, lack of intensive glucose monitoring and management, less than strict adherence to glycemic control protocols, and less than strict adherence to timely glucose measurements.

Table 3 Glycemic targets in intensive care unit by casemix and variability

Casemix	Blood sample	Method	Glycemic target	Evidence
Medical-surgical	Arterial, venous	Glucometer	Glucose variability (COV ≥ 20%)	Increased ICU and hospital mortality in patients without DM; Obs[26]
Medical-surgical	Arterial, capillary	Glucometer or blood gas analyzer	Glucose variability > 6 mmol/L	Increased ICU and hospital mortality; Obs[44]
Medical-surgical	Arterial	Glucometer or blood gas analyzer	Glucose variability > 4 mmol/L	Increased hospital mortality; Obs[10]
Post-CA	Arterial	Blood gas analyzer	Glucose variability < 5 mmol/L	Decreased hypoglycemia and mortality; Obs [45]
Post-CA	Not stated	Not stated	GG-min < 3.9 mmol/L	Better neurological recovery; Obs[95]

COV: Coefficient of variation; GG: Glycemic gap; GG-min: Minimum glycemic gap = minimum blood glucose - [(1.59 × HbA1c) - 2.59], HbA1c being used to estimate average glucose concentration over the prior 3 mo; ICU: Intensive care unit; Obs: Observational study.

Table 4 Choosing lower *vs* higher glycemic target ranges

Glycemic target range	Considerations favoring choice of glycemic target range
Lower glycemic target range (*i.e.*, glucose 4.5-7.8 mmol/L)	(1) Patients without DM; (2) Patients with TBI; (3) Post-surgical patients at risk of surgical site infections; (4) Availability of intensive glucose monitoring and management; (5) Strict adherence to glycemic control protocols; and (6) Strict adherence to timely glucose measurements
Higher glycemic target range (*i.e.*, glucose 7.8-10 mmol/L)	(1) Default choice for most patients; (2) Patients with DM; (3) Lack of intensive glucose monitoring and management; (4) Less than strict adherence to glycemic control protocols; and (5) Less than strict adherence to timely glucose measurements

DM: Diabetes mellitus; TBI: Traumatic brain injury.

This review's recommendations are in line with current guidelines (Table 5). For hospitalized patients in general, the American Diabetes Association recommends a glycemic target range of 7.8-10 mmol/L[47]. The same glycemic range is recommended for post-resuscitation care of cardiac arrest patients by the European Resuscitation Council[48]. For sepsis patients, the Surviving Sepsis Campaign recommends an upper blood glucose limit of 10 mmol/L[49]. Both the American Diabetes Association and Surviving Sepsis Campaign guidelines mention that lower targets may be appropriate for selected patients if they can be achieved without significant hypoglycemia[47,49].

Other guidelines have made less definite recommendations. For surgical patients, the World Health Organization recommends glucose control, though no target range was defined[50]. For patients with TBI, the Brain Trauma Foundation does not mention glycemic control[51]. The findings and recommendations from this review can therefore help fill any gaps in these latter guidelines.

FUTURE DIRECTIONS

To increase the safety of lower glycemic targets, technical advances for blood glucose measurement and control would help. Autocorrecting point-of-care glucose measurement devices can adjust for interfering substances (*e.g.*, ascorbic acid and non-glucose sugars) and abnormal hematocrit in critically ill patients[52], enabling these devices to become as accurate as central laboratory plasma glucose measurements. Monte Carlo simulation suggests that glycemic control in critically ill patients is optimal with a blood glucose measurement interval no longer than 1 h, with incremental benefit using shorter measurement intervals of 15 min[53]. This means that devices that can continuously assay blood glucose would be needed. More accurate and frequent blood glucose measurements can feed into automated and closed-loop glycemic control systems[54-62]. For instance, even when targeting a lower range of 4.4-8.3 mmol/L, one such system limited severe hypoglycemic episodes to only 0.01% of all blood glucose measurements and 0.8% of patients[59].

Table 5 Selected guideline recommendations

Casemix	Guideline (Year)	Recommended glycemic target range
Medical-Surgical	American Diabetes Association: Diabetes Care in the Hospital (2021) [47]	7.8-10 mmol/L. Lower targets may be appropriate for selected patients if they can be achieved without significant hypoglycemia
Post-CA	European Resuscitation Council and European Society of Intensive Care Medicine guidelines (2021)[48]	7.8-10 mmol/L
Sepsis	Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock (2016)[49]	< 10 mmol/L and avoid hypoglycemia. Lower targets may be appropriate for selected patients if they can be achieved without significant hypoglycemia
Surgical	WHO recommendations on intraoperative and postoperative measures for surgical site infection prevention: an evidence-based global perspective (2016)[50]	Unable to define target range, though glucose control protocols recommended
TBI	Brain Trauma Foundation's Guidelines for the Management of Severe Traumatic Brain Injury, Fourth Edition (2016)[51]	No recommendation

CA: Cardiac arrest; TBI: Traumatic brain injury; WHO: World Health Organization.

Optimization of glucose control protocols with respect to the following aspects may also be investigated: (1) Addition of bolus insulin "mid-protocol" during an insulin infusion to reduce peak insulin rates for insulin-resistant patients[63]; (2) transition of insulin administration route from intravenous to subcutaneous[64], and (3) use of DM-specific enteral formula for both DM and non-DM patients[65-67].

Given the influence of casemix on the optimal glycemic target range, further work may be done to personalize recommendations for various conditions[68]. For patients with DM, it remains unclear if the upper limit of blood glucose can be safely pushed beyond 10 mmol/L[69], given the risk of ketoacidosis or ketonemia[70]. To address this uncertainty, the LUCID trial will investigate if liberal blood glucose (target 10.0-14.0 mmol/L) will result in less incident hypoglycemia compared to usual care (target 6.0-10.0 mmol/L), while maintaining good clinical outcomes[71].

CONCLUSION

When choosing glycemic targets, one should keep the glycemic variability < 4 mmol/L and avoid targeting a lower limit of blood glucose < 4.4 mmol/L. The upper limit of blood glucose should be set according to casemix and the quality of glucose control. A lower glycemic target range (*i.e.*, blood glucose 4.5-7.8 mmol/L) would be favored for patients without diabetes mellitus, with traumatic brain injury, or who are at risk of surgical site infection. To avoid harm from hypoglycemia, strict adherence to glycemic control protocols and timely glucose measurements are required. In contrast, a higher glycemic target range (*i.e.*, blood glucose 7.8-10 mmol/L) would be favored as a default choice for medical-surgical patients and patients with diabetes mellitus. These targets may be modified if technical advances for blood glucose measurement and control can be achieved.

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