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**Glycemic targets in critically ill adults: A mini-review**

See KC. Glycemic targets in critically ill adults

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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

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**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.

**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 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.

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]

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.

**REFERENCES**

1 **Van den Berghe G**, Schetz M, Vlasselaers D, Hermans G, Wilmer A, Bouillon R, Mesotten D. Clinical review: Intensive insulin therapy in critically ill patients: NICE-SUGAR or Leuven blood glucose target? *J Clin Endocrinol Metab* 2009; **94**: 3163-3170 [PMID: 19531590 DOI: 10.1210/jc.2009-0663]

2 **Honiden S**, Inzucchi SE. Metabolic Management during Critical Illness: Glycemic Control in the ICU. *Semin Respir Crit Care Med* 2015; **36**: 859-869 [PMID: 26595046 DOI: 10.1055/s-0035-1565253]

3 **Avanzini F**, Mafrici A, Riva E, Franzosi MG, Milani V, Giudici V, Marelli G, Mariani G, Piatti PM, Roncaglioni MC; GLICINE-SPIDER Collaborative Group. A multicenter observational study on the management of hyperglycemia in patients with acute coronary syndrome. *Nutr Metab Cardiovasc Dis* 2015; **25**: 916-923 [PMID: 26298425 DOI: 10.1016/j.numecd.2015.07.007]

4 **Savioli M**, Cugno M, Polli F, Taccone P, Bellani G, Spanu P, Pesenti A, Iapichino G, Gattinoni L. Tight glycemic control may favor fibrinolysis in patients with sepsis. *Crit Care Med* 2009; **37**: 424-431 [PMID: 19114908 DOI: 10.1097/CCM.0b013e31819542da]

5 **Meier R**, Béchir M, Ludwig S, Sommerfeld J, Keel M, Steiger P, Stocker R, Stover JF. Differential temporal profile of lowered blood glucose levels (3.5 to 6.5 mmol/L *vs* 5 to 8 mmol/L) in patients with severe traumatic brain injury. *Crit Care* 2008; **12**: R98 [PMID: 18680584 DOI: 10.1186/cc6974]

6 **Stamou SC**, Nussbaum M, Carew JD, Dunn K, Skipper E, Robicsek F, Lobdell KW. Hypoglycemia with intensive insulin therapy after cardiac surgery: predisposing factors and association with mortality. *J Thorac Cardiovasc Surg* 2011; **142**: 166-173 [PMID: 21397274 DOI: 10.1016/j.jtcvs.2010.09.064]

7 **Tickoo M**. The Long and Winding Road to Personalized Glycemic Control in the Intensive Care Unit. *Semin Respir Crit Care Med* 2019; **40**: 571-579 [PMID: 31826258 DOI: 10.1055/s-0039-1697603]

8 **Liu WY**, Lin SG, Zhu GQ, Poucke SV, Braddock M, Zhang Z, Mao Z, Shen FX, Zheng MH. Establishment and Validation of GV-SAPS II Scoring System for Non-Diabetic Critically Ill Patients. *PLoS One* 2016; **11**: e0166085 [PMID: 27824941 DOI: 10.1371/journal.pone.0166085]

9 **Hermanides J**, Vriesendorp TM, Bosman RJ, Zandstra DF, Hoekstra JB, Devries JH. Glucose variability is associated with intensive care unit mortality. *Crit Care Med* 2010; **38**: 838-842 [PMID: 20035218 DOI: 10.1097/CCM.0b013e3181cc4be9]

10 **Meyfroidt G**, Keenan DM, Wang X, Wouters PJ, Veldhuis JD, Van den Berghe G. Dynamic characteristics of blood glucose time series during the course of critical illness: effects of intensive insulin therapy and relative association with mortality. *Crit Care Med* 2010; **38**: 1021-1029 [PMID: 20124887 DOI: 10.1097/CCM.0b013e3181cf710e]

11 **Juneja R**, Roudebush CP, Nasraway SA, Golas AA, Jacobi J, Carroll J, Nelson D, Abad VJ, Flanders SJ. Computerized intensive insulin dosing can mitigate hypoglycemia and achieve tight glycemic control when glucose measurement is performed frequently and on time. *Crit Care* 2009; **13**: R163 [PMID: 19822000 DOI: 10.1186/cc8129]

12 **Sadhu AR**, Serrano IA, Xu J, Nisar T, Lucier J, Pandya AR, Patham B. Continuous Glucose Monitoring in Critically Ill Patients With COVID-19: Results of an Emergent Pilot Study. *J Diabetes Sci Technol* 2020; **14**: 1065-1073 [PMID: 33063556 DOI: 10.1177/1932296820964264]

13 **Gottschalk A**, Welp HA, Leser L, Lanckohr C, Wempe C, Ellger B. Continuous Glucose Monitoring in Patients Undergoing Extracorporeal Ventricular Assist Therapy. *PLoS One* 2016; **11**: e0148778 [PMID: 26963806 DOI: 10.1371/journal.pone.0148778]

14 **Wollersheim T**, Engelhardt LJ, Pachulla J, Moergeli R, Koch S, Spies C, Hiesmayr M, Weber-Carstens S. Accuracy, reliability, feasibility and nurse acceptance of a subcutaneous continuous glucose management system in critically ill patients: a prospective clinical trial. *Ann Intensive Care* 2016; **6**: 70 [PMID: 27439710 DOI: 10.1186/s13613-016-0167-z]

15 **Punke MA**, Decker C, Petzoldt M, Reuter DA, Wodack KH, Reichenspurner H, Kubik M, Kluge S. Head-to-head comparison of two continuous glucose monitoring systems on a cardio-surgical ICU. *J Clin Monit Comput* 2019; **33**: 895-901 [PMID: 30421152 DOI: 10.1007/s10877-018-0221-5]

16 **De Block CE**, Gios J, Verheyen N, Manuel-y-Keenoy B, Rogiers P, Jorens PG, Scuffi C, Van Gaal LF. Randomized Evaluation of Glycemic Control in the Medical Intensive Care Unit Using Real-Time Continuous Glucose Monitoring (REGIMEN Trial). *Diabetes Technol Ther* 2015; **17**: 889-898 [PMID: 26305390 DOI: 10.1089/dia.2015.0151]

17 **Galindo RJ**, Umpierrez GE, Rushakoff RJ, Basu A, Lohnes S, Nichols JH, Spanakis EK, Espinoza J, Palermo NE, Awadjie DG, Bak L, Buckingham B, Cook CB, Freckmann G, Heinemann L, Hovorka R, Mathioudakis N, Newman T, O'Neal DN, Rickert M, Sacks DB, Seley JJ, Wallia A, Shang T, Zhang JY, Han J, Klonoff DC. Continuous Glucose Monitors and Automated Insulin Dosing Systems in the Hospital Consensus Guideline. *J Diabetes Sci Technol* 2020; **14**: 1035-1064 [PMID: 32985262 DOI: 10.1177/1932296820954163]

18 **van Steen SC**, Rijkenberg S, Limpens J, van der Voort PH, Hermanides J, DeVries JH. The Clinical Benefits and Accuracy of Continuous Glucose Monitoring Systems in Critically Ill Patients-A Systematic Scoping Review. *Sensors (Basel)* 2017; **17** [PMID: 28098809 DOI: 10.3390/s17010146]

19 **Eerdekens GJ**, Rex S, Mesotten D. Accuracy of Blood Glucose Measurement and Blood Glucose Targets. *J Diabetes Sci Technol* 2020; **14**: 553-559 [PMID: 32046520 DOI: 10.1177/1932296820905581]

20 **Le HT**, Harris NS, Estilong AJ, Olson A, Rice MJ. Blood glucose measurement in the intensive care unit: what is the best method? *J Diabetes Sci Technol* 2013; **7**: 489-499 [PMID: 23567008 DOI: 10.1177/193229681300700226]

21 **Liang Y**, Wanderer J, Nichols JH, Klonoff D, Rice MJ. Blood Gas Analyzer Accuracy of Glucose Measurements. *Mayo Clin Proc* 2017; **92**: 1030-1041 [PMID: 28645518 DOI: 10.1016/j.mayocp.2017.03.009]

22 **Garingarao CJ**, Buenaluz-Sedurante M, Jimeno CA. Accuracy of point-of-care blood glucose measurements in critically ill patients in shock. *J Diabetes Sci Technol* 2014; **8**: 937-944 [PMID: 25172876 DOI: 10.1177/1932296814538608]

23 **Van den Berghe G**, Wilmer A, Hermans G, Meersseman W, Wouters PJ, Milants I, Van Wijngaerden E, Bobbaers H, Bouillon R. Intensive insulin therapy in the medical ICU. *N Engl J Med* 2006; **354**: 449-461 [PMID: 16452557 DOI: 10.1056/NEJMoa052521]

24 **De La Rosa Gdel C**, Donado JH, Restrepo AH, Quintero AM, González LG, Saldarriaga NE, Bedoya M, Toro JM, Velásquez JB, Valencia JC, Arango CM, Aleman PH, Vasquez EM, Chavarriaga JC, Yepes A, Pulido W, Cadavid CA; Grupo de Investigacion en Cuidado intensivo: GICI-HPTU. Strict glycaemic control in patients hospitalised in a mixed medical and surgical intensive care unit: a randomised clinical trial. *Crit Care* 2008; **12**: R120 [PMID: 18799004 DOI: 10.1186/cc7017]

25 **Arabi YM**, Dabbagh OC, Tamim HM, Al-Shimemeri AA, Memish ZA, Haddad SH, Syed SJ, Giridhar HR, Rishu AH, Al-Daker MO, Kahoul SH, Britts RJ, Sakkijha MH. Intensive *vs* conventional insulin therapy: a randomized controlled trial in medical and surgical critically ill patients. *Crit Care Med* 2008; **36**: 3190-3197 [PMID: 18936702 DOI: 10.1097/CCM.0b013e31818f21aa]

26 **Krinsley JS**, Maurer P, Holewinski S, Hayes R, McComsey D, Umpierrez GE, Nasraway SA. Glucose Control, Diabetes Status, and Mortality in Critically Ill Patients: The Continuum From Intensive Care Unit Admission to Hospital Discharge. *Mayo Clin Proc* 2017; **92**: 1019-1029 [PMID: 28645517 DOI: 10.1016/j.mayocp.2017.04.015]

27 **Schlussel AT**, Holt DB, Crawley EA, Lustik MB, Wade CE, Uyehara CF. Effects of hyperglycemia and continuous intravenous insulin on outcomes of surgical patients. *J Surg Res* 2012; **176**: 202-209 [PMID: 21920548 DOI: 10.1016/j.jss.2011.07.004]

28 **Ng RR**, Myat Oo A, Liu W, Tan TE, Ti LK, Chew ST. Changing glucose control target and risk of surgical site infection in a Southeast Asian population. *J Thorac Cardiovasc Surg* 2015; **149**: 323-328 [PMID: 25439770 DOI: 10.1016/j.jtcvs.2014.08.076]

29 **Leibowitz G**, Raizman E, Brezis M, Glaser B, Raz I, Shapira O. Effects of moderate intensity glycemic control after cardiac surgery. *Ann Thorac Surg* 2010; **90**: 1825-1832 [PMID: 21095319 DOI: 10.1016/j.athoracsur.2010.07.063]

30 **Hermanides J**, Plummer MP, Finnis M, Deane AM, Coles JP, Menon DK. Glycaemic control targets after traumatic brain injury: a systematic review and meta-analysis. *Crit Care* 2018; **22**: 11 [PMID: 29351760 DOI: 10.1186/s13054-017-1883-y]

31 **NICE-SUGAR Study Investigators.**, Finfer S, Chittock DR, Su SY, Blair D, Foster D, Dhingra V, Bellomo R, Cook D, Dodek P, Henderson WR, Hébert PC, Heritier S, Heyland DK, McArthur C, McDonald E, Mitchell I, Myburgh JA, Norton R, Potter J, Robinson BG, Ronco JJ. Intensive *vs* conventional glucose control in critically ill patients. *N Engl J Med* 2009; **360**: 1283-1297 [PMID: 19318384 DOI: 10.1056/NEJMoa0810625]

32 **Kutcher ME**, Pepper MB, Morabito D, Sunjaya D, Knudson MM, Cohen MJ. Finding the sweet spot: identification of optimal glucose levels in critically injured patients. *J Trauma* 2011; **71**: 1108-1114 [PMID: 22071916 DOI: 10.1097/TA.0b013e318232e35b]

33 **Borgquist O**, Wise MP, Nielsen N, Al-Subaie N, Cranshaw J, Cronberg T, Glover G, Hassager C, Kjaergaard J, Kuiper M, Smid O, Walden A, Friberg H; TTM-Trial Investigators. Dysglycemia, Glycemic Variability, and Outcome After Cardiac Arrest and Temperature Management at 33°C and 36°C. *Crit Care Med* 2017; **45**: 1337-1343 [PMID: 28708678 DOI: 10.1097/CCM.0000000000002367]

34 **Umpierrez G**, Cardona S, Pasquel F, Jacobs S, Peng L, Unigwe M, Newton CA, Smiley-Byrd D, Vellanki P, Halkos M, Puskas JD, Guyton RA, Thourani VH. Randomized Controlled Trial of Intensive Versus Conservative Glucose Control in Patients Undergoing Coronary Artery Bypass Graft Surgery: GLUCO-CABG Trial. *Diabetes Care* 2015; **38**: 1665-1672 [PMID: 26180108 DOI: 10.2337/dc15-0303]

35 **Kar P**, Plummer MP, Bellomo R, Jenkins AJ, Januszewski AS, Chapman MJ, Jones KL, Horowitz M, Deane AM. Liberal Glycemic Control in Critically Ill Patients With Type 2 Diabetes: An Exploratory Study. *Crit Care Med* 2016; **44**: 1695-1703 [PMID: 27315191 DOI: 10.1097/CCM.0000000000001815]

36 **NICE-SUGAR Study Investigators.**, Finfer S, Liu B, Chittock DR, Norton R, Myburgh JA, McArthur C, Mitchell I, Foster D, Dhingra V, Henderson WR, Ronco JJ, Bellomo R, Cook D, McDonald E, Dodek P, Hébert PC, Heyland DK, Robinson BG. Hypoglycemia and risk of death in critically ill patients. *N Engl J Med* 2012; **367**: 1108-1118 [PMID: 22992074 DOI: 10.1056/NEJMoa1204942]

37 **D'Ancona G**, Bertuzzi F, Sacchi L, Pirone F, Stringi V, Arcadipane A, Bellazzi R, Pilato M. Iatrogenic hypoglycemia secondary to tight glucose control is an independent determinant for mortality and cardiac morbidity. *Eur J Cardiothorac Surg* 2011; **40**: 360-366 [PMID: 21256761 DOI: 10.1016/j.ejcts.2010.11.065]

38 **Graffagnino C**, Gurram AR, Kolls B, Olson DM. Intensive insulin therapy in the neurocritical care setting is associated with poor clinical outcomes. *Neurocrit Care* 2010; **13**: 307-312 [PMID: 21086066 DOI: 10.1007/s12028-010-9469-4]

39 **Durao MS**, Marra AR, Moura DF, Almeida SM, Fernandes CJ, Akamine N, Hidal JT, Santos OF. Tight glucose control *vs* intermediate glucose control: a quasi-experimental study. *Anaesth Intensive Care* 2010; **38**: 467-473 [PMID: 20514954 DOI: 10.1177/0310057X1003800309]

40 **Yamada T**, Shojima N, Noma H, Yamauchi T, Kadowaki T. Glycemic control, mortality, and hypoglycemia in critically ill patients: a systematic review and network meta-analysis of randomized controlled trials. *Intensive Care Med* 2017; **43**: 1-15 [PMID: 27637719 DOI: 10.1007/s00134-016-4523-0]

41 **Yatabe T**, Inoue S, Sakaguchi M, Egi M. The optimal target for acute glycemic control in critically ill patients: a network meta-analysis. *Intensive Care Med* 2017; **43**: 16-28 [PMID: 27686353 DOI: 10.1007/s00134-016-4558-2]

42 **van den Berghe G**, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, Vlasselaers D, Ferdinande P, Lauwers P, Bouillon R. Intensive insulin therapy in critically ill patients. *N Engl J Med* 2001; **345**: 1359-1367 [PMID: 11794168 DOI: 10.1056/NEJMoa011300]

43 **Egi M**, Bellomo R, Stachowski E, French CJ, Hart G. Variability of blood glucose concentration and short-term mortality in critically ill patients. *Anesthesiology* 2006; **105**: 244-252 [PMID: 16871057 DOI: 10.1097/00000542-200608000-00006]

44 **Al-Dorzi HM**, Tamim HM, Arabi YM. Glycaemic fluctuation predicts mortality in critically ill patients. *Anaesth Intensive Care* 2010; **38**: 695-702 [PMID: 20715734 DOI: 10.1177/0310057X1003800413]

45 **Cueni-Villoz N**, Devigili A, Delodder F, Cianferoni S, Feihl F, Rossetti AO, Eggimann P, Vincent JL, Taccone FS, Oddo M. Increased blood glucose variability during therapeutic hypothermia and outcome after cardiac arrest. *Crit Care Med* 2011; **39**: 2225-2231 [PMID: 21705888 DOI: 10.1097/CCM.0b013e31822572c9]

46 **Brunkhorst FM**, Engel C, Bloos F, Meier-Hellmann A, Ragaller M, Weiler N, Moerer O, Gruendling M, Oppert M, Grond S, Olthoff D, Jaschinski U, John S, Rossaint R, Welte T, Schaefer M, Kern P, Kuhnt E, Kiehntopf M, Hartog C, Natanson C, Loeffler M, Reinhart K; German Competence Network Sepsis (SepNet). Intensive insulin therapy and pentastarch resuscitation in severe sepsis. *N Engl J Med* 2008; **358**: 125-139 [PMID: 18184958 DOI: 10.1056/NEJMoa070716]

47 **American Diabetes Association.**. 15. Diabetes Care in the Hospital: *Standards of Medical Care in Diabetes-2021*. *Diabetes Care* 2021; **44**: S211-S220 [PMID: 33298426 DOI: 10.2337/dc21-S015]

48 **Nolan JP**, Sandroni C, Böttiger BW, Cariou A, Cronberg T, Friberg H, Genbrugge C, Haywood K, Lilja G, Moulaert VRM, Nikolaou N, Olasveengen TM, Skrifvars MB, Taccone F, Soar J. European Resuscitation Council and European Society of Intensive Care Medicine guidelines 2021: post-resuscitation care. *Intensive Care Med* 2021; **47**: 369-421 [PMID: 33765189 DOI: 10.1007/s00134-021-06368-4]

49 **Rhodes A**, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, Kumar A, Sevransky JE, Sprung CL, Nunnally ME, Rochwerg B, Rubenfeld GD, Angus DC, Annane D, Beale RJ, Bellinghan GJ, Bernard GR, Chiche JD, Coopersmith C, De Backer DP, French CJ, Fujishima S, Gerlach H, Hidalgo JL, Hollenberg SM, Jones AE, Karnad DR, Kleinpell RM, Koh Y, Lisboa TC, Machado FR, Marini JJ, Marshall JC, Mazuski JE, McIntyre LA, McLean AS, Mehta S, Moreno RP, Myburgh J, Navalesi P, Nishida O, Osborn TM, Perner A, Plunkett CM, Ranieri M, Schorr CA, Seckel MA, Seymour CW, Shieh L, Shukri KA, Simpson SQ, Singer M, Thompson BT, Townsend SR, Van der Poll T, Vincent JL, Wiersinga WJ, Zimmerman JL, Dellinger RP. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. *Crit Care Med* 2017; **45**: 486-552 [PMID: 28098591 DOI: 10.1097/CCM.0000000000002255]

50 **Allegranzi B**, Zayed B, Bischoff P, Kubilay NZ, de Jonge S, de Vries F, Gomes SM, Gans S, Wallert ED, Wu X, Abbas M, Boermeester MA, Dellinger EP, Egger M, Gastmeier P, Guirao X, Ren J, Pittet D, Solomkin JS; WHO Guidelines Development Group. New WHO recommendations on intraoperative and postoperative measures for surgical site infection prevention: an evidence-based global perspective. *Lancet Infect Dis* 2016; **16**: e288-e303 [PMID: 27816414 DOI: 10.1016/S1473-3099(16)30402-9]

51 **Carney N**, Totten AM, O'Reilly C, Ullman JS, Hawryluk GW, Bell MJ, Bratton SL, Chesnut R, Harris OA, Kissoon N, Rubiano AM, Shutter L, Tasker RC, Vavilala MS, Wilberger J, Wright DW, Ghajar J. Guidelines for the Management of Severe Traumatic Brain Injury, Fourth Edition. *Neurosurgery* 2017; **80**: 6-15 [PMID: 27654000 DOI: 10.1227/NEU.0000000000001432]

52 **Tran NK**, Godwin ZR, Steele AN, Wolf SE, Palmieri TL. Clinical Impact of Accurate Point-of-Care Glucose Monitoring for Tight Glycemic Control in Severely Burned Children. *Pediatr Crit Care Med* 2016; **17**: e406-e412 [PMID: 27472251 DOI: 10.1097/PCC.0000000000000877]

53 **Krinsley JS**, Bruns DE, Boyd JC. The impact of measurement frequency on the domains of glycemic control in the critically ill--a Monte Carlo simulation. *J Diabetes Sci Technol* 2015; **9**: 237-245 [PMID: 25568143 DOI: 10.1177/1932296814566507]

54 **Emamdjomeh AS**, Warren JN, Harper CL, Olin JL. Impact of Initial eGlycemic Management System Dosing Strategy on Time to Target Blood Glucose Range. *J Diabetes Sci Technol* 2021; **15**: 242-250 [PMID: 33588608 DOI: 10.1177/1932296821992352]

55 **Shelden D**, Ateya M, Jensen A, Arnold P, Bellomo T, Gianchandani R. Improving Hospital Glucometrics, Workflow, and Outcomes with a Computerized Intravenous Insulin Dose Calculator Built into the Electronic Health Record. *J Diabetes Sci Technol* 2021; **15**: 271-278 [PMID: 33355001 DOI: 10.1177/1932296820974767]

56 **Valk T**, McMorrow C. Managing hyperglycemia during the COVID-19 pandemic: Improving outcomes using new technologies in intensive care. *SAGE Open Med* 2020; **8**: 2050312120974174 [PMID: 33282306 DOI: 10.1177/2050312120974174]

57 **Salinas PD**, Mendez CE. Glucose Management Technologies for the Critically Ill. *J Diabetes Sci Technol* 2019; **13**: 682-690 [PMID: 30638048 DOI: 10.1177/1932296818822838]

58 **Tamura T**, Yatabe T, Namikawa T, Hanazaki K, Yokoyama M. Glucose control using a closed-loop device decreases inflammation after cardiovascular surgery without increasing hypoglycemia risk. *J Artif Organs* 2019; **22**: 154-159 [PMID: 30456660 DOI: 10.1007/s10047-018-1082-x]

59 **Blaha J**, Barteczko-Grajek B, Berezowicz P, Charvat J, Chvojka J, Grau T, Holmgren J, Jaschinski U, Kopecky P, Manak J, Moehl M, Paddle J, Pasculli M, Petersson J, Petros S, Radrizzani D, Singh V, Starkopf J. Space GlucoseControl system for blood glucose control in intensive care patients--a European multicentre observational study. *BMC Anesthesiol* 2016; **16**: 8 [PMID: 26801983 DOI: 10.1186/s12871-016-0175-4]

60 **Yatabe T**, Yamazaki R, Kitagawa H, Okabayashi T, Yamashita K, Hanazaki K, Yokoyama M. The evaluation of the ability of closed-loop glycemic control device to maintain the blood glucose concentration in intensive care unit patients. *Crit Care Med* 2011; **39**: 575-578 [PMID: 21178768 DOI: 10.1097/CCM.0b013e318206b9ad]

61 **Pachler C**, Plank J, Weinhandl H, Chassin LJ, Wilinska ME, Kulnik R, Kaufmann P, Smolle KH, Pilger E, Pieber TR, Ellmerer M, Hovorka R. Tight glycaemic control by an automated algorithm with time-variant sampling in medical ICU patients. *Intensive Care Med* 2008; **34**: 1224-1230 [PMID: 18297268 DOI: 10.1007/s00134-008-1033-8]

62 **Dortch MJ**, Mowery NT, Ozdas A, Dossett L, Cao H, Collier B, Holder G, Miller RA, May AK. A computerized insulin infusion titration protocol improves glucose control with less hypoglycemia compared to a manual titration protocol in a trauma intensive care unit. *JPEN J Parenter Enteral Nutr* 2008; **32**: 18-27 [PMID: 18165443 DOI: 10.1177/014860710803200118]

63 **Marvin MR**, Inzucchi SE, Besterman BJ. Minimization of Hypoglycemia as an Adverse Event During Insulin Infusion: Further Refinement of the Yale Protocol. *Diabetes Technol Ther* 2016; **18**: 480-486 [PMID: 27257910 DOI: 10.1089/dia.2016.0101]

64 **Weant KA**, Ladha A. Conversion from continuous insulin infusions to subcutaneous insulin in critically ill patients. *Ann Pharmacother* 2009; **43**: 629-634 [PMID: 19336649 DOI: 10.1345/aph.1L629]

65 **Mesejo A**, Montejo-González JC, Vaquerizo-Alonso C, Lobo-Tamer G, Zabarte-Martinez M, Herrero-Meseguer JI, Acosta-Escribano J, Blesa-Malpica A, Martinez-Lozano F. Diabetes-specific enteral nutrition formula in hyperglycemic, mechanically ventilated, critically ill patients: a prospective, open-label, blind-randomized, multicenter study. *Crit Care* 2015; **19**: 390 [PMID: 26549276 DOI: 10.1186/s13054-015-1108-1]

66 **van Steen SC**, Rijkenberg S, Sechterberger MK, DeVries JH, van der Voort PHJ. Glycemic Effects of a Low-Carbohydrate Enteral Formula Compared With an Enteral Formula of Standard Composition in Critically Ill Patients: An Open-Label Randomized Controlled Clinical Trial. *JPEN J Parenter Enteral Nutr* 2018; **42**: 1035-1045 [PMID: 30133840 DOI: 10.1002/jpen.1045]

67 **Doola R**, Deane AM, Tolcher DM, Presneill JJ, Barrett HL, Forbes JM, Todd AS, Okano S, Sturgess DJ. The effect of a low carbohydrate formula on glycaemia in critically ill enterally-fed adult patients with hyperglycaemia: A blinded randomised feasibility trial. *Clin Nutr ESPEN* 2019; **31**: 80-87 [PMID: 31060838 DOI: 10.1016/j.clnesp.2019.02.013]

68 **Wang CH**, Huang CH, Chang WT, Tsai MS, Yu PH, Wu YW, Chen WJ. Associations between blood glucose level and outcomes of adult in-hospital cardiac arrest: a retrospective cohort study. *Cardiovasc Diabetol* 2016; **15**: 118 [PMID: 27557653 DOI: 10.1186/s12933-016-0445-y]

69 **Plummer MP**, Bellomo R, Cousins CE, Annink CE, Sundararajan K, Reddi BA, Raj JP, Chapman MJ, Horowitz M, Deane AM. Dysglycaemia in the critically ill and the interaction of chronic and acute glycaemia with mortality. *Intensive Care Med* 2014; **40**: 973-980 [PMID: 24760120 DOI: 10.1007/s00134-014-3287-7]

70 **Luethi N**, Cioccari L, Crisman M, Bellomo R, Eastwood GM, Mårtensson J. Prevalence of ketosis, ketonuria, and ketoacidosis during liberal glycemic control in critically ill patients with diabetes: an observational study. *Crit Care* 2016; **20**: 297 [PMID: 27633987 DOI: 10.1186/s13054-016-1462-7]

71 **Poole AP**, Finnis ME, Anstey J, Bellomo R, Bihari S, Biradar V, Doherty S, Eastwood G, Finfer S, French CJ, Ghosh A, Heller S, Horowitz M, Kar P, Kruger PS, Maiden MJ, Mårtensson J, McArthur CJ, McGuinness SP, Secombe PJ, Tobin AE, Udy AA, Young PJ, Deane AM; LUCID Study Investigators; ANZICS Clinical Trials Group. Study protocol and statistical analysis plan for the Liberal Glucose Control in Critically Ill Patients with Pre-existing Type 2 Diabetes (LUCID) trial. *Crit Care Resusc* 2020; **22**: 133-141 [PMID: 32389105]

72 **Hemmila MR**, Taddonio MA, Arbabi S, Maggio PM, Wahl WL. Intensive insulin therapy is associated with reduced infectious complications in burn patients. *Surgery* 2008; **144**: 629-35; discussion 635-7 [PMID: 18847648 DOI: 10.1016/j.surg.2008.07.001]

73 **Hersh AM**, Hirshberg EL, Wilson EL, Orme JF, Morris AH, Lanspa MJ. Lower Glucose Target Is Associated With Improved 30-Day Mortality in Cardiac and Cardiothoracic Patients. *Chest* 2018; **154**: 1044-1051 [PMID: 29705217 DOI: 10.1016/j.chest.2018.04.025]

74 **Luethi N**, Cioccari L, Biesenbach P, Lucchetta L, Kagaya H, Morgan R, Di Muzio F, Presello B, Gaafar D, Hay A, Crisman M, Toohey R, Russell H, Glassford NJ, Eastwood GM, Ekinci EI, Deane AM, Bellomo R, Mårtensson J. Liberal Glucose Control in ICU Patients With Diabetes: A Before-and-After Study. *Crit Care Med* 2018; **46**: 935-942 [PMID: 29509570 DOI: 10.1097/CCM.0000000000003087]

75 **Luethi N**, Cioccari L, Eastwood G, Biesenbach P, Morgan R, Sprogis S, Young H, Peck L, Knee Chong C, Moore S, Moon K, Ekinci EI, Deane AM, Bellomo R, Mårtensson J. Hospital-acquired complications in intensive care unit patients with diabetes: A before-and-after study of a conventional *vs* liberal glucose control protocol. *Acta Anaesthesiol Scand* 2019; **63**: 761-768 [PMID: 30882892 DOI: 10.1111/aas.13354]

76 **Lanspa MJ**, Hirshberg EL, Phillips GD, Holmen J, Stoddard G, Orme J. Moderate glucose control is associated with increased mortality compared with tight glucose control in critically ill patients without diabetes. *Chest* 2013; **143**: 1226-1234 [PMID: 23238456 DOI: 10.1378/chest.12-2072]

77 **Lacherade JC**, Jabre P, Bastuji-Garin S, Grimaldi D, Fangio P, Théron V, Outin H, De Jonghe B. Failure to achieve glycemic control despite intensive insulin therapy in a medical ICU: incidence and influence on ICU mortality. *Intensive Care Med* 2007; **33**: 814-821 [PMID: 17431584 DOI: 10.1007/s00134-007-0543-0]

78 **COIITSS Study Investigators.**, Annane D, Cariou A, Maxime V, Azoulay E, D'honneur G, Timsit JF, Cohen Y, Wolf M, Fartoukh M, Adrie C, Santré C, Bollaert PE, Mathonet A, Amathieu R, Tabah A, Clec'h C, Mayaux J, Lejeune J, Chevret S. Corticosteroid treatment and intensive insulin therapy for septic shock in adults: a randomized controlled trial. *JAMA* 2010; **303**: 341-348 [PMID: 20103758 DOI: 10.1001/jama.2010.2]

79 **Preiser JC**, Devos P, Ruiz-Santana S, Mélot C, Annane D, Groeneveld J, Iapichino G, Leverve X, Nitenberg G, Singer P, Wernerman J, Joannidis M, Stecher A, Chioléro R. A prospective randomised multi-centre controlled trial on tight glucose control by intensive insulin therapy in adult intensive care units: the Glucontrol study. *Intensive Care Med* 2009; **35**: 1738-1748 [PMID: 19636533 DOI: 10.1007/s00134-009-1585-2]

80 **Siegelaar SE**, Hermanides J, Oudemans-van Straaten HM, van der Voort PH, Bosman RJ, Zandstra DF, DeVries JH. Mean glucose during ICU admission is related to mortality by a U-shaped curve in surgical and medical patients: a retrospective cohort study. *Crit Care* 2010; **14**: R224 [PMID: 21143980 DOI: 10.1186/cc9369]

81 **Kalfon P**, Giraudeau B, Ichai C, Guerrini A, Brechot N, Cinotti R, Dequin PF, Riu-Poulenc B, Montravers P, Annane D, Dupont H, Sorine M, Riou B; CGAO-REA Study Group. Tight computerized *vs* conventional glucose control in the ICU: a randomized controlled trial. *Intensive Care Med* 2014; **40**: 171-181 [PMID: 24420499 DOI: 10.1007/s00134-013-3189-0]

82 **Finney SJ**, Zekveld C, Elia A, Evans TW. Glucose control and mortality in critically ill patients. *JAMA* 2003; **290**: 2041-2047 [PMID: 14559958 DOI: 10.1001/jama.290.15.2041]

83 **Van den Berghe G**, Wilmer A, Milants I, Wouters PJ, Bouckaert B, Bruyninckx F, Bouillon R, Schetz M. Intensive insulin therapy in mixed medical/surgical intensive care units: benefit *vs* harm. *Diabetes* 2006; **55**: 3151-3159 [PMID: 17065355 DOI: 10.2337/db06-0855]

84 **Al-Tarifi A**, Abou-Shala N, Tamim HM, Rishu AH, Arabi YM. What is the optimal blood glucose target in critically ill patients? A nested cohort study. *Ann Thorac Med* 2011; **6**: 207-211 [PMID: 21977065 DOI: 10.4103/1817-1737.84774]

85 **Krinsley JS**, Preiser JC. Time in blood glucose range 70 to 140 mg/dL >80% is strongly associated with increased survival in non-diabetic critically ill adults. *Crit Care* 2015; **19**: 179 [PMID: 25927986 DOI: 10.1186/s13054-015-0908-7]

86 **Lanspa MJ**, Krinsley JS, Hersh AM, Wilson EL, Holmen JR, Orme JF, Morris AH, Hirshberg EL. Percentage of Time in Range 70 to 139 mg/dL Is Associated With Reduced Mortality Among Critically Ill Patients Receiving IV Insulin Infusion. *Chest* 2019; **156**: 878-886 [PMID: 31201784 DOI: 10.1016/j.chest.2019.05.016]

87 **Lee TF**, Drake SM, Roberts GW, Bersten A, Stranks SN, Heilbronn LK, Mangoni AA, Burt MG. Relative Hyperglycemia Is an Independent Determinant of In-Hospital Mortality in Patients With Critical Illness. *Crit Care Med* 2020; **48**: e115-e122 [PMID: 31939810 DOI: 10.1097/CCM.0000000000004133]

88 **Zhou D**, Li Z, Shi G, Zhou J. Proportion of time spent in blood glucose range 70 to 140 mg/dL is associated with increased survival in patients admitted to ICU after cardiac arrest: A multicenter observational study. *Medicine (Baltimore)* 2020; **99**: e21728 [PMID: 32872055 DOI: 10.1097/MD.0000000000021728]

89 **Lecomte P**, Van Vlem B, Coddens J, Cammu G, Nollet G, Nobels F, Vanermen H, Foubert L. Tight perioperative glucose control is associated with a reduction in renal impairment and renal failure in non-diabetic cardiac surgical patients. *Crit Care* 2008; **12**: R154 [PMID: 19055829 DOI: 10.1186/cc7145]

90 **Okabayashi T**, Shima Y, Sumiyoshi T, Kozuki A, Tokumaru T, Iiyama T, Sugimoto T, Kobayashi M, Yokoyama M, Hanazaki K. Intensive *vs* intermediate glucose control in surgical intensive care unit patients. *Diabetes Care* 2014; **37**: 1516-1524 [PMID: 24623024 DOI: 10.2337/dc13-1771]

91 **Giakoumidakis K**, Eltheni R, Patelarou E, Theologou S, Patris V, Michopanou N, Mikropoulos T, Brokalaki H. Effects of intensive glycemic control on outcomes of cardiac surgery. *Heart Lung* 2013; **42**: 146-151 [PMID: 23453011 DOI: 10.1016/j.hrtlng.2012.12.007]

92 **NICE-SUGAR Study Investigators for the Australian and New Zealand Intensive Care Society Clinical Trials Group and the Canadian Critical Care Trials Group.**, Finfer S, Chittock D, Li Y, Foster D, Dhingra V, Bellomo R, Cook D, Dodek P, Hebert P, Henderson W, Heyland D, Higgins A, McArthur C, Mitchell I, Myburgh J, Robinson B, Ronco J. Intensive *vs* conventional glucose control in critically ill patients with traumatic brain injury: long-term follow-up of a subgroup of patients from the NICE-SUGAR study. *Intensive Care Med* 2015; **41**: 1037-1047 [PMID: 26088909 DOI: 10.1007/s00134-015-3757-6]

93 **Griesdale DE**, Tremblay MH, McEwen J, Chittock DR. Glucose control and mortality in patients with severe traumatic brain injury. *Neurocrit Care* 2009; **11**: 311-316 [PMID: 19636972 DOI: 10.1007/s12028-009-9249-1]

94 **Gale SC**, Sicoutris C, Reilly PM, Schwab CW, Gracias VH. Poor glycemic control is associated with increased mortality in critically ill trauma patients. *Am Surg* 2007; **73**: 454-460 [PMID: 17520998 DOI: 10.1177/000313480707300507]

95 **Wang CH**, Chang JL, Huang CH, Chang WT, Tsai MS, Yu PH, Wu YW, Chen WJ, Tseng WK. The association between long-term glycaemic control, glycaemic gap and neurological outcome of in-hospital cardiac arrest in diabetics: A retrospective cohort study. *Resuscitation* 2018; **133**: 18-24 [PMID: 30261218 DOI: 10.1016/j.resuscitation.2018.09.017]

**Footnotes**

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**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.

**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.

**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**

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| **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.

**Table 5 Selected guideline recommendations**

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| **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.