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Management of hyperglycemia in hospitalized patients

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Abstract

Hyperglycemia is a common occurrence in hospitalized patients, and several studies have shown a strong association between hyperglycemia and the risk of complications, prolonged hospitalization, and death for patients with and without diabetes. Past studies have shown that glucose management in the intensive care setting improves clinical outcomes by reducing the risk of multiorgan failure, systemic infection, and mortality, and that the importance of hyperglycemia also applies to noncritically ill patients. Based on several past observational and interventional studies, aggressive control of blood glucose had been recommended for most adult patients with critical illness. Recent randomized controlled trials, however, have shown that aggressive glycemic control compared to conventional control with higher blood glucose targets is associated with an increased risk of hypoglycemia and may not result in the improvement in clinical outcomes. This review aims to give an overview of the evidence for tight glycemic control (blood glucose targets <140 mg/dL), the evidence against tight glycemic control, and the updated recommendations for the inpatient management of diabetes in the critical care setting and in the general wards.

Keywords

inpatient hyperglycemia; guidelines; intensive care unit; general wards; hypoglycemia

Introduction

The prevalence of diabetes mellitus is steadily on the rise, such that nearly 1 in every 13 individuals in the United States is affected. In turn, the number of hospital discharges with diabetes as any listed diagnosis has more than doubled between 1980 and 2006. Patients with diabetes have a threefold greater chance of hospitalization compared to those without diabetes, and it is estimated that 20% of all adults discharged have diabetes, with 30% of them requiring two or more hospitalizations in any given year. The exact prevalence of hospital hyperglycemia is not known, but it varies based on the definition used in previous reports and the population studied. Observational studies have reported a prevalence of hyperglycemia ranging from 32% to 38% in community hospitals, to 70% of diabetic patients with acute coronary syndrome, and ~80% of cardiac surgery patients in the perioperative period. Although stress hyperglycemia typically resolves as the acute illness or medico-surgical stress decreases, it is important to identify and track those patients that are affected, as one small study showed that 60% of patients with admission hyperglycemia had confirmed diabetes at 1 year.
There is a strong association between hyperglycemia and complications occurring in hospitalized patients with and without a history of diabetes.\textsuperscript{5,11–13} This association is well documented not only upon admission, but also for the mean glucose level during the hospital stay.\textsuperscript{14–16} Cross-sectional studies have shown that the risk of complications and mortality relates to the severity of hyperglycemia, with a higher risk observed inpatients without a history of diabetes (new onset and stress-induced hyperglycemia) compared to those with a known diagnosis. Evidence from observational studies indicates that development of hyperglycemia in critically ill patients is associated with an increased risk of hospital complications, mortality, and a higher total hospitalization cost.\textsuperscript{9,17,18} The importance of hyperglycemia also applies to noncritically ill patients admitted to general medicine and surgery services. In such patients, the presence of hyperglycemia is associated with prolonged hospital stay, infection, disability after hospital discharge, and death.\textsuperscript{5,19,20} This review aims to present updated recommendations for the in patient management of diabetes in the critical care setting and in the general medicine/surgical wards.

### Critical care setting

Several observational and prospective studies in hospitalized patients with and without diabetes indicate that hyperglycemia is an independent predictor of poor outcome in critically ill patients.\textsuperscript{5,16,21–24} These studies link hyperglycemia with increased risk of inpatient complications, prolonged hospitalization, and death. Falciglia and colleagues dissected the data further in a retrospective cohort study of over 250,000 veterans admitted to various intensive care units (ICUs) and found that in addition to inpatient hyperglycemia being an independent risk for mortality, hyperglycemia-related risk varies with the admission diagnosis such that individuals with cardiac diagnoses, sepsis, respiratory failure, and pulmonary embolism are at increased risk for mortality.\textsuperscript{14} More importantly, larger, milestone studies showed that aggressively controlling glucose levels after open-heart surgery and in the ICU setting with continuous insulin infusion (CII) significantly lowered the risk of these poor outcomes (Table 1).\textsuperscript{9,16,17} In a nonrandomized prospective study, Furnary followed 3,554 patients with diabetes that underwent coronary artery bypass graft and were treated with either subcutaneous insulin (SCI) or CII for hyperglycemia. Compared to patients treated with SCI that had an average blood glucose of 11.9 mmol/L (214 mg/dL), patients treated with CII with an average blood glucose of 9.8 mmol/L (177 mg/dL) had significantly fewer deep sternal wound infections\textsuperscript{16} and a reduction in risk-adjusted mortality by 50%.\textsuperscript{18} A follow-up analysis in a subset of this study population revealed that patients with blood glucose levels >11.1 mmol/L (>200 mg/dL) had higher mortality than those with blood glucose levels <11.1 mmol/L (<200 mg/dL) (5.0% vs. 1.8%, $P < 0.001$).\textsuperscript{16}

The Leuven SICU study could likely be considered the main randomized controlled trial (RCT) that set the stage for aggressive glycemic control in the critical care setting a decade ago. This study randomized 1,548 patients admitted to the surgical ICU (63% cardiac cases, 13% with diabetes, early parenteral nutrition use) to either conventional therapy to maintain target BG levels 10–11.1 mmol/L (180–200 mg/dL) or intensive therapy to maintain target blood glucose (BG) levels 4.4–6.1 mmol/L (80–110 mg/dL). Compared to patients in the conventional arm that had a daily BG average of 8.5 mmol/L (153 mg/dL), patients in the intensive arm with a daily average BG of 5.7 mmol/L (103 mg/dL) had significantly less bacteremia, fewer antibiotic requirements, lower length of ventilator dependency, and an overall 34% reduction in in-hospital mortality. When the data were further examined, it was found that in addition to the above benefits, those patients that had exposure to at least 5 days of treatment with CII also had significantly fewer ICU days and lower ICU mortality.\textsuperscript{9} A similar study was performed by the same study group in the medical ICU setting (18% with diabetes) and during this trial, although the mean, daily BG in the intensive arm of 6.2 mmol/L (111 mg/dL) was just above the targeted range (4.4–6.1 mmol/L; 80–110 mg/dL),

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these patients experienced less ICU and total hospital mortality after 3 days of treatment with CII. These two studies together, based on the positive outcomes on morbidity and mortality, suggested a glycemic target in the ICU of 4.4–6.1 mmol/L (80–110 mg/dL). In addition, several multicenter trials have failed to show significant improvement in clinical outcome and have even shown increased mortality risk with intensive glycemic control (Table 2). The Glucontrol trial, a seven-country, multicenter RCT, randomized patients in medical and surgical ICUs to tight glycemic control (BG 4.4–6.1 mmol/L; 80–110 mg/dL) versus conventional glycemic control (BG 7.8–10 mmol/L; 140–180 mg/dL). The study was discontinued prematurely due to protocol violations and safety concerns about hypoglycemia in the intensive arm (threefold higher) and thus was underpowered. The time spent at target BG, however, in each group was similar, and the investigators did not find a significant difference in mortality between the two groups. The Efficacy of Volume Substitution and Insulin Therapy in Sepsis (VISEP) study was another trial that attempted to reproduce the data from the Leuven trial. The study was a multicenter study in Germany that randomized patients with sepsis to receive CII therapy to maintain BG levels 10–11.1 mmol/L (180–200 mg/dL), versus the intensive arm of 4.4–6.1 (80–110 mg/dL). The investigators evaluated differences between the groups in 28- and 90-day mortality, sepsis-related organ failure, ICU stay, and frequency of hypoglycemia (BG < 2.2 mmol/L; < 40 mg/dL). Like the Glucontrol trial, the study was stopped after reaching only ~2/3 of the projected enrollment due to an interim analysis showing no difference in 28- or 90-day mortality between patients treated in the conventional arm versus those in the intensive arm (21.6% vs. 21.9%; 29.5 vs. 32.8%, respectively). The interim analysis also revealed that patients in the intensive arm experienced a significantly greater amount of severe hypoglycemia (12.1% vs. 2.1%).

The NICE-SUGAR trial, with over 6,000 subjects from three countries, stands as the largest trial to determine if there is benefit in treating ICU hyperglycemia aggressively. The trial randomized patients to receive either conventional glycemic control (BG < 10 mmol/L; <180 mg/dL) or intensive glycemic control (4.5–6 mmol/L; 81–108 mg/dL) and found that in addition to there being no difference in the primary outcome of 90-day mortality, that more aggressive glycemic control was associated with increased mortality at 90 days (24.9% vs. 27.5%, P = 0.02). The clinical question then shifted to whether the increased mortality was due to the increased frequency of hypoglycemia in the intensive arm (6.8% vs. 0.5%), and why the results of the NICE-SUGAR study were different of those in the Leuven trials. It has been suggested that the study outcomes differed due to a number of possible reasons, including less BG separation between the conventional and intervention groups in the NICE-SUGAR trial compared to the Leuven trials; different nutritional strategies (more parenteral nutrition in the Leuven trials); variability in devices, techniques, and frequency for blood glucose measurements across many institutions; and varying levels of expertise in the respective units.

Based on the results of recent trials, the American Association of Clinical Endocrinologist (AACE) and American Diabetes Association (ADA) task force on inpatient glycemic control recommended different glycemic targets in the ICU setting. Current guidelines suggest targeting a BG level between 7.8 and 10.0 mmol/L (140 and 180 mg/dL) for the majority of ICU patients and a lower glucose targets between 6.1 and 7.8 mmol/L (110 and 140 mg/dL) in selected ICU patients (i.e., centers with extensive experience and appropriate nursing support, cardiac surgical patients, patients with stable glycemic control without hypoglycemia). Glucose targets >10 mmol/L (>180 mg/dL) or <6.1 mmol/L (<110 mg/dL) are not recommended in ICU patients.
Noncritically ill patients

The importance of hyperglycemia also applies to noncritically ill patients admitted to general medicine and surgery services. In such patients, hyperglycemia is associated with poor hospital outcomes including prolonged hospital stay, infections, disability after hospital discharge, and death.\textsuperscript{5,35} In a retrospective study of 1,886 patients admitted to a community hospital, mortality in the general floors was significantly higher in patients with newly diagnosed hyperglycemia and those with known diabetes compared to those who were normoglycemic. (10% vs. 1.7% vs. 0.8%, respectively; \( P < 0.01 \)).\textsuperscript{5} Admission hyperglycemia has also been linked to worse outcomes in patients with community-acquired pneumonia (CAP).\textsuperscript{21} In a prospective cohort multicenter study of 2,471 patients with CAP, those with admission glucose levels of >11 mmol/L (198 mg/dL) had a greater risk of mortality and complications than those with glucose < 11 mmol/L. The risk of in-hospital complications increased 3% for each 1 mmol/L (18 mg/dL) increase in admission glucose. In a retrospective study of 348 patients with chronic obstructive pulmonary disease and respiratory tract infection, the relative risk of death was 2.1 in those with a blood glucose of 7–8.9 mmol/L (126–160 mg/dL), and 3.4 for those with a blood glucose of >9.0 mmol/L (>162 mg/dL), compared to patients with a blood glucose of 6.0 mmol/L (108 mg/dL).\textsuperscript{36}

General surgery patients with hyperglycemia during the perioperative period are also at increased risk for adverse outcomes. In a case-control study, elevated preoperative glucose levels increased the risk of postoperative mortality in patients undergoing elective noncardiac nonvascular surgery.\textsuperscript{37} Patients with glucose levels of 5.6–11.1 mmol/L (110–200 mg/dL) and those with glucose levels of >11.1 mmol/L (>200 mg/dL) had, respectively, 1.7-fold and 2.1-fold increased mortality compared to those with glucose levels <5.6 mmol/L (<110 mg/dL). In another study, patients with glucose levels > 12.2 mmol/L (>220 mg/dL) on the first postoperative day had a rate of infection 2.7 times higher than those who had serum glucose levels <12.2 mmol/L. A more recent study\textsuperscript{38} showed an increase of postoperative infection rate by 30% for every 2.2 mmol/L (40 mg/dL) rise in postoperative BG level above 50 mmol/L (110 mg/dL).

Complications due to hyperglycemia

The cause of stress hyperglycemia is multifactorial, likely due to a combination of acute illness, medical treatments, and patient predilection that in turn leads to a physiologic rise in counter-regulatory hormones, activation of the inflammatory cascade, and oxidative stress (Table 3).\textsuperscript{39,40} Counter-regulatory hormones such as cortisol and epinephrine negatively impact carbohydrate metabolism by increasing peripheral insulin resistance, increasing hepatic gluconeogenesis and glycogenolysis, and decreasing insulin production.\textsuperscript{41,42} Elevations in mediators of inflammation and proinflammatory transcription factors are also associated with episodes of hyperglycemia. Inflammatory mediators such as tumor necrosis factor-alpha, and cytokine interleukin 1 inhibit postreceptor insulin signaling.\textsuperscript{39,43} The activation of proinflammatory transcription factors intra-nuclear factor kappa B (\( \text{NF_{\kappa B}} \)) binding and activator protein-1 binding\textsuperscript{44,45} are linked to increased expression of genes that produce proteins that mediate inflammation, platelet aggregation, apoptosis, and endothelial dysfunction.\textsuperscript{45} Finally, reactive oxygen species from oxidative stress during acute illness and hyperglycemia further lend to more hyperglycemia via damage to lipids, proteins, and DNA.\textsuperscript{42,46} Of importance, investigators have noted that several of the hormonal and proinflammatory aberrations associated with stress hyperglycemia return to normal after the treatment with insulin and resolution of hyperglycemia.\textsuperscript{46} Insulin acts to suppress counter-regulatory hormones, proinflammatory transcription factors, and may even suppress the formation of reactive oxidation species.\textsuperscript{47,48} Contrary to early literature suggesting that insulin directly increases the risk of cardiovascular events,\textsuperscript{49} subsequent studies have shown...
more so that hyperinsulinemia is simply a marker of underlying insulin resistance syndromes (i.e., metabolic syndrome and diabetes) that are associated with increased cardiovascular morbidity and mortality.\textsuperscript{50} In fact, insulin can reverse variables such as vasoconstriction, lipolysis, overproduction of free fatty acids, platelet aggregation, and inflammation which increase cardiovascular risks.\textsuperscript{47,51} Thus, guided treatment of significant hyperglycemia and the use of insulin in the inpatient setting appear to be tools for decreasing the risks associated with increased morbidity and mortality associated with hyperglycemia.

In addition to avoiding extremes of glucose elevation to improve outcomes, several investigators have linked extremes of glucose variability (GV) to endothelial dysfunction, oxidative stress, and mortality.\textsuperscript{52–55} In a retrospective study, Krinsley and colleagues showed that mortality was threefold higher ICU patients with the lowest GV versus patients with the highest GV (12.1\% vs. 37.8\%).\textsuperscript{56} Goyal and colleagues reported that in 1,469 subjects with acute myocardial infarction the baseline glucose and the 24-hour change, particularly a BG change of > 1.7 mmol/L (>30 mg/dL), were significant predictors of 180-day mortality in nondiabetic patients.\textsuperscript{57} Although the relationship between GV and mortality is consistent, GV targets have not yet been established and may differ for different patient populations in the ICU setting.

\section*{Inpatient hyperglycemia in the ICU}

In the critical care setting, a variety of intravenous infusion protocols have been shown to be effective in achieving glycemic control with low rate of hypoglycemic event and in improving hospital out-come.\textsuperscript{9,16,18,58–61} Formal recommendations for the management of inpatient hyperglycemia in critically ill patients in the ICU setting were released on May 8, 2009 by the American Association of Clinical Endocrinologists and the American Diabetes Association, and were published online in the June issues of \textit{Endocrine Practice} and \textit{Diabetes Care} (Figure 1).\textsuperscript{25,26} The guidelines outline that insulin therapy, preferably with validated intravenous CII protocols, should be initiated for treatment of persistent hyperglycemia starting at a threshold of no greater than 10 mmol/L (180 mg/dL). Once insulin therapy has been started, a glucose range of 7.8– 81 mmol/L (140–180 mg/dL) is recommended for the majority of critically ill patients; however, more stringent targets may be appropriate based on the clinical scenario and expertise of the medical staff. The consensus panel stresses that patients should be monitored closely for hypoglycemia and that the CII protocol should undergo modification as necessary for unexplained hypoglycemia (<3.9 mmol/L; <70 mg/dL). Finally, the panel suggests less aggressive therapy for patients that are terminally ill or have severe comorbidities.

Although hypoglycemia should be avoided and appears to be, just as hyperglycemia, a marker of poor outcome, there has been no evidence indicating that ICU hypoglycemia \textit{directly} causes increased mortality.\textsuperscript{7,62} With a well-equipped and staffed medical team, the consensus is that intensive insulin therapy via a CII protocol can be used effectively and safely, and it is the opinion of the authors that the benefits of tight control (defined as blood glucose <140 mg/dL) may outweigh the deleterious effects in individuals that are healthier, are in the SICU, do not have severe renal failure or sepsis, have had an acute cardiovascular insult, receive parenteral nutrition, or have hyperglycemia during the first 24 h of admission.

Recent meta-analyses of hyperglycemia studies suggest that patients with cardiovascular and cardiac surgery may benefit more from tight glycemic control than conventional control in the ICU. Two recent studies reporting on the impact of intensive glycemic control in the outpatient setting and cardiovascular outcome were published in September 2009.\textsuperscript{63,64} These studies found that compared with conventional control, intensive glucose control reduces the risk of nonfatal myocardial infarction but not cardiovascular death or all-cause death.
mortality. The Griesdale meta-analysis of 26 studies with 13,567 patients (including the NICE-SUGAR trial) showed that although associated with a significantly higher risk of hypoglycemia, patients admitted to the surgical ICU had a mortality reduction of ∼40% with intensive glycemic control (RR 0.63, CI 0.44–0.91). Thus, patients with surgical procedures, particularly open-heart surgeries, may be prime candidates for setting a target BG goal of 5.6–7.8 mmol/L (100–140 mg/dL).

Treatment in the noncritical care setting

The use of insulin is the preferred therapeutic agent for blood glucose control in the hospital setting. Of the three primary categories of oral agents—secretagogues (sulfonylureas and meglitinides), biguanides, and thiazolidinediones—none have been systematically studied for inpatient use. The major limitation to the use of these oral antidiabetic agents for hospital use is their slow onset of action that does not allow rapid glycemic control and/or dose adjustment to meet the changing needs of the acutely ill patient. In addition, all three groups have additional limitations that may limit their use for inpatient glucose control. A long-standing controversy exists regarding the vascular effects of sulfonylureas in patients with cardiac and cerebral ischemia. Sulfonylureas inhibit adenosine triphosphate (ATP)-sensitive potassium channels, resulting in cell membrane depolarization and increased intracellular calcium concentration. This mechanism may inhibit ischemic preconditioning and may lead to increased risk of vascular events. Sulfonylureas may also increase the risk of hypoglycemia in the hospitalized patient with poor appetite or ordered dietary restrictions. A large number of patients have one or more contraindications to the use of metformin upon admission, including acute congestive heart failure, renal or liver dysfunction, hypoperfusion, and chronic pulmonary disease. Finally, the use of thiazolidinediones is limited as they can increase intravascular volume and may precipitate or worsen congestive heart failure and peripheral edema.

No single insulin regimen meets the needs for all subjects with type 2 diabetes. Continuous intravenous insulin therapy is effective at achieving and maintaining desired levels of glycemic control in noncritically ill patients outside of a critical care area. In one study, glycemic parameters in 156 noncritically ill patients treated with IV insulin were compared with historic controls. Patients treated with IV insulin experienced a shorter duration of hyperglycemia without an increase in frequency of hyperglycemia. More recently, the efficacy of CII was noted in 200 patients admitted to a general medicine or surgical service that received CII for a target BG of 8.3 mmol/L (150 mg/dL). The glycemic goal was achieved in 85% of patients; however, hypoglycemia (BG < 3.3 mmol/L; < 60 mg/dL) occurred at least once in 22% of patients, and severe hypoglycemia (BG < 2.2 mmol/L; < 40 mg/dL) occurred in 5% of patients, which is similar to hypoglycemia rates reported in CII trials in critically ill patient populations.

Scheduled SCI therapy with basal or intermediate acting insulin given once or twice a day in combination with short or rapid acting insulin administered prior to meals is preferred as an effective and safe strategy for glycemic management in noncritically ill patients. The practice of discontinuing oral diabetes medications and/or insulin therapy and starting sliding scale insulin (SSI) results in undesirable levels of hypoglycemia and hyperglycemia. The SSI regimen, although straightforward and easy to use, is faced with several challenges that include inadequate coverage of glycemic excursions and insulin stacking. The safety of scheduled subcutaneous (SC) basal bolus insulin has been demonstrated in different studies in hospitalized patients with type 2 diabetes. In one study that included insulin naive patients with type 2 diabetes, glycemic control was achieved more effectively with basal bolus insulin than with SSI. Mean glucose levels of < 10 mmol/L (< 180 mg/dL) were achieved by the second day of hospitalization without an
increase in the frequency of hypoglycemia in those randomized to the basal bolus regimen. The incidence of hypoglycemia, defined as a BG < 3.3 mmol/L (<60 mg/dL), was low in this study. Among patients randomized to SSI alone, 14% required rescue therapy with basal bolus insulin due to persistent BG > 13.3 mmol/L (>240 mg/dL). A second study compared two different basal bolus insulin regimens (detemir plus aspart vs. NPH plus regular insulin) in hospitalized patients with type 2 diabetes, some of whom were receiving insulin therapy prior to hospitalization. There were no significant differences in the levels of glycemic control or in the frequency of hypoglycemia.

The recent Rabbit Surgery trial, a randomized multicenter study, compared the efficacy and safety of improving glycemic control with a basal bolus regimen compared to sliding scale regular insulin (SSI) in 211 patients with type 2 diabetes undergoing general surgery. Study outcomes included differences in daily BG levels and a composite of postoperative complications including wound infection, pneumonia, respiratory failure, acute renal failure, and bacteremia. Patients were randomized to receive basal bolus regimen with glargine and glulisine at a starting dose of 0.5 unit/kg/day or SSI given 4 times/day. The basal bolus regimen resulted in significant improvement in glycemic control and reduced the frequency of the composite outcome. The results of the Rabbit Surgery trial indicate that treatment with glargine once daily plus rapid-acting insulin before meals improves glycemic control and reduces hospital complications compared to SSI in general surgery patients with type 2 diabetes.

Using these studies as a guide, the AACE/ADA outlines that insulin can be used to maintain random BG levels <180 mg/dL for the majority of noncritically-ill patients. In conjunction with this, premeal BG targets should generally be <140 mg/dL as long as they can be achieved safely (Figure 2). A suggested method for determining starting doses of scheduled insulin therapy in the non-critical care setting can be based on a patient’s body weight and administered as a range of 0.3 to 0.5 units per kg as the total daily dose. Approximately 50% of the calculated dose can be administered as basal insulin and 50% as prandial or nutritional insulin in divided doses. Adjustments of insulin doses are based on results of bedside glucose monitoring to achieve glycemic targets and minimize risks for hypoglycemia. An alternative method for calculating the total daily insulin dose is based on the amount of correction insulin administered over the preceding 24 h and distributing this into basal and nutritional components.

**Summary**

Studies have clearly found that inpatient hyperglycemia is associated with poor outcomes and that improved glycemic control can result in better clinical outcomes and reduce mortality in certain clinical scenarios. What is not quite clear, however, is what the glucose target cutoffs are for lack or gain of benefit. Intravenous insulin infusion is the preferred regimen for critically ill patients in the ICU. Scheduled subcutaneous administration of basal, nutritional, and correction components rather than the sole use of SSI is the preferred method for achieving and maintaining glucose control in non-ICU setting. Oral antidiabetic agents are typically not appropriate for most hospitalized patients due to potential nausea/appetite changes, unpredictable timing of meal delivery, variable diet status (i.e., NPO), and potential reactions/toxicities associated with oral agents (i.e., metformin and IV contrast). Several guidelines and position statements offer medical institutions evidence-based guidelines for the management of inpatient hyperglycemia in both the ICU and non-ICU settings; however, more research is needed to further delineate the patient populations that would benefit most from tighter glycemic control and which insulin regimens are the safest and most effective.
Acknowledgments

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References


Initiate insulin therapy for persistent hyperglycemia of blood glucose >10 mmol/L

Maintain blood glucose values 7.8-10 mmol/L for the majority of critically-ill patients
- Potential exists for greater benefit at lower end of range
- Lower targets (6.1-7.8 mmol/L) may be appropriate in selected patients

Frequent glucose monitoring essential

Attempt to avoid hypoglycemia

Figure 1.
AACE/ADA target glucose level recommendations in the intensive care setting.26
Figure 2.
AACE/ADA target glucose level recommendations in the non-ICU setting.²⁶
Table 1

Randomized control trials showing no benefit for tight glycemic control

<table>
<thead>
<tr>
<th>Study</th>
<th>Setting</th>
<th>Population</th>
<th>Target BG (IT vs. CT arm)</th>
<th>Mean BG achieved (IT vs. CT arm)</th>
<th>Clinical outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ghandi, 2007</td>
<td>Operating room</td>
<td>Mixed, cardiac surgery</td>
<td>4.4–5.6 mmol/L versus &lt; 11.1 mmol/L</td>
<td>114 mg/dL versus 157 mg/dL</td>
<td>No difference in mortality; ↑ in stroke rate in IT arm</td>
</tr>
<tr>
<td>VISEP, 2008</td>
<td>Medical ICU</td>
<td>Mixed w/sepsis</td>
<td>4.4–5.6 mmol/L versus 10–11.1 mmol/L</td>
<td>112 mg/dL versus 151 mg/dL</td>
<td>No difference in 28-day or 90-day mortality, end-organ failure, LOSa</td>
</tr>
<tr>
<td>De La Rosa, 2008</td>
<td>Med-surgical ICU</td>
<td>Mixed</td>
<td>4.4–5.6 mmol/L versus 10–11.1 mmol/L</td>
<td>117 mg/dL versus 148 mg/dL</td>
<td>No difference in 28-day mortality or infection rate</td>
</tr>
<tr>
<td>Glucontrol, 2009</td>
<td>Med-surgical ICU</td>
<td>Mixed</td>
<td>4.4–5.6 mmol/L versus 140–7.8–10 mmol/L</td>
<td>117 mg/dL versus 144 mg/dL</td>
<td>No difference in 28-day mortalitya</td>
</tr>
<tr>
<td>NICE-SUGAR, 2009</td>
<td>Med-surgical ICU</td>
<td>Mixed</td>
<td>4.5–6 mmol/L versus ≤ 10 mmol/L</td>
<td>115 mg/dL versus 144 mg/dL</td>
<td>No difference in 90-day mortality</td>
</tr>
</tbody>
</table>

aStudy underpowered due to premature discontinuation.

IT = intensive therapy; CT = conventional therapy.
Mixed = nondiabetics and diabetics.
### Table 2

Randomized control trials showing benefit of tight glycemic control

<table>
<thead>
<tr>
<th>Study</th>
<th>Setting</th>
<th>Population</th>
<th>Clinical outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malmberg, 1995</td>
<td>CCU</td>
<td>Mixed</td>
<td>↓28% mortality after 1 year</td>
</tr>
<tr>
<td>Furnary, 1999</td>
<td>CCU</td>
<td>DM undergoing CABG</td>
<td>↓65% reduction in deep sterna wound infection rate</td>
</tr>
<tr>
<td>Van den Berghe, 2001</td>
<td>Surgical ICU</td>
<td>Mixed, with CABG</td>
<td>↓34% mortality</td>
</tr>
<tr>
<td>Furnary, 2003</td>
<td>CCU</td>
<td>DM undergoing CABG</td>
<td>↓50% reduction in adjusted mortality rate</td>
</tr>
<tr>
<td>Krinsley, 2004</td>
<td>Med-surgical ICU</td>
<td>Mixed, noncardiac</td>
<td>↓29% reduction in mortality</td>
</tr>
<tr>
<td>Lazar, 2004</td>
<td>OR and ICU</td>
<td>DM with CABG</td>
<td>↓60% reduction of postoperative atrial fibrillation</td>
</tr>
<tr>
<td>Van den Berghe, 2006</td>
<td>Medical ICU</td>
<td>Mixed</td>
<td>↓18% mortality</td>
</tr>
</tbody>
</table>

*Intention-to-treat analysis

Mixed = nondiabetics and diabetics
### Table 3

Counter-regulatory hormones and mediators of inflammation associated with stress hyperglycemia

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortisol</td>
<td>↑ skeletal muscle IR, ↑ lipolysis → substrate for ↑ gluconeogenesis</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>↑ skeletal muscle IR, ↑ gluconeogenesis and glycogenolysis, ↑ lipolysis, ↓ insulin secretion</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>↑ gluconeogenesis (at high levels), ↑ lipolysis</td>
</tr>
<tr>
<td>Glucagon</td>
<td>↑ gluconeogenesis and glycogenolysis</td>
</tr>
<tr>
<td>Growth hormone</td>
<td>↑ skeletal muscle IR, ↑ gluconeogenesis, ↑ lipolysis</td>
</tr>
<tr>
<td>Inflammation mediators</td>
<td>Effect</td>
</tr>
<tr>
<td>Tumor necrosis factor</td>
<td>↑ skeletal and hepatic IR</td>
</tr>
<tr>
<td>Interleukin-1</td>
<td></td>
</tr>
<tr>
<td>Interleukin-6</td>
<td></td>
</tr>
</tbody>
</table>

IR = insulin resistance; TNF = tumor necrosis factor.