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**Management of critically ill patients with diabetes**

Silva-Perez LJ *et al*. Management of diabetes in ICU

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**Abstract**

Disorders of glucose homeostasis, such as stress-induced hypoglycemia and hyperglycemia, are common complications in patients in the intensive care unit. Patients with preexisting diabetes mellitus (DM) are more susceptible to hyperglycemia, as well as a higher risk from glucose overcorrection, that may results in severe hypoglycemia. In critically ill patients with DM, it is recommended to maintain a blood glucose range between 140–180 mg/dL. In neurological patients and surgical patients, tighter glycemic control (*i.e.*, 110–140 mg/d) is recommended if hypoglycemia can be properly avoided. There is limited evidence that shows that critically ill diabetic patients with a glycosylated hemoglobin levels above 7% may benefit from looser glycemic control, in order to reduce the risk of hypoglycemia and significant glycemic variability.

**Key words:** Diabetes mellitus; Critical care; Stress hyperglycemia; Hypoglycemia; Glycemic control; Intensive care unit

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**Core tip:** Diabetes mellitus is a common comorbidity found in critically ill patients. Although strict glycemic control in the past was considered a standard therapeutic intervention, newer clinical trials have shown that moderate glycemic control (*i.e.*, glucose levels between 140-180 mg/dL) reduces mortality and morbidity in such patients.

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**Introduction**

Stress-induced hyperglycemia, or diabetes injury as originally described by Claude Bernard in 1877, has become the subject of significant debate, as recent guidelines have called for stricter glucose control in critically ill patients[1,2]. Occurring as a result of catecholamine-induced stress response, this hyperglycemia is a common occurrence in critically ill patients[1]. With the rising population of diabetic and pre-diabetic individuals in the United States, the risk of severe hyperglycemia among critically ill patients is quite high, particularly in patients with undiagnosed diabetes mellitus (DM), who have inadequate glycemic control previous to hospitalization[1,3].

On the other hand, one of the important complications in dealing with stress-induced hyperglycemia is severe hypoglycemia. This significant decrease in blood glucose, however, is not due to some underlying physiological process, but it is often the consequence of inadequate glucose monitoring, and incorrect dosage of hypoglycemic medication, usually insulin. Hypoglycemia in critically ill patients is an important factor that can increase mortality in the intensive care unit (ICU), and is an important complication that needs to be prevented in patients that require glycemic control therapy[4]. Increased glycemic variability may be an issue with inadequate hypoglycemic treatment, which leads to increased oxidative stress and may be more dangerous than persistent hyperglycemia[5].

Appropriate hypoglycemic therapy is required in order to reduce mortality and morbidity of uncontrolled hyperglycemia in critically ill patients[6]. In this article, we review the current state-of-evidence on ideal glycemic goals that should be set for diabetic patients in the ICU.

**Epidemiology**

In 2014, the United States National Diabetes Statistic Report, documented 21 million individuals suffering from DM, accounting for 6.7% of the total population and approximately 8.1 million undiagnosed DM, which would raise the percentage of American population with diabetes to 9.3%[7]. This report also indicated that the prevalence of diabetes was highest among those older than 65 years of age and above[7]. Patients in this age group, account for up to 45.7% of ICU patients[8]. In addition, approximately 50% of ICU patients, have pre- existing diagnostic criteria for DM[9].

**Pathophysiology**

During periods of stress, the body reacts by producing elevated levels of catecholamines[10]. This reaction, is modulated by the suprarenal glands and activated by either the sympathetic nervous system in acute stress and by feedback to the pituitary gland in chronic stress[11,12]. Any period of disease can be considered a period of stress, and therefore, some degree of hyperglycemia is normal during these times, and can be seen as initially protective and part of the adaptive response for survival[13]. However, in acute and severe diseases, the resulting hyperglycemia can be much too high and require glycemic control therapy to manage[1].

Severe hyperglycemia, is a well-documented marker of illness severity, rather than a direct cause of poor outcome[13]. This condition often subsides after the affecting illness (*i.e.*, sepsis) has resolved[1]. In the acute setting, it is believed that the resulting hyperglycemia is due to insufficient insulin secretion that is unable to overcome the hyperglycemic effect of catecholamine.[14] It is also believed that insulin resistance plays a factor in chronic disease with significant amounts of tissue injury[1,14].

Patients with pre-existing DM tend to have a persistent state of hyperglycemia due to insulin resistance (or insulin absence in DM type 1), and hyperglucagonaemia that are the consequences of the disease’s natural progression. As a result of these factors, during periods of acute illness, the resulting stress-induced hyperglycemia can be much more severe than in non-diabetic patients, and more likely to require control with hypoglycemic medications and strict glucose monitoring[14]. See table 1 for factors that lead to hyperglycemia and hypoglycemia in critically ill patients.

**Stress-Induced Hyperglycemia**

Stress-induced hyperglycemia (SIH) is a common finding among critically ill patients, particularly among cardiovascular patients, neurocritical patients, and patients undergoing surgical procedures, even in the absence of preexisting DM[14]. In non-diabetic patients, SIH has been arbitrarily defined as a blood glucose level greater than 140 mg/dL or glycosylated hemoglobin (HbA1c) greater than 6.5%[15]. In diabetic patients, SIH is be defined as blood glucose levels greater than 180-220 mg/dL[15]. This clinical condition increases the morbidity and mortality in critically ill patients and leads to poor outcomes and prognosis[15]. Some have advocated that in these patients, it is necessary to maintain a strict glycemic control to directly improve their outcomes[14,15].

Part of the controversy as to the precise level of strict glycemic control started with a clinical study published in 2001, consisting of 1548 patients in a surgical ICU in Belgium[16]. In this study, van den Berghe and coauthors reported that intensive insulin therapy, aimed at maintaining blood glucose below 110 mg/dL reduced mortality and morbidity in critically ill patients by 42%. The reduction in mortality was apparent among patients who stayed in the ICU for more than five days[16]. A follow-up study, by the same investigators in 2006, aimed at comparing strict blood glycemic control (blood glucose: 80–110 mg/dL) *vs* a much looser control (blood glucose: 180–215 mg/dL) in this study on 1200 medical ICU patients and found that the strict glucose control group had a mortality reduction rate of 32% in patients who stayed more than three days in the ICU[17]. Of note, in this study, strict glucose control increased mortality in patients with short ICU stays (< 3 d), due to the increased rate of severe hypoglycemia.

A series of additional clinical trials followed these 2 seminal investigations. One of the most quoted in the medical literature was the Normoglycemia in Intensive Care Evaluation-Survival Using Glucose Algorithm Regulation (NICE-SUGAR) multicenter trial, with 6,104 ICU patients that compared strict glucose control (81–108 mg/dL) *vs* a more moderate glucose target (< 180 mg/dl)[18]. This study reported that moderate glycemic control lead to a reduction in cardiovascular mortality in critically ill patients.

***Glycemic variability and hypoglycemia***

As noted above, in diabetic patients, particularly those with persistent hyperglycemia, significantly lowering glucose levels and strict glycemic control may lead to symptomatic and life-threatening hypoglycemia and glycemic variability[19]. Glycemic variability has been defined as acute glycemic fluctuations; with both upwards fluctuations (in hypoglycemic correction) and downward fluctuations (in initial overbearing hypoglycemic treatment) leading to increased oxidative stress (which in turn leads to endothelial dysfunction and vascular damage). It is well documented that glycemic variability is much more dangerous than persistent hyperglycemia in critically ill patients[19,20].

Two retrospective studies found that glycemic variability conferred an increased risk of mortality in critically ill patients[21,22]. The mortality risk increased by 25.7% in critically ill non-diabetic patients[21,22]. Although no current consensus exists on the adequate range of acceptable glycemic variability in critically ill patients, Monnier and associates proposed a range of 40 mg/dL, as this corresponds to the normal variability found in non-diabetic healthy individuals[20].

Hypoglycemia is another dangerous situation in both diabetic and non-diabetic ICU patients. This clinical entity is directly related to cardiovascular mortality as it has been associated with increased QT waves in the electrocardiogram and changes in cardiac cell repolarization[23,24]. A study performed in 2005 reported that diabetic patients hospitalized with acute myocardial infarction, had a 93% increased mortality rate when hypoglycemia was present during their hospitalization[25]. In another study published last year, 2601 patients were evaluated and analyzed ICU mortality when moderate or severe hypoglycemia was present as compared to no hypoglycemia. Patients with severe and moderate hypoglycemia had a 34% and 18% increase, respectively, in 90-day mortality, when compared to patients with no hypoglycemia. Those patients that presented multiple hypoglycemic events had a 44% increase in mortality when compared to patients with no hypoglycemic events[26].

There is significant evidence that hypoglycemia poses significant risk of cardiovascular mortality among diabetic patients in critical care scenarios. Alongside the theoretical benefits of reducing glycemic variability, having a much looser glycemic control in critically ill diabetic patients, may aid in reducing cardiovascular mortality[27]. Further studies are necessary on the subject of glycemic variability, in an effort to find its real-world impact on diabetic patients in and out of critical care.

**Guidelines Recommendations**

The American Diabetes Association recommends starting insulin in patients with persistent hyperglycemia above 180 mg/dL in critically ill patients, and to maintain the glycemic range between 140–180 mg/dL. It also states that stricter glycemic control (110–140 mg/dL) can be appropriate for certain patients, such as patients with acute cardiac ischemia or patients with acute neurological event, as long as significant hypoglycemia can be avoided[28]. They also recommend active prevention of hypoglycemia by having a treatment plan if hypoglycemia were to develop and to change the current therapy if serum glucose levels fall below 70 mg/dL[28]. These recommendations were based on a consensus form American Association of Clinical Endocrinologists, which involved two meta-analyses of several clinical trials, including the NICE-SUGAR study, the largest randomized controlled trial, addressing this issue[28-31].

The American College of Physicians recommends serum glucose levels between 140–200 mg/dL independent of diabetic status, and recommends avoiding blood sugar levels below 140 mg/d, due to the associated risks of hypoglycemia and glycemic variability[32]. The Society of Critical Care Medicine (SCCM) recommends maintaining the serum glucose level between 150–180 mg/dL[33].

However, a 2011 study conducted in the ICU among diabetic patients found that patients with uncontrolled diabetes (HbA1C above 7%) had different mortality when hyperglycemia was present when compared to non-diabetic patients or patients with better controlled diabetes (HbA1C below 7%)[34]. Additional newer studies have concluded similarly, that diabetic patients do not share the same mortality with hyperglycemia as non-diabetic patients, and that these diabetic patients may benefit from higher glycemic ranges to reduce the risk of hypoglycemia and glycemic variability[35-37].Moreover, another study recommended maintaining serum glucose levels between 160–220 mg/dL in patients with HbA1C above 7%, and to maintain serum glucose levels between 140–200 mg/dL in patients with an HbA1c below 7%[19].

It is recommended that glycemic control be maintained with insulin due to the effectiveness, quick action, and few contraindications as it relates to this therapy[28,29]. However, the use of continuing metformin therapy in ICU patients with type 2 diabetes is seeing resurgence among certain patients, as the risk of hypoglycemia is lower; although its use should be cautious among patient with renal insufficiency, which is very common in the ICU[38].

In the following sections, we describe the evidence and recommendations for glycemic control among different patient groups who may be presenting in the ICU. Details are depicted in Table 2.

***Patients in the surgical ICU***

The Society of Thoracic Surgeons created guidelines in 2009 for glucose management in adult cardiac surgery patients, including diabetics.[39] For preoperative care, maintenance with insulin therapy with a serum glucose goal below 180 mg/dL was recommended. It was also recommended to check HbA1c level pre-operative for proper glycemic management. Intraopertavely, insulin therapy was also recommended for glycemic values above 180 mg/dL, and intravenous insulin infusion was recommended for persistent glycemic levels above 180 mg/dL intra-operatively or postoperatively in the ICU[39]. The recommendation was to keep a goal of 180 mg/dL throughout their stay in the ICU unless they are expected to remain in the critical care unit more than 3 days, or if the patient is ventilator-dependent, or requires therapy with inotropes, intra-aortic balloon pump, left ventricular assist device, anti-dysrhythmic medications, dialysis, or hemofiltration. In aforementioned cases, it is recommended to have the blood glucose levels below 150 mg/dL[39,40].

A recent study in 447 patients, found that a glucose level of 80-110 mg/dL, when compared to 140-180 mg/dL, reduces surgical site infections[41]. However, this study did not focus on over-all patient mortality and had a challenge of small sample size.

***Patients with neurological events***

A large clinical trial by van den Berghe and collaborators in 2001, suggested that strict glucose control (< 110 mg/dL) reduces mortality in critically ill patients[16]. For a period of time, following the findings of this trial, the standard of care was to maintain neurocritically ill patients blood glucose below 110 mg/dL[16]. However, the publication of the NICE-SUGAR study, and a prospective study of intensive insulin therapy in patients with recent neurosurgery, both published in 2009, showed that strict glucose control led to increased mortality mainly secondary to hypoglycemia[18,42].

In 2012, a systematic review and meta-analysis of 16 clinical trials on optimal glycemic control in neurocritical care patients, revealed that strict glycemic control (70–140 mg/dL) had no impact on patient mortality, but did increased the incidence of hypoglycemia[43]. Loose glycemic control (> 200 mg/dL) was shown to increased mortality when compared to a moderate glycemic control (140–180 mg/dL)[43]. The ADA states that blood glucose level of 110–140 mg/dL may be appropriate if significant hypoglycemia can be avoided[28].

***Patient with an acute myocardial infarction***

In 2008, the American Heart Association released a statement on glucose management in acute coronary syndrome, which recommended a glucose levels between 90-140 mg/dL in ICU patients with acute coronary syndrome.[44] The recommendations were later updated in 2009, suggesting an upper limit of serum glucose to 180 mg/dL[45].

The European Society of Cardiology published their most recent guidelines in 2012 on management of acute myocardial infarction with ST-segment elevation[46]. They recommend loose glycemic control in the acute phase, by maintaining the patient serum glucose below 200 mg/dL, as hypoglycemia was felt to be an important factor which increases the mortality[46]. This conclusion is based on a consensus reached by the National Institute Health and Care Excellence in 2011, that stated that no high quality studies were available to reach an evidence-based conclusion[47].

A 2012 meta-analysis, focusing on type 2 diabetics with acute myocardial infarction, involving 3 studies (for a total of 2113 patients), concluded that stricter glucose control with intensive insulin therapy did not reduced the patient mortality but significantly increased the incidence of hypoglycemia while offering no overall reduction in cardiovascular mortality[48].

***Patients with sepsis***

In response to the study on glucose control in surgical ICU patients, a study specifically on patients with sepsis, the Surviving Sepsis Campaign recommended a stricter range of glycemic control, with an upper goal of 110 mg/dL of serum glucose[17,49,50].With the advent of the NICE-SUGAR trial in 2009, which also included septic patients, the 2013 update of the Surviving Sepsis Campaign modified its recommendation to a looser goal of 180 mg/dL[51]. Due to increased risk of hypoglycemia and hypoglycemia-related mortality, the Surviving Sepsis Campaign deemed that there was no apparent benefit from strict glucose control[51]. Insulin therapy was recommended to be started after two consecutive blood glucose measurements were above 180 mg/dL and to maintain a blood glucose of less than 180 mg/dL[51].

***Pregnant patients***

Gestational diabetes accounts for 2% to 9% of all pregnancies[52]. Hyperglycemia is an important factor to consider in all pregnancies, especially among hospitalized patients. During pregnancy, maternal cells have increased insulin resistance, due to elevated levels of human placental lactogen, progesterone, and estrogen[53]. This mild increase in insulin resistance is protective, and allows glucose absorption to be prioritized in the fetus, however in some patients, this mild resistance can be combined with insulin resistance, leading to persistent hyperglycemia[53,54].

It is generally agreed that treatment of gestational diabetes-related hyperglycemia is important in reducing perinatal mortality, as well as reducing hyperglycemia in postpartum mothers and improving overall health[52]. No consensus currently exists on the ideal range of serum glucose levels in critically ill pregnant patients[55]. It is difficult to recommend moderate or loose glycemic control in these patients, as even mild hyperglycemia can lead to adverse outcomes in infants[56]. On the other hand, tight glycemic control may lead to increased risk of hypoglycemia, which is also a factor that increases both maternal and infant mortality. Future clinical trials are necessary to be able to reach a consensus on how glycemic care should be managed in this population.

**Glycemic Control Therapy**

While several studies have been performed on glycemic control in non-diabetic patients in the ICU, few of such studies have been performed on diabetic individuals. Table 3 depicts recent studies on this topic. Three of the four studies focused on surgical patients, and recommend a stricter glucose control for infection prevention, and hyperglycemia prevention[57-59]. The fourth study takes into account the risk of hypoglycemia, and recommends looser glycemic control to reduce moderate to severe hypoglycemia and glycemic variability[9]. However, all of these studies fail to take into account that diabetic individuals with persistent hyperglycemia (HbA1c above 7%) who are at higher risk from hypoglycemia-related mortality than hyperglycemia-related mortality[19,34]. A 2016 study on diabetic ICU patients, recommended keeping serum glucose levels below 250 mg/dL in patients with HbA1c above 7% upon admission to the ICU[9]. This study found that this loose glycemic control prevented glycemic variability and reduced the incidence of moderate and severe hypoglycemia[9].

Measurement of glucose should be performed every 2 to 4 h to allow for proper monitoring. If the patient’s serum glucose concentration is fluctuating, it may be necessary to measure glucose every 30 or 60 min[60]. Currently, technology for continuous blood glucose monitoring using vascular catheter blood sampling is currently undergoing clinical trials and may become the standard of care and can allow tighter glycemic control in addition to preventing severe hypoglycemia or hyperglycemia[61].Research has shown promise, as the technology is capable of detecting changes in glycemia that may otherwise be missed in our current practice, and has shown that glucose levels correlate well with standard arterial glycemic measurement[62-64].

**Conclusion**

Glycemic control in the ICU continues to be challenging at best. Although the glycemic control strategy does not vary among diabetic individuals without persistent hyperglycemia from non-diabetic individuals (serum glucose goal of 140–180 mg/dL), it is important to note the cases where exceptions should be made. In neurological patients and surgical patients, a stricter glycemic strategy can be maintained (110–140 mg/dL and < 150 mg/dL, respectively) as long as adequate hypoglycemia can be avoided. In patients with a history of persistent hyperglycemia (HbA1c above 7%), liberal glycemic control may be beneficial in reducing the risk of hypoglycemia and glycemic variability, which is known to increase cardiovascular mortality, but further evidence and studies are necessary before a strong recommendation can be given. Further randomized control studies are suggested to further evaluate the variability in the target blood glucose level among different conditions.

**References**

1. **Dungan KM**, Braithwaite SS, Preiser JC. Stress hyperglycaemia. *Lancet* 2009; **373**: 1798-1807 [PMID: 19465235 DOI: 10.1016/S0140-6736(09)60553-5]
2. **Bernard C**. Leçons sur le diabète et la glycogenèse animale. Paris: JB Bailliere et Fils, 1877
3. **Mesotten D**, Preiser JC, Kosiborod M. Glucose management in critically ill adults and children. *Lancet Diabetes Endocrinol* 2015; **3**: 723-733 [PMID: 26071884 DOI: 10.1016/S2213-8587(15)00223-5]
4. **Fahy BG**, Sheehy AM, Coursin DB. Glucose control in the intensive care unit. *Crit Care Med* 2009; **37**: 1769-1776 [PMID: 19325461 DOI: 10.1097/CCM.0b013e3181a19ceb]
5. **Monnier L**, Mas E, Ginet C, Michel F, Villon L, Cristol JP, Colette C. Activation of oxidative stress by acute glucose fluctuations compared with sustained chronic hyperglycemia in patients with type 2 diabetes. *JAMA* 2006; **295**: 1681-1687 [PMID: 16609090 DOI: 10.1001/jama.295.14.1681]
6. **Falciglia M**, Freyberg RW, Almenoff PL, D'Alessio DA, Render ML. Hyperglycemia-related mortality in critically ill patients varies with admission diagnosis. *Crit Care Med* 2009; **37**: 3001-3009 [PMID: 19661802 DOI: 10.1097/CCM.0b013e3181b083f7]
7. **Centers for Disease Control and Prevention**. National Diabetes Statistics Report: Estimates of Diabetes and Its Burden in the United States, 2014. Atlanta, GA: US Department of Health and Human Services, 2014
8. **Fuchs L**, Chronaki CE, Park S, Novack V, Baumfeld Y, Scott D, McLennan S, Talmor D, Celi L. ICU admission characteristics and mortality rates among elderly and very elderly patients. *Intensive Care Med* 2012; **38**: 1654-1661 [PMID: 22797350 DOI: 10.1007/s00134-012-2629-6]
9. **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]
10. **Goldstein DS**. Adrenal responses to stress. *Cell Mol Neurobiol* 2010; **30**: 1433-1440 [PMID: 21061156 DOI: 10.1007/s10571-010-9606-9]
11. **Herman JP**, Figueiredo H, Mueller NK, Ulrich-Lai Y, Ostrander MM, Choi DC, Cullinan WE. Central mechanisms of stress integration: hierarchical circuitry controlling hypothalamo-pituitary-adrenocortical responsiveness. *Front Neuroendocrinol* 2003; **24**: 151-180 [PMID: 14596810]
12. **Chrousos GP**, Gold PW. The concepts of stress and stress system disorders. Overview of physical and behavioral homeostasis. *JAMA* 1992; **267**: 1244-1252 [PMID: 1538563]
13. **Marik PE**, Bellomo R. Stress hyperglycemia: an essential survival response! *Crit Care* 2013; **17**: 305 [PMID: 23470218 DOI: 10.1186/cc12514]
14. **Harp JB**, Yancopoulos GD, Gromada J. Glucagon orchestrates stress-induced hyperglycaemia. *Diabetes Obes Metab* 2016; **18**: 648-653 [PMID: 27027662 DOI: 10.1111/dom.12668]
15. **Viana MV**, Moraes RB, Fabbrin AR, Santos MF, Gerchman F. [Assessment and treatment of hyperglycemia in critically ill patients]. *Rev Bras Ter Intensiva* 2014; **26**: 71-76 [PMID: 24770692]
16. **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]
17. **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]
18. **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 versus conventional glucose control in critically ill patients. *N Engl J Med* 2009; **360**: 1283-1297 [PMID: 19318384 DOI: 10.1056/NEJMoa0810625]
19. **Marik PE**, Egi M. Treatment thresholds for hyperglycemia in critically ill patients with and without diabetes. *Intensive Care Med* 2014; **40**: 1049-1051 [PMID: 24859623 DOI: 10.1007/s00134-014-3344-2]
20. **Monnier L**, Colette C, Owens DR. Glycemic variability: the third component of the dysglycemia in diabetes. Is it important? How to measure it? *J Diabetes Sci Technol* 2008; **2**: 1094-1100 [PMID: 19885298]
21. **Krinsley JS**. Glycemic variability: a strong independent predictor of mortality in critically ill patients. *Crit Care Med* 2008; **36**: 3008-3013 [PMID: 18824908 DOI: 10.1097/CCM.0b013e31818b38d2]
22. **Krinsley JS**. Glycemic variability and mortality in critically ill patients: the impact of diabetes. *J Diabetes Sci Technol* 2009; **3**: 1292-1301 [PMID: 20144383]
23. **Landstedt-Hallin L**, Adamson U, Lins PE. Oral glibenclamide suppresses glucagon secretion during insulin-induced hypoglycemia in patients with type 2 diabetes. *J Clin Endocrinol Metab* 1999; **84**: 3140-3145 [PMID: 10487677 DOI: 10.1210/jcem.84.9.6002]
24. **Robinson RT**, Harris ND, Ireland RH, Macdonald IA, Heller SR. Changes in cardiac repolarization during clinical episodes of nocturnal hypoglycaemia in adults with Type 1 diabetes. *Diabetologia* 2004; **47**: 312-315 [PMID: 14712347 DOI: 10.1007/s00125-003-1292-4]
25. **Svensson AM**, McGuire DK, Abrahamsson P, Dellborg M. Association between hyper- and hypoglycaemia and 2 year all-cause mortality risk in diabetic patients with acute coronary events. *Eur Heart J* 2005; **26**: 1255-1261 [PMID: 15821004 DOI: 10.1093/eurheartj/ehi230]
26. **Kalfon P**, Le Manach Y, Ichai C, Bréchot N, Cinotti R, Dequin PF, Riu-Poulenc B, Montravers P, Annane D, Dupont H, Sorine M, Riou B. Severe and multiple hypoglycemic episodes are associated with increased risk of death in ICU patients. *Crit Care* 2015; **19**: 153 [PMID: 25888011 DOI: 10.1186/s13054-015-0851-7]
27. **Saisho Y**. Glycemic variability and oxidative stress: a link between diabetes and cardiovascular disease? *Int J Mol Sci* 2014; **15**: 18381-18406 [PMID: 25314300 DOI: 10.3390/ijms151018381]
28. Professional Practice Committee for the Standards of Medical Care in Diabetes-2016. *Diabetes Care* 2016; **39 Suppl 1**: S107-S108 [PMID: 26696673 DOI: 10.2337/dc16-S018]
29. **Moghissi ES**, Korytkowski MT, DiNardo M, Einhorn D, Hellman R, Hirsch IB, Inzucchi SE, Ismail-Beigi F, Kirkman MS, Umpierrez GE. American Association of Clinical Endocrinologists and American Diabetes Association consensus statement on inpatient glycemic control. *Diabetes Care* 2009; **32**: 1119-1131 [PMID: 19429873 DOI: 10.2337/dc09-9029]
30. **Wiener RS**, Wiener DC, Larson RJ. Benefits and risks of tight glucose control in critically ill adults: a meta-analysis. *JAMA* 2008; **300**: 933-944 [PMID: 18728267 DOI: 10.1001/jama.300.8.933]
31. **Griesdale DE**, de Souza RJ, van Dam RM, Heyland DK, Cook DJ, Malhotra A, Dhaliwal R, Henderson WR, Chittock DR, Finfer S, Talmor D. Intensive insulin therapy and mortality among critically ill patients: a meta-analysis including NICE-SUGAR study data. *CMAJ* 2009; **180**: 821-827 [PMID: 19318387 DOI: 10.1503/cmaj.090206]
32. **Qaseem A**, Chou R, Humphrey LL, Shekelle P, Clinical Guidelines Committee of the American College. Inpatient glycemic control: best practice advice from the Clinical Guidelines Committee of the American College of Physicians. *Am J Med Qual* 2014; **29**: 95-98 [PMID: 23709472 DOI: 10.1177/1062860613489339]
33. **Jacobi J**, Bircher N, Krinsley J, Agus M, Braithwaite SS, Deutschman C, Freire AX, Geehan D, Kohl B, Nasraway SA, Rigby M, Sands K, Schallom L, Taylor B, Umpierrez G, Mazuski J, Schunemann H. Guidelines for the use of an insulin infusion for the management of hyperglycemia in critically ill patients. *Crit Care Med* 2012; **40**: 3251-3276 [PMID: 23164767 DOI: 10.1097/CCM.0b013e3182653269]
34. **Egi M**, Bellomo R, Stachowski E, French CJ, Hart GK, Taori G, Hegarty C, Bailey M. The interaction of chronic and acute glycemia with mortality in critically ill patients with diabetes. *Crit Care Med* 2011; **39**: 105-111 [PMID: 20975552 DOI: 10.1097/CCM.0b013e3181feb5ea]
35. **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]
36. **Egi M**, Bellomo R, Stachowski E, French CJ, Hart GK, Hegarty C, Bailey M. Blood glucose concentration and outcome of critical illness: the impact of diabetes. *Crit Care Med* 2008; **36**: 2249-2255 [PMID: 18664780 DOI: 10.1097/CCM.0b013e318181039a]
37. **Krinsley JS**, Egi M, Kiss A, Devendra AN, Schuetz P, Maurer PM, Schultz MJ, van Hooijdonk RT, Kiyoshi M, Mackenzie IM, Annane D, Stow P, Nasraway SA, Holewinski S, Holzinger U, Preiser JC, Vincent JL, Bellomo R. Diabetic status and the relation of the three domains of glycemic control to mortality in critically ill patients: an international multicenter cohort study. *Crit Care* 2013; **17**: R37 [PMID: 23452622 DOI: 10.1186/cc12547]
38. **Dungan KM**. Hyperglycemia in the intensive care unit: is insulin the only option? *Crit Care* 2013; **17**: 1012 [PMID: 25169675 DOI: 10.1186/cc13107]
39. **Lazar HL**, McDonnell M, Chipkin SR, Furnary AP, Engelman RM, Sadhu AR, Bridges CR, Haan CK, Svedjeholm R, Taegtmeyer H, Shemin RJ, Society of Thoracic Surgeons Blood Glucose Guideline Task F. The Society of Thoracic Surgeons practice guideline series: Blood glucose management during adult cardiac surgery. *Ann Thorac Surg* 2009; **87**: 663-669 [PMID: 19161815 DOI: 10.1016/j.athoracsur.2008.11.011]
40. **Furnary AP**, Wu Y, Bookin SO. Effect of hyperglycemia and continuous intravenous insulin infusions on outcomes of cardiac surgical procedures: the Portland Diabetic Project. *Endocr Pract* 2004; **10 Suppl 2**: 21-33 [PMID: 15251637 DOI: 10.4158/EP.10.S2.21]
41. **Okabayashi T**, Shima Y, Sumiyoshi T, Kozuki A, Tokumaru T, Iiyama T, Sugimoto T, Kobayashi M, Yokoyama M, Hanazaki K. Intensive versus intermediate glucose control in surgical intensive care unit patients. *Diabetes Care* 2014; **37**: 1516-1524 [PMID: 24623024 DOI: 10.2337/dc13-1771]
42. **Bilotta F**, Caramia R, Paoloni FP, Delfini R, Rosa G. Safety and efficacy of intensive insulin therapy in critical neurosurgical patients. *Anesthesiology* 2009; **110**: 611-619 [PMID: 19237874 DOI: 10.1097/ALN.0b013e318198004b]
43. **Kramer AH**, Roberts DJ, Zygun DA. Optimal glycemic control in neurocritical care patients: a systematic review and meta-analysis. *Crit Care* 2012; **16**: R203 [PMID: 23082798 DOI: 10.1186/cc11812]
44. **Deedwania P**, Kosiborod M, Barrett E, Ceriello A, Isley W, Mazzone T, Raskin P, American Heart Association Diabetes Committee of the Council on Nutrition PA, Metabolism. Hyperglycemia and acute coronary syndrome: a scientific statement from the American Heart Association Diabetes Committee of the Council on Nutrition, Physical Activity, and Metabolism. *Circulation* 2008; **117**: 1610-1619 [PMID: 18299505 DOI: 10.1161/CIRCULATIONAHA.107.188629]
45. **Kushner FG**, Hand M, Smith SC, King SB, Anderson JL, Antman EM, Bailey SR, Bates ER, Blankenship JC, Casey DE, Green LA, Hochman JS, Jacobs AK, Krumholz HM, Morrison DA, Ornato JP, Pearle DL, Peterson ED, Sloan MA, Whitlow PL, Williams DO. 2009 Focused Updates: ACC/AHA Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction (updating the 2004 Guideline and 2007 Focused Update) and ACC/AHA/SCAI Guidelines on Percutaneous Coronary Intervention (updating the 2005 Guideline and 2007 Focused Update): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation* 2009; **120**: 2271-2306 [PMID: 19923169 DOI: 10.1161/CIRCULATIONAHA.109.192663]
46. **Task Force on the management of STseamiotESoC**, Steg PG, James SK, Atar D, Badano LP, Blömstrom-Lundqvist C, Borger MA, Di Mario C, Dickstein K, Ducrocq G, Fernandez-Aviles F, Gershlick AH, Giannuzzi P, Halvorsen S, Huber K, Juni P, Kastrati A, Knuuti J, Lenzen MJ, Mahaffey KW, Valgimigli M, van 't Hof A, Widimsky P, Zahger D. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J* 2012; **33**: 2569-2619 [PMID: 22922416 DOI: 10.1093/eurheartj/ehs215]
47. Hyperglycaemia in Acute Coronary Syndromes: Management of Hyperglycaemia in People with Acute Coronary Syndromes. London, 2011
48. **Chatterjee S**, Sharma A, Lichstein E, Mukherjee D. Intensive glucose control in diabetics with an acute myocardial infarction does not improve mortality and increases risk of hypoglycemia-a meta-regression analysis. *Curr Vasc Pharmacol* 2013; **11**: 100-104 [PMID: 22724474]
49. **Ellger B**, Westphal M, Stubbe HD, Van den Heuvel I, Van Aken H, Van den Berghe G. [Glycemic control in sepsis and septic shock: friend or foe?]. *Anaesthesist* 2008; **57**: 43-48 [PMID: 18034219 DOI: 10.1007/s00101-007-1285-7]
50. **Martin-Loeches I**, Levy MM, Artigas A. Management of severe sepsis: advances, challenges, and current status. *Drug Des Devel Ther* 2015; **9**: 2079-2088 [PMID: 25926718 DOI: 10.2147/DDDT.S78757]
51. **Dellinger RP**, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, Sevransky JE, Sprung CL, Douglas IS, Jaeschke R, Osborn TM, Nunnally ME, Townsend SR, Reinhart K, Kleinpell RM, Angus DC, Deutschman CS, Machado FR, Rubenfeld GD, Webb S, Beale RJ, Vincent JL, Moreno R. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock, 2012. *Intensive Care Med* 2013; **39**: 165-228 [PMID: 23361625 DOI: 10.1007/s00134-012-2769-8]
52. **Crowther CA**, Hiller JE, Moss JR, McPhee AJ, Jeffries WS, Robinson JS**,** Australian Carbohydrate Intolerance Study in Pregnant Women Trial G. Effect of treatment of gestational diabetes mellitus on pregnancy outcomes. *N Engl J Med* 2005; **352**: 2477-2486 [PMID: 15951574 DOI: 10.1056/NEJMoa042973]
53. **Baz B**, Riveline JP, Gautier JF. ENDOCRINOLOGY OF PREGNANCY: Gestational diabetes mellitus: definition, aetiological and clinical aspects. *Eur J Endocrinol* 2016; **174**: R43-R51 [PMID: 26431552 DOI: 10.1530/EJE-15-0378]
54. **Catalano PM**. Trying to understand gestational diabetes. *Diabet Med* 2014; **31**: 273-281 [PMID: 24341419 DOI: 10.1111/dme.12381]
55. **Van de Velde MSH**, Plante, L. Maternal Critical Care. . Cambridge University Press, The Edinburgh Building, Cambridge CB2 8RU, United Kingdom: Cambridge University Press, 2013
56. **Metzger BE**, Lowe LP, Dyer AR, Trimble ER, Chaovarindr U, Coustan DR, Hadden DR, McCance DR, Hod M, McIntyre HD, Oats JJ, Persson B, Rogers MS, Sacks DA. Hyperglycemia and adverse pregnancy outcomes. *N Engl J Med* 2008; **358**: 1991-2002 [PMID: 18463375 DOI: 10.1056/NEJMoa0707943]
57. **Lecomte P**, Foubert L, Coddens J, Dewulf B, Nobels F, Casselman F, Cammu G. Management of tight intraoperative glycemic control during off-pump coronary artery bypass surgery in diabetic and nondiabetic patients. *J Cardiothorac Vasc Anesth* 2011; **25**: 937-942 [PMID: 21640613 DOI: 10.1053/j.jvca.2011.03.173]
58. **Yuan J**, Liu T, Zhang X, Si Y, Ye Y, Zhao C, Wang Q, Shen X. Intensive Versus Conventional Glycemic Control in Patients with Diabetes During Enteral Nutrition After Gastrectomy. *J Gastrointest Surg* 2015; **19**: 1553-1558 [PMID: 26084869 DOI: 10.1007/s11605-015-2871-7]
59. **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]
60. **Clement S**, Braithwaite SS, Magee MF, Ahmann A, Smith EP, Schafer RG, Hirsch IB; American Diabetes Association Diabetes in Hospitals Writing C. Management of diabetes and hyperglycemia in hospitals. *Diabetes Care* 2004; **27**: 553-591 [PMID: 14747243]
61. **Joseph JI**, Torjman MC, Strasma PJ. Vascular Glucose Sensor Symposium: Continuous Glucose Monitoring Systems (CGMS) for Hospitalized and Ambulatory Patients at Risk for Hyperglycemia, Hypoglycemia, and Glycemic Variability. *J Diabetes Sci Technol* 2015; **9**: 725-738 [PMID: 26078254 DOI: 10.1177/1932296815587938]
62. **De Block C**, Manuel-Y-Keenoy B, Van Gaal L, Rogiers P. Intensive insulin therapy in the intensive care unit: assessment by continuous glucose monitoring. *Diabetes Care* 2006; **29**: 1750-1756 [PMID: 16873775 DOI: 10.2337/dc05-2353]
63. **De Block C**, Manuel-y-Keenoy B, Rogiers P, Jorens P, Van Gaal L. Glucose control and use of continuous glucose monitoring in the intensive care unit: a critical review. *Curr Diabetes Rev* 2008; **4**: 234-244 [PMID: 18690906]
64. **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]
65. **Hsu CW**. Glycemic control in critically ill patients. *World J Crit Care Med* 2012; **1**: 31-39 [PMID: 24701399 DOI: 10.5492/wjccm.v1.i1.31]
66. **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]

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**Table 1 Factors leading to hyperglycemia and hypoglycemia in critically ill patients**

|  |  |
| --- | --- |
| **Hyperglycemia[65]**  | **Hypoglycemia[66]** |
| Release of stress hormones (Glucagon, epinephrine, cortisol, and TNF-α)Certain medications (exogenous glucocorticoids, vasopressors, lithium, and β-blockers)OverfeedingIntravenous dextrose Parenteral nutritionPersistent bed restIncreased insulin resistance (DM type 2)Deficient insulin secretion (DM type 1) | Severe sepsisTraumaDMPrior insulin treatmentPrior glucocorticoid treatmentCardiovascular failureIntensive glucose control |

DM: diabetes mellitus.

**Table 2 Glycemic control recommendation based on patient condition**

|  |  |  |  |
| --- | --- | --- | --- |
| **Condition** | **Glucose control recommendation** | **Studies with patient number** | **Ref.** |
| Non-diabetic ICU patients | 140-180 mg/dL | 29 studies with 8432 total patients and 26 studies with 13567 total patients | Wiener *et al*[29] (2008) and Griesdale *et al*[30] (2009), respectively |
| Diabetic ICU patients | If HbA1c < 7%: 140–180 mg/dLIf HbA1c > 7%: > 200 mg/dL | 1 retrospective study with 415 total patients | Egi *et al*[33] (2011) |
| Surgical ICU | If ICU stay is for more than 3 d, ventilator dependent, on dialysis, or with cardiac comorbidities: < 150 mg/dLIf not: < 180 mg/dL | 1 prospective study with 4864 total patients across 17 yr | Furnary *et al*[36] (2004) |
| Neurocritical ICU patients | If hypoglycemia can be prevented: 110–140 mg/dLIf not: 140–180 mg/dL | 16 studies with 1258 total patients | Kramer *et al*[39] (2012) |
| STEMI ICU patients | < 200 mg/dL | No high quality studies available Consensus by NICE | Nice Guidelines[43] (2011) |
| Sepsis ICU patients | < 180 mg/dL | 1 randomized control trial with 6104 patients | Based of NICE-SUGAR study[17] |
| Pregnant ICU patients | No consensus | N/A | Van de Velde *et al*[51] (2013) |

ICU: intensive care unit.

**Table 3 Strict glycemic control *vs* moderate glycemic control in critically ill patients with diabetes**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Study** | **Study design/ cohort** | **Sample size** | **Control group** | **Therapies employed** | **Conclusion** | **Favored therapy** |
| Lecomte *et al*[53] (2011)  | Diabetics undergoing off-pump cardiac bypass surgery | 60 | Matched 60 non-diabetics | Strict Glycemic Control (80-110 mg/dL) | Strict glycemic control was feasible and efficientMinimal risks for hypo- or hyperglycemia | Strict Glycemic control |
| Yuan *et al*[54] (2015)  | Diabetic patients receiving enteral nutrition after gastrectomy | 212 | None | Strict glycemic control (80–110 mg/dl) and moderate glycemic control (< 200 mg/dl) | Strict glycemic control lead to higher rates of severe hypoglycemia but lower rates of severe hyperglycemiaSurgical site infection rate was higher with moderate glycemic controlRates of other complications were similar in the two groups | Strict Glycemic Control |
| Umpierrez *et al*[55] (2015)  | Diabetic patients after coronary artery bypass surgery | 152 | 150 non-diabetics | Strict glycemic control (100-140 mg/dL) and moderate glycemic control (141-180 mg/dL) | No significant differences between the two in the rate and severity of complications | Neither |
| Kar *et al*[8] (2016)  | Diabetic ICU patients with HbA1c ≥ 7.0% admission | 83 | None | Moderate glycemic control (< 180 mg/dL) and Loose glycemic control (< 250 mg/dL) | Loose glycemic control reduces glycemic variability and moderate to severe hypoglycemia | Loose glycemic control |