

# How Low Should You Go? The Limbo of Glycemic Control in Intensive Care Units

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Hyperglycemia, a common finding in critically ill patients, is linked to poor outcomes in multiple conditions. The Leuven I study published in 2001 was the first evaluation of intensive insulin therapy, and the 3.4% absolute reduction in mortality in a single-center surgical intensive care unit led to widespread endorsement of the therapy. In a subsequent study in a medical intensive care unit, reduction in mortality was not significant. Two multicenter studies were stopped early because of significantly higher rates of hypoglycemia in the patients receiving intensive insulin therapy. The episodes of hypoglycemia were linked to increased mortality. In the largest prospective study conducted to date, mortality was significantly higher ( $P = .02$ ) in patients who had intensive therapy (27.5%) than in control patients (24.9%). Thus, after years of research, intensive insulin therapy does not appear to convey the original benefit in all critically ill patients. Several organizations have proposed alternative blood glucose targets, such as 140 to 180 mg/dL, to both provide glycemic control and reduce the opportunity for hypoglycemic episodes. (*Critical Care Nurse*. 2011;31[4]:e9-e18)

**H**yperglycemia is a common clinical finding in patients in intensive care units (ICUs).<sup>1,4</sup> Nearly 24 million people, or 8% of the US population, have type 2 diabetes mellitus, but the true incidence of hyperglycemia in inpatients is largely unknown.<sup>2-4</sup> Compared with the general medical population, critically ill patients have a dramatically higher incidence of hyperglycemia. At least 50% of ICU patients experience

hyperglycemia, including patients with preexisting diabetes and patients who become hyperglycemic as a result of their illness.<sup>5</sup>

Elevated blood glucose concentrations are associated with increased mortality in many conditions, such as acute myocardial infarction, burns, and stroke.<sup>6-10</sup> The benefits of intensive insulin therapy (IIT) and tight glycemic control in outpatients with diabetes paved the way for research on glucose control in critically ill patients.<sup>11,12</sup> In a landmark trial, van den Berghe et al<sup>13</sup> reported a 3.4% absolute reduction in mortality for an IIT protocol with a target

blood glucose concentration of 80 to 110 mg/dL (to convert to millimoles per liter, multiply by 0.0555). However, these benefits could not be replicated in subsequent studies<sup>14,15</sup>; rates of hypoglycemia (blood glucose <40 mg/dL) were significantly higher than in the study by van den Berghe et al.<sup>13</sup> This lack of benefit, combined with the risk of hypoglycemia, forced the early discontinuation of 2 large, multicenter, randomized trials.<sup>16,17</sup> These discordant results show that treating elevations in blood glucose levels requires a delicate balance between the risks of hypoglycemia and any benefit in decreased mortality that might be derived from tight glycemic control.

## Pathophysiology

Unlike diabetes mellitus, which is a chronic health condition, hyperglycemia in the ICU is an acute physiological stress response.<sup>5,6</sup> Conditions associated with acute elevations in blood glucose level include infection, sepsis, shock, trauma, total parenteral nutrition, older age, and the use of diabetogenic drugs.<sup>3,5</sup> Elevations in glucose levels occur in ICU patients regardless of whether or

**Table 1** Hormonal regulation of glucose during stress<sup>a</sup>

Mechanism	Hormone <sup>b</sup>				
	Epinephrine	Norepinephrine	Glucocorticoids	Glucagon	Tumor necrosis factor
Induces skeletal muscle insulin resistance	✓		✓		✓
Increases gluconeogenesis	✓	✓	✓	✓	
Increases glycogenolysis	✓		✓	✓	
Increases lipolysis	✓	✓	✓		
Increases glucagon release			✓		
Directly suppresses secretion of insulin by pancreatic beta cells	✓			✓	

<sup>a</sup> Based on data from Clement et al<sup>1</sup> and McCowen et al.<sup>5</sup>

<sup>b</sup> For each hormone, check marks indicate mechanisms of action.

not the patients have preexisting diabetes. These conditions trigger a hypermetabolic state similar to the fight-or-flight response, resulting in the release of stress hormones.<sup>5,6</sup> Hormones linked with stress-induced hyperglycemia (Table 1) include not only endogenously released products but also exogenously administered medications (eg, vasopressor agents). The primary mechanisms of hyperglycemia in critical illness are insulin resistance (hepatic and skeletal muscle), gluconeogenesis, and glycogenolysis.<sup>1,5</sup> These mechanisms indicate why patients with extreme physiological demands are at a heightened risk for stress-induced hyperglycemia.

Although hyperglycemia is considered a pathological finding, elevations in blood glucose in the peripheral circulation are essential to provide an adequate supply of glucose to the central nervous system.<sup>5,6,17</sup> Astrocytes store glucose as glycogen, but the amount stored is only sufficient to fuel a glucose-deprived brain for minutes and is for short-term emergencies. The brain and central nervous system are almost completely dependent on glucose in the peripheral circulation for energy; during episodes of stress, hyperglycemia ensures an adequate supply of carbohydrate-based energy for the insulin-insensitive cells of the brain. Deprivation of these cells of

glucose may result in anaerobic metabolism and production of reactive oxygen species (ROS), leading to areas of ischemia and foci for seizures. Left untreated, hypoglycemia results in coma and brain death.<sup>17</sup>

Clement et al<sup>1</sup> described the pathophysiological consequences of hyperglycemia, including inflammation, direct cellular damage, apoptosis, ischemia, necrosis, and acidosis. These authors proposed 3 mechanisms that can lead to the poor outcomes associated with prolonged hyperglycemia.

The first mechanism is immune system dysfunction. In addition to the overabundance of an energy source in the blood, microorganisms proliferate in an overall state of immunosuppression. In vitro studies<sup>18,19</sup> have indicated that hyperglycemia reduces neutrophil activity and decreases phagocyte adherence and chemotaxis, thereby inhibiting the ability to perform the basic function of phagocytosis despite elevated levels of inflammatory cytokines. Transient elevations in blood glucose have also been linked to lymphocyte reduction.

In the second mechanism, extreme insulin resistance forces

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insulin-sensitive tissues to use protein and lipids for energy and to convert to anaerobic metabolism.<sup>6</sup> These changes lead to increases in free fatty acid, lactic acid, and production of ROS and ultimately, oxidative damage. In the third mechanism, as shown in vitro, endothelial cells exposed to hyperglycemic environments change from production of nitric oxide to production of ROS.<sup>1,5</sup> ROS can cause apoptosis, nucleic acid damage, and protein denaturation. Generation of ROS also results in activation of transcription factors and inflammatory mediators such as tumor necrosis factor- $\alpha$ .

### Adverse Clinical Effects Associated With Hyperglycemia

Hyperglycemia is a physiological reaction to stressful situations to ensure adequate glucose perfusion of the central nervous system; however, this reaction is unfortunately associated with adverse clinical outcomes. Gore et al<sup>7</sup> observed a 7-fold increased risk for death in children with burns whose blood glucose values were greater than 140 mg/dL for 40% or more of the hospital stay. Similarly, blood glucose values greater than 144 mg/dL were predictive of worse outcomes after myocardial infarction or stroke.<sup>8-10</sup> In patients with head trauma treated surgically for evacuation of an intracranial hematoma, admission or postoperative blood glucose values greater than 200 mg/dL were predictive of poor outcomes, which were defined as death or a persistent vegetative state.<sup>20</sup> Because of the immune system dysfunction described earlier, hyperglycemia predisposes patients

to infectious complications. Perioperative hyperglycemia can increase the risk of postoperative infections and prolong length of stay in patients who have general or vascular surgery, regardless of the patients' diabetic status.<sup>21</sup>

Hyperglycemia is also associated with neuromuscular abnormalities in patients with critical illnesses.<sup>22,23</sup> Stevens et al<sup>23</sup> conducted a systematic review of neuromuscular abnormalities in ICU patients and identified hyperglycemia, administration of catecholamines, development of systemic inflammatory response syndrome or sepsis, and multiple organ failure as predictors for the abnormalities.

### Adverse Effects Associated With Hypoglycemia

The most common signs and symptoms of hypoglycemia (diaphoresis, agitation, and confusion) are difficult to assess in critically ill patients. Severe hypoglycemia, typically defined as a blood glucose level of 40 mg/dL or less, may result in seizures, coma, and death.<sup>17,24</sup> Several investigators have evaluated the effect of hypoglycemic episodes on mortality in hospitalized patients. In a study by Krinsley and Grover,<sup>25</sup> compared with patients who had no episodes of hypoglycemia, patients who experienced just a single episode had a 16.4% increase in mortality (odds ratio, 2.28;  $P < .001$ ). This relationship was further supported in a study by Hermanides et al.<sup>26</sup> Even after adjustment for scores on the Sequential Organ Failure Assessment, age, sex, sepsis, and diabetes mellitus, a single episode of hypoglycemia conferred a higher incidence of ICU mortality (odds ratio, 2.1;

95% confidence interval [CI], 1.6-2.8;  $P < .001$ ).

### Intensive Glucose Control in Patients With Diabetes

The Diabetes Mellitus Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) trial<sup>11</sup> was the stimulus for other evaluations of intensive glucose control in critically ill patients.<sup>13</sup> The investigators in the DIGAMI trial enrolled 602 patients who had had a suspected myocardial infarction within the previous 24 hours who either had known diabetes or a blood glucose level of 198 mg/dL or greater at the time of admission to the hospital. Patients were randomized to either standard care (treatment of blood glucose level withheld until deemed clinically necessary) or IIT (target blood glucose, 126-196 mg/dL). Treatment was started with an insulin infusion for at least 24 hours and was continued with subcutaneous insulin for at least 3 months. After a mean follow-up of 344 days, patients in the IIT group had lower levels of blood glucose and hemoglobin A<sub>1c</sub> than did patients in the standard-care group. Mortality rates at discharge and at 3 months were lower for the IIT group and remained significantly lower at 1 year follow-up (26.1% vs 18.6%;  $P = .03$ ). Hypoglycemia occurred only in the IIT group and resulted in discontinuation of subcutaneous insulin in 10% of the group. The investigators<sup>11</sup> concluded that IIT in these patients corresponded to a reduction in 1-year mortality and that hypoglycemic events were not severe enough to outweigh the mortality benefit. To confirm the results of the DIGAMI study and explore the effect of early

vs early and sustained blood glucose control, Malmberg et al<sup>27</sup> conducted a prospective study (DIGAMI 2) in 1253 patients with diabetes who had had a myocardial infarction. Patients were randomized to receive either a 24-hour insulin infusion followed by subcutaneous long-term glucose control, a 24-hour insulin infusion followed by standard glucose control, or glucose management according to local practice. Unlike the findings in the first study, differences in mortality between the 3 study groups (23.4% vs 22.6% vs 19.3%;  $P > .05$ ) were not significant. Hypoglycemia, defined in DIGAMI 2 as a blood glucose level less than 54 mg/dL, was experienced by 12.7%, 9.6%, and 1.0% of patients in groups 1, 2, and 3, respectively.

### Clinical Trials of Glycemic Control in the ICU

In this review, we focus on publications chronologically. Thus, we accentuate the nuances of the different studies and trials and then provide a recommendation for glycemic control in the ICU.

In 2001, van den Berghe et al<sup>13</sup> reported on the first trial to evaluate intensive glycemic control in the ICU. The purpose of the trial was to determine whether intensive glycemic control with insulin improved morbidity and mortality in critically ill surgical patients. The study was a single-center, prospective, randomized, controlled trial (referred to as Leuven I). Adult patients admitted to the surgical ICU (SICU) between February 2000 and January 2001 were randomized to receive IIT or conventional insulin therapy (CIT). The blood glucose goals were 80 to 110 mg/dL and 180 to 200 mg/dL,

respectively. The primary outcome measure of Leuven I was all-cause ICU mortality.

Although the investigators originally planned to enroll 2500 patients, the trial was stopped after the enrollment of only 1548 patients because ICU mortality was significantly less ( $P < .04$ ) in the IIT group (4.6%) than in the CIT group (8.0%). This difference was primarily due to a 2-fold reduction in mortality in patients who required at least 5 days of ICU care: 10.6% for the IIT group and 20.2% for the CIT group ( $P = .005$ ). Many of the secondary end points (in-hospital mortality, ICU stays >14 days, mechanical ventilation >14 days, neuromuscular abnormalities, need for dialysis, and bacteremia) were significantly lower in the IIT patients than in the CIT patients. Van den Berghe et al<sup>13</sup> concluded that IIT reduced morbidity and mortality in SICU patients. Although Leuven I paved the way for the widespread adoption of IIT in many ICUs in the United States, the trial had several important subtleties. In the 24-hour immediate postoperative period, all patients received 200 to 300 g of intravenous dextrose. This treatment may have led to iatrogenic hyperglycemia and, more important, may have attenuated episodes of hypoglycemia, possibly explaining the relatively low rate of hypoglycemia compared with the rate in later trials.<sup>14-16</sup> Despite the glucose infusion, severe hypoglycemia was experienced by more patients in the IIT group (5.1%) than in the CIT group (0.8%). Leuven I was a single-center study with a protocol implemented by nurses responsible solely for the study patients. Therefore, the results of the trial may not be

generalizable to situations without such intense nursing support, although this notion has been a point of contention by the Leuven I investigators. The trial was stopped early because of the observed benefits, an issue that we explore later.

After the Leuven I study, some facilities adopted protocols for intensive glycemic control. In 2004, Krinsley<sup>28</sup> reported the results of using an IIT protocol at Stamford Hospital in Stamford, Connecticut. Krinsley compared outcomes of a prospective cohort treated with IIT ( $n = 800$ ) with the outcomes of a retrospective cohort ( $n = 800$ ). This observational study was done at a single mixed medical-surgical ICU. The targeted blood glucose level for the IIT group was less than 140 mg/dL, and subcutaneous insulin was used unless 2 consecutive blood glucose values were greater than 200 mg/dL; at that point, an insulin infusion was started. Hospital mortality was reduced after adoption of the IIT protocol: 20.9% for the control group vs 14.8% for the IIT group ( $P = .002$ ). Hypoglycemia was low overall, and only mild hypoglycemia differed between the 2 groups: 1.02% for the IIT group vs 0.54% for the control group ( $P = .02$ ).<sup>28,29</sup> Krinsley concluded that the IIT protocol reduced relative mortality by 29.3% and shortened ICU stay by about half a day.

In the same year that the results of Krinsley's study were published, the American Diabetes Association (ADA) released a statement on glycemic control in the ICU.<sup>1</sup> The ADA endorsed the findings of the Leuven I study; IIT with a blood glucose goal of 80 to 110 mg/dL was assigned a grade A level of evidence. On the basis of this statement,

many centers in the United States adopted a goal of 80 to 110 mg/dL for blood glucose levels in critically ill patients.

To test the applicability of their SICU findings in the medical ICU (MICU), van den Berghe et al<sup>14</sup> undertook a second study of IIT (Leuven II). This study was conducted in the MICU of the same institution as their previous study,<sup>13</sup> and the protocol and the goals were the same as before. From March 2002 to May 2005, a total of 1200 MICU patients expected to require at least 3 days of ICU-level care were enrolled in the study. Patients were excluded if they were taking any nutrition by mouth. The enrolled patients were randomized to receive either IIT or CIT. The primary outcome was all-cause in-hospital mortality, with secondary outcomes of ICU mortality, 28- and 90-day mortality, length of hospitalization, duration of mechanical ventilation, incidence of acute renal failure, and development of bacteremia.

In contrast to the results of Leuven I, the findings of Leuven II showed no mortality benefit with the use of IIT. In-hospital mortality was 37.3% with IIT and 40% with CIT ( $P=.33$ ; hazard ratio, 0.94; 95% CI, 0.84-1.06;  $P=.31$ ). In addition, the IIT group did not differ significantly from the CIT group for ICU (24.2% vs 26.8%;  $P=.33$ ), 28-day (29.9% vs 30%;  $P=.95$ ), and 90-day (35.9% vs 37.7%;  $P=.53$ ) mortality. However, when patients who required fewer than 3 days of ICU level care were excluded, IIT conveyed a significant mortality benefit over CIT (43% vs 52.5%;  $P=.009$ ; hazard ratio, 0.84; 95% CI, 0.73-0.97;  $P=.02$ ). For all secondary end points, with the

exception of development of bacteremia, outcomes were improved in the IIT group compared with the CIT group. On the basis of these results, van den Berghe et al<sup>14</sup> concluded that IIT reduced morbidity in the intention-to-treat cohort and, according to subgroup analysis, reduced both morbidity and mortality among patients who required at least 3 days in the ICU.

Although these results are a departure from the findings of Leuven I, van den Berghe et al<sup>14</sup> drew attention to the subgroup that required at least 3 days of ICU care. However, predicting a priori which patients will require this length of stay is difficult. Patients taking nutrition by mouth were excluded in an attempt to select patients who would require 3 days of ICU care, yet only 64% of the patients in Leuven II met this criterion. The enteral route accounted for less than 50% of patients' caloric intake until day 7 through day 9 of their hospital stay. These results are somewhat of a divergence from the Society of Critical Care Medicine (SCCM) and the American Society of Parenteral and Enteral Nutrition (ASPEN) guidelines,<sup>30</sup> which, in general, reserve parenteral nutrition for patients who do not meet nutrition goals within 7 days after admission. Hypoglycemia was higher in the IIT group (18.7%) than in the CIT group (3.1%), diminishing some of the potential benefits of IIT. Treatment with IIT was an independent predictor of hypoglycemic events (hazard ratio, 7.5; 95% CI, 4.5-12.5;  $P<.001$ ), and mortality was increased 2- to 3-fold with hypoglycemia.<sup>14</sup> Therefore, IIT may have, in some regard,

increased mortality via higher rates of hypoglycemia.

In the 2 years after the 2006 publication of the results of Leuven II, the findings of 2 key European trials<sup>15,16</sup> began to turn the tide on IIT in the ICU. The Glucontrol study<sup>15</sup> was a highly anticipated, prospective, randomized, controlled, multicenter trial conducted in 7 European nations to further evaluate the impact of tight glycemic control on mortality. Adult patients admitted to a study MICU or SICU were randomized to 1 of 2 levels of glycemic control. On the basis of Leuven I,<sup>13</sup> the goals were a less intensive target of 140 to 180 mg/dL blood glucose for group 1 and 80 to 110 mg/dL for group 2. In the Glucontrol study, the primary outcome was ICU mortality; the secondary end points were in-hospital and 28-day mortality, length of stay, hypoglycemia, new infection, and/or organ failure. After 1101 of the projected 3500 patients had been enrolled in the study, the safety steering committee terminated the study early because of high rates of severe hypoglycemia and unintended protocol violations (>60% of time spent outside the target blood glucose ranges). Median blood glucose values were 144 (intraquartile range, 128-162) mg/dL in group 1 and 117 (intraquartile range, 108-130) mg/dL in group 2 ( $P<.001$ ), and the median proportion of time spent in the desired range was 34.3% for the first group and 39.3% for the second group. Hypoglycemia occurred in 2.7% of the patients in group 1 and in 8.7% of those in group 2 ( $P<.001$ ). Although the study was underpowered, ICU mortality was similar between the 2 groups: 15.3%

in group 1 and 17.2% in group 2 ( $P = .41$ ).

The results of the Intensive Insulin Therapy and Pentastarch Resuscitation in Severe Sepsis (VISEP) study<sup>16</sup> were similar to those of the Glucontrol trial. The VISEP study was a randomized, multicentered, 2 × 2 factorial trial to evaluate both IIT and 10% pentastarch in patients with sepsis and septic shock. The trial was conducted in 18 German MICUs, and the blood glucose targets were the same as in the Leuven trials (IIT, 80-110 mg/dL; CIT, 180-200 mg/dL). Outcomes included all-cause 28-day mortality, scores on the Sequential Organ Failure Assessment, length of ICU stay, 90-day mortality, duration of mechanical ventilation, and a safety end point of severe hypoglycemia. After 488 of the planned 600 patients had been enrolled, the study was stopped prematurely because of a 6-fold higher rate of hypoglycemia ( $P < .001$ ) in the IIT group (12.1%) compared with the CIT group (2.1%). The hypoglycemia associated with IIT was more severe, more likely to be classified as life-threatening, and led to prolonged hospitalization. Hypoglycemia was also identified as an independent risk factor for mortality. Excluding mortality associated with hypoglycemia, neither 28- nor 90-day mortality differed significantly between the 2 groups: 24.7% for the IIT group vs 26% for the CIT group at 28 days and 39.7% vs 35.4% at 90 days. The investigators<sup>16</sup> concluded that IIT with a blood glucose goal of 80 to 110 mg/dL had no measurable benefit in the MICU and resulted in a higher rate of hypoglycemia, which was independently linked to poor outcomes.

In study of more than 10 000 patients, Treggiari et al<sup>31</sup> evaluated their institution's experience with IIT in the ICU. They compared mortality among 3 time periods of patients, all of whom were managed by using different glycemic goals. Period I (March 2001 through February 2002) included 2366 patients and blood glucose targets were 120 to 180 mg/dL. Period II (March 2002 through June 2003) included 3322 patients and had a tighter glycemic goal of 80 to 130 mg/dL for blood glucose. Finally, period III (July 2003 through February 2005) included 4768 patients and further reduced the glycemic goal to the goal in the Leuven I study<sup>13</sup> of 80 to 110 mg/dL for blood glucose. Baseline characteristics between all 3 cohorts were well balanced; 60% to 65% of all patients were admitted to a surgical service. Even after adjustments for age, diabetic status, severity of illness score, admitting service, and treatment with mechanical ventilation, mortality was not reduced by the use of a more intensive glycemic goal. Compared with period I, the odds ratio for mortality was 1.11 (95% CI, 0.93-1.31) for period II and 1.15 (95% CI, 0.98-1.32) for period III. Although mortality was not reduced, hypoglycemia was a much more common occurrence with progressively lower glycemic goals. Severe hypoglycemia (blood glucose <40 mg/dL) increased 2-fold during the study periods, and mild hypoglycemia (blood glucose <65 mg/dL) increased 4-fold ( $P < .01$  for both comparisons).

The largest prospective trial that had been reported when this review was written was the NICE-SUGAR study<sup>32</sup> published in 2009. In NICE-SUGAR, the combined effort of

Canadian, Australian, and New Zealand research groups, the investigators compared 90-day mortality in patients treated with IIT and patients treated with CIT. The study was a 42-center, randomized, controlled trial in adult MICU and SICU patients who were expected to require at least 3 days in the ICU. Patients were randomized to IIT (blood glucose goal, 81-108 mg/dL) or CIT (blood glucose goal, <180 mg/dL), and insulin doses were determined by using an electronic algorithm. The investigators planned to enroll 6100 patients for 90% power for their primary outcome. Additional outcomes included survival time, cause of death, length of stay, 28-day mortality, duration of mechanical ventilation, and incidence of bacteremia.

A total of 6104 patients were enrolled; 6032 were evaluated for the outcomes described. In contrast to the results of the Leuven trials, patients treated with IIT in NICE-SUGAR had higher 90-day mortality than did patients treated with CIT: 27.5% vs 24.9% (odds ratio, 1.14; 95% CI, 1.02-1.28;  $P = .02$ ). Median survival time was shorter in the IIT group ( $P = .03$ ), and cardiovascular-related death was increased with IIT ( $P = .02$ ). NICE-SUGAR results also did not indicate any morbidity benefit from IIT. Length of stay, duration of mechanical ventilation, incidence of bacteremia, and need for dialysis were similar between the 2 groups of patients. Much like patients in the Glucontrol and VISEP studies, patients randomized to IIT had significantly higher rates ( $P < .001$ ) of severe hypoglycemia (6.8%) than the control group did (0.5%). On the basis of the higher mortality rates with strict glucose control,

the investigators<sup>32</sup> recommended modifying the blood glucose goal to less than 180 mg/dL.

The results of NICE-SUGAR transformed the approach to ICU glycemic control to a new, less intensive goal. With IIT, the number needed to harm was 38 (ie, for every 38 patients treated with IIT, 1 additional patient will die).<sup>32</sup> A large proportion of patients in the IIT group had blood glucose levels greater than the glycemic goal (mean blood glucose level, 115 mg/dL; SD, 18), and mean blood glucose values for the 2 groups had a marked amount of overlap: 115 (SD, 18) mg/dL for the IIT group and 144 (SD, 23) mg/dL for the control group. Unlike the situation in the Leuven studies, more than 70% of patients were given enteral feeding. One of the biggest critiques of NICE-SUGAR is the selection of a 90-day mortality outcome, especially because the median length of stay was 6 days in each group. However, SCCM has suggested that a 90-day mortality end point is preferred for sepsis and septic shock trials,<sup>33</sup> and that suggestion was the impetus for the NICE-SUGAR investigators to adopt this parameter as a primary outcome.

The most recent trial of IIT in septic shock is the Corticosteroid Treatment and Intensive Insulin Therapy for Septic Shock in Adults (COITSS) study.<sup>34</sup> In a multicenter, 2 × 2 factorial trial involving 509 patients, the investigators sought to evaluate (1) the benefit of oral fludrocortisone added to intravenous hydrocortisone and (2) IIT (80-110 mg/dL) vs CIT (180-200 mg/dL) in patients treated with corticosteroids for septic shock. The primary outcome (in-hospital mortality) was similar (relative risk,

1.07; 95% CI, 0.88-1.30;  $P = .50$ ) between the IIT group (45.9%) and the CIT group (42.9%). However, patients in the IIT group had significantly more episodes of hypoglycemia: a difference of 0.15 episodes per patient ( $P = .003$ ). The investigators<sup>34</sup> concluded that IIT did not improve mortality in patients treated with corticosteroids for septic shock but that it did increase the risk for hypoglycemia.

### Guideline Recommendations

Several US organizations have released statements about IIT in the ICU. The 2008 Surviving Sepsis Campaign<sup>35</sup> recommends a blood glucose level less than 150 mg/dL. Current SCCM/ASPEN guidelines<sup>30</sup> recommend a target blood glucose level of 110 to 150 mg/dL. In 2009, the ADA and the American Association of Clinical Endocrinologists released a joint statement recommending a blood glucose target of 140 to 180 mg/dL for most critically ill patients; this recommendation was carried forward into the 2010 ADA guidelines.<sup>34</sup> In contrast to earlier guidelines, current guidelines no longer recommend IIT.

### Discordant Findings

A primary question about ICU glycemic control is how multiple, large, randomized, controlled trials could have shown such markedly different results. On the most basic level, the studies have marked differences in study design, protocol, and patients. The features of the largest clinical trials are summarized in Table 2. Of note are the differences in Acute Physiology and Chronic Health Evaluation (APACHE II) scores between the 3 studies.<sup>13,14,32</sup> The mean

APACHE II score in Leuven I is significantly lower than the mean scores in the 2 other large studies. This finding may coincide with the higher mortality in NICE-SUGAR. IIT may be more detrimental in a higher risk population.

The SICU patients account for the minority of the participants in the published studies. In patients with a lower APACHE II score (eg, a young trauma patient), IIT may be beneficial, as in Leuven I. In the NICE-SUGAR subgroup of trauma patients, IIT tended to be beneficial.<sup>32</sup> Additionally, a meta-analysis of the literature, Griesdale et al<sup>36</sup> concluded that IIT may be beneficial in SICU patients (relative risk, 0.63; 95% CI, 0.44-0.91).

Nutrition was another difference between the 3 studies. Parenteral nutrition was used more often in Leuven I and II than in NICE-SUGAR. Additionally, the Leuven I protocol included 200 to 300 g of intravenous dextrose immediately postoperatively. These nutritional differences reflect different nutrition guidelines (European, American, Canadian, and Australian/New Zealand). Although all guidelines preferentially recommend enteral nutrition, differences exist about starting parenteral nutrition. The European Society of Parenteral and Enteral Nutrition<sup>37</sup> advocates initiating parenteral nutrition within 24 to 48 hours of ICU admission for patients not expected to receive full enteral feedings within 3 days. For previously healthy patients, SCCM/ASPEN guidelines<sup>30</sup> reserve parenteral nutrition for patients without nutritional support for more than 7 days and recommend early parenteral nutrition only for

**Table 2** Comparison of study characteristics<sup>a</sup>

Characteristic	Study				
	Leuven I <sup>3</sup>	Leuven II <sup>4</sup>	UISEP <sup>16</sup>	GLUCONTROL <sup>15</sup>	NICE-SUGAR <sup>32</sup>
No. of patients	1548	1200	537	1101	6104
Study population	Surgical ICU (>60% cardiac surgery)	Medical ICU	Medical ICU	Mixed ICU (60% surgical)	Mixed ICU (37% surgical)
Design	Single center	Single center	Multicenter	Multicenter	Multicenter
Age, mean, y	63	64	65	65	60
APACHE II score	9 (7-13) <sup>b</sup>	23 (9.5) <sup>c</sup>	20 (6.7) <sup>c</sup>	15 (11-21) <sup>b</sup>	21 (8) <sup>c</sup>
IIT BG target, mg/dL	80-110	80-110	80-110	80-110	81-108
CIT BG target, mg/dL	180-200	180-200	180-200	140-180	<180
Nutrition	Primarily parenteral; 200-300 g intravenous dextrose in first 24 hours after surgery	Primarily parenteral; patients taking anything by mouth at enrollment were excluded	Primarily enteral; >35% given enteral nutrition on day 1	Primarily enteral; twice as many calories via enteral route as via parenteral route	Primarily enteral; early enteral feeding stressed
Morning BG target attainment, mg/dL <sup>d</sup>	103 (19) vs 153 (33) <sup>c</sup>	111 (29) vs 153 (31) <sup>c</sup>	112 (15) vs 151 (26) <sup>c</sup>	110 (99-122) vs 39 (121-158) <sup>b</sup>	118 (25) vs 145 (26) <sup>c</sup>
Mortality, % <sup>d,e</sup>	4.6 vs 8.0 (P=.04)	24.2 vs 26.8 (P=.31)	24.7 vs 26.0 (P=.74)	17.2 vs 15.3 (P=.41)	27.5 vs 24.9 (P=.02)
BG ≤40 mg/dL, % <sup>d</sup>	5.1 vs 0.8 (P=NR)	18.7 vs 3.1 (P<.001)	17.0 vs 4.1 (P<.001)	8.7 vs 2.7 (P<.001)	6.8 vs 0.5 (P<.001)

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; BG, blood glucose; CIT, conventional insulin therapy; ICU, intensive care unit; IIT, intensive insulin therapy; NR, not reported; UISEP, Intensive Insulin Therapy and Pentastarch Resuscitation in Severe Sepsis.

<sup>a</sup> Values are reported for the entire study population. In some cases, these are approximations because the true values are not reported in the studies.

<sup>b</sup> Median (interquartile range).

<sup>c</sup> Mean (SD).

<sup>d</sup> Expressed as IIT vs CIT.

<sup>e</sup> Study primary outcome.

patients malnourished upon admission to the ICU. Because parenteral nutrition can result in serious complications (eg, catheter-related bloodstream infections, electrolyte derangements, hepatotoxic effects), the differences in parenteral nutrition may have influenced the outcomes.<sup>38</sup> Both the intravenous dextrose used in Leuven I and parenteral nutrition are iatrogenic sources of glucose and may have protected patients from hypoglycemia, a possible explanation for why hypoglycemia was not as apparent in Leuven I as in later trials.

Because both Leuven studies were done at a single medical center, the results from these 2 trials may

reflect idiosyncrasies in the specific patients or in the study center, limiting the external validity for other populations and centers.<sup>39,40</sup> Because of these questions of generalizability, SCCM has advocated multicentered trials before the adoption of new interventions in sepsis and septic shock.<sup>33</sup>

The Leuven I trial was stopped when an interim analysis indicated the superiority of IIT in SICU patients. The effect of stopping a trial early for benefit may tend to (1) overinflate the true results, (2) catch the treatment effect at a “random high,” and (3) lead to adoption of the results, exaggerating the true

therapeutic benefit.<sup>41</sup> In a meta-analysis,<sup>42</sup> compared with nontruncated trials, truncated trials were associated with exaggerated effect sizes. Many examples of this phenomenon exist.<sup>43-47</sup> One example of early stopping for benefit was the Recombinant human protein C Worldwide Evaluation in Severe Sepsis study,<sup>45</sup> in which researchers evaluated drotrecogin alfa in the treatment of septic shock. In the original trial, the absolute risk reduction with the use of drotrecogin alfa was 6.1%; however, a subgroup analysis<sup>46</sup> and another trial<sup>47</sup> indicated that use of the protein in some patients may be inappropriate



and that only patients with an APACHE II score of 25 or greater should be considered candidates for the drug.

### Future Directions

Recently, the issue of blood glucose variability has added a whole new dimension to ICU glycemic control. Studies<sup>48,49</sup> have shown that patients with wide shifts in blood glucose have a higher mortality rate than do patients with minimal glucose excursion. This finding suggests that the optimal glucose control may not depend solely on a specific blood glucose goal but may be more dependent on consistent maintenance within a range.

Another topic of debate is the most appropriate method for measuring blood glucose levels in the ICU, especially in patients who are receiving vasopressors or who have poor skin perfusion. Numerous researchers<sup>50,51</sup> have evaluated the differences between glucose values obtained by analyzing various blood sources and have shown a general disagreement between testing sources; however, no recommendation is available on the optimal method for evaluating a patient's true blood glucose level.

Trials of IIT in which different populations of patients are examined or in which closed-circuit, continuous blood glucose monitoring is used are ongoing.<sup>52-54</sup> Because ICU glycemic control has evolved rapidly, the results of these trials may be influential in the development of future glycemic goals.

### Conclusions

Although a specific, optimal numerical target for glycemic control

is still not known, the evidence suggests that tight control (80-110 mg/dL) does not confer any advantage and may lead to hypoglycemia and harm. Whereas NICE-SUGAR showed that mortality was lower when a blood glucose level less than 180 mg/dL was the target, reverting to previous practices of using only subcutaneous sliding-scale insulin for glucose control seems inappropriate. This practice often leads to blood glucose values greater than 180 mg/dL, which have also been linked to poor outcomes.

On the basis of the literature, both the goal of 110 to 150 mg/dL of the SCCM and the ASPEN and the goal of 140 to 180 mg/dL of the ADA and the American Association of Clinical Endocrinologists are reasonable treatment options. Patients should be optimally managed by using an algorithm-based approach to avoid dysglycemia and large shifts in blood glucose. If an algorithm-based approach and a higher target range are used, the number and severity of hypoglycemic episodes can be reduced and the potential mortality benefit associated with tighter glycemic control preserved, especially in vulnerable patients such as the elderly or patients with organ failure. **CC1**

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