Control of Blood Glucose in the ICU: Reconciling the Conflicting Data

Steven E. Nissen MD

Disclosure

Consulting: Many pharmaceutical companies

Clinical Trials: AbbVie, Amgen, Astra Zeneca, Esperion, Eli Lilly, Ethicon, Novartis, Novo Nordisk, and Pfizer.

Companies are directed to pay any honoraria, speaking or consulting fees directly to charity so that neither income nor a tax deduction is received.
Stress-Induced Hyperglycemia In Critical Illness

- Multiple studies showing worse outcomes for ICU patients with incident hyperglycemia (increased complications, length of stay and mortality).

- Worse outcomes have been demonstrated in trauma patients, other general medical and surgical patients admitted to ICUs.

- However, this observation does not prove that hyperglycemia is the cause or increased morbidity-mortality (may be marker of severity of illness).
## Trauma Patients Stratified by Glucose Level

<table>
<thead>
<tr>
<th>Variable</th>
<th>Glucose &lt; 200 mg/dL (n=748)</th>
<th>Glucose &gt; 200 mg/dL (n=225)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>43</td>
<td>45</td>
<td>NS</td>
</tr>
<tr>
<td>Injury severity</td>
<td>23±8</td>
<td>25±10</td>
<td>NS</td>
</tr>
<tr>
<td>Infection</td>
<td>32%</td>
<td>52%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ventilator days</td>
<td>11±11</td>
<td>13±12</td>
<td>0.02</td>
</tr>
<tr>
<td>ICU days</td>
<td>12±10</td>
<td>13.4±11</td>
<td>0.09</td>
</tr>
<tr>
<td>Hospital days</td>
<td>14.7±12</td>
<td>17.8±15</td>
<td>0.003</td>
</tr>
<tr>
<td>Mortality</td>
<td>12%</td>
<td>26%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

## Multivariable Linear Regression Analysis
Controlling for Age, Trauma Severity, Glucose

<table>
<thead>
<tr>
<th>Variable</th>
<th>Relative Risk</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital Length of Stay</td>
<td>5.9 (1.47-7.9)</td>
<td>0.009</td>
</tr>
<tr>
<td>ICU Length of Stay</td>
<td>6.9 (1.1-9.8)</td>
<td>0.02</td>
</tr>
<tr>
<td>Ventilator days</td>
<td>4.9 (1.1-7.6)</td>
<td>0.01</td>
</tr>
<tr>
<td>Infection</td>
<td>3.0 (1.3-6.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mortality</td>
<td>2.2 (1.4-3.4)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mean Blood Glucose</th>
<th>Mortality Rate (%)</th>
<th>Percent of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>80-99</td>
<td>9.6%</td>
<td>14.5%</td>
</tr>
<tr>
<td>100-119</td>
<td>12.2%</td>
<td>26.9%</td>
</tr>
<tr>
<td>120-139</td>
<td>15.1%</td>
<td>18.5%</td>
</tr>
<tr>
<td>140-159</td>
<td>18.8%</td>
<td>11.1%</td>
</tr>
<tr>
<td>160-179</td>
<td>28.4%</td>
<td>7.7%</td>
</tr>
<tr>
<td>180-199</td>
<td>29.4%</td>
<td>5.6%</td>
</tr>
<tr>
<td>200-249</td>
<td>37.5%</td>
<td>7.9%</td>
</tr>
<tr>
<td>250-299</td>
<td>32.9%</td>
<td>3.8%</td>
</tr>
<tr>
<td>&gt;300</td>
<td>42.5%</td>
<td>2.2%</td>
</tr>
</tbody>
</table>


*Medical and surgical patients
Hospital Mortality Rate and Mean Glucose (n=1826)

Medical and surgical ICU patients

Mortality, %


Mean ICU glucose, mg/dL

Mortality across different mean ICU glucose levels is shown. The highest mortality is observed in patients with mean glucose levels of ≥300 mg/dL, with a mortality rate of 42.5%. This trend continues with increasing mean glucose levels, indicating a significant correlation between higher glucose levels and increased mortality in ICU patients.
Mortality Rate and Diabetes Status (n=2030)

New hyperglycemia greater risk than known diabetes

J Clin Endocrinol Metab. 2002;87(3):978–982.
Admission Glucose in Critically Ill Children

PiCU Mortality

**P<0.01

Stress-Induced Hyperglycemia in Critical Illness

- Largely occurs in non-diabetic patients
- Origins include increased cortisol, catecholamines, glucagon, growth hormone, gluconeogenesis, and glycogenolysis
- Insulin resistance plays a key role (demonstrated in more than 80 percent of critically ill patients).
- Prior to 2001, considered an adaptive response in non-diabetic patients essential to survival and generally not treated
A long, long time ago

in a galaxy far far away
INTENSIVE INSULIN THERAPY IN CRITICALLY ILL PATIENTS

GREET VAN DEN BERGHE, M.D., PH.D., PIETER WOUTERS, M.SC., FRANK WEEKERS, M.D., CHARLES VERWAEST, M.D., FRANS BRUYNINCKX, M.D., MIET SCETZ, M.D., PH.D., DIRK VLAASLEAERS, M.D., PATRICK FERDINANDE, M.D., PH.D., PETER LAUWERS, M.D., AND ROGER BOUILLON, M.D., PH.D.

ABSTRACT

Background  Hyperglycemia and insulin resistance are common in critically ill patients, even if they have not previously had diabetes. Whether the normalization of blood glucose levels with insulin therapy improves the prognosis for such patients is not known.

Methods  We performed a prospective, randomized, controlled study involving adults admitted to our surgical intensive care unit who were receiving mechanical ventilation. On admission, patients were randomly

CRITICALLY ill patients who require intensive care for more than five days have a 20 percent risk of death and substantial morbidity. Critical-illness polyneuropathy and skeletal-muscle wasting prolong the need for mechanical ventilation. Moreover, increased susceptibility to severe infections and failure of vital organs amplify the risk of an adverse outcome.

Hyperglycemia associated with insulin resistance
Study Design

• Unblinded, randomized controlled single center (Leuven) trial of 1548 patients in a surgical ICU

• Included only patients requiring mechanical ventilation

• Hyperglycemia treated with insulin infusion:

  – Intensive group targeted a blood glucose of 80-110 mg/dL.

  – Conventional group targeted a blood glucose of 180-200 mg dL with insulin administered only for glucose >215 mg/dL
## Insulin Therapy and Control of Blood Glucose

<table>
<thead>
<tr>
<th>Variable</th>
<th>Conventional</th>
<th>Intensive</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin use</td>
<td>39.2%</td>
<td>98.7%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean daily dose</td>
<td>33 units</td>
<td>71 units</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Percent of ICU stay using insulin</td>
<td>67%</td>
<td>100%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Morning FBG</td>
<td>153 mg/dL</td>
<td>103 mg/dL</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Effect of Intensive Glucose Control in ICU

ICU Survival

- Intensive treatment
- Conventional treatment

8.0% vs. 4.6%
P=0.04

Hospital Survival

- Intensive treatment
- Conventional treatment

10.9% vs. 7.2%
P=0.01

Hypoglycemia (defined as a blood glucose <40 mg/dL) occurred in just **39 patients** in the intensive-treatment group and **6 patients** in the conventional-treatment group.
Authors Conclusions

• “The use of exogenous insulin to maintain blood glucose at a level no higher than 110 mg per deciliter reduced morbidity and mortality among critically ill patients in the surgical intensive care unit, regardless of whether they had a history of diabetes.”
What about Medical ICU Patients?
Intensive insulin therapy reduces morbidity and mortality in patients in surgical intensive care units (ICUs), but its role in patients in medical ICUs is unknown.

METHODS
In a prospective, randomized, controlled study of adult patients admitted to our medical ICU, we studied patients who were considered to need intensive care for at least three days. On admission, patients were randomly assigned to strict normalization of blood glucose levels (80 to 110 mg per deciliter [4.4 to 6.1 mmol per liter]) with the use of insulin infusion or to conventional therapy (insulin administered when the blood glucose level exceeded 215 mg per deciliter [12 mmol per liter], with

From the Departments of Intensive Care Medicine (G.V.B., P.J.W., I.M.) and Medical Intensive Care Medicine (A.W., G.H., W.M., E.V.W., H.B.) and the Laboratory for Experimental Medicine and Endocrinology (R.B.), Catholic University of Leuven, Leuven, Belgium. Address reprint requests to Dr. Van den Berghe at the Department of Intensive Care Medicine, Catholic University of Leuven, B-3000 Leuven, Belgium, or at greta.vandenberghe@med.kuleuven.be.
Study Design

- Unblinded, randomized controlled single center (Leuven) trial of 1200 patients in a medical ICU
- Only included patients requiring an ICU stay greater than 3 days.
- Conventional group targeted a blood glucose of 180-200 mg/dL with insulin infusion administered only for glucose >215 mg/dL
- Intensive group received insulin infusion for blood glucose >100 mg/dL and targeted a blood glucose of 80-110 mg/dL

Medical ICU Patients: Control of Blood Glucose

Primary Endpoint: In-Hospital Survival

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All randomized patients (N=1200)

Patients with ICU stay > 3 days (N=767)

P=0.40

P=0.02

Landmark Analysis: 30 Day Survival

All randomized patients (N=1200)  
Patients with ICU stay > 3 days (N=767)

Weaning from Mechanical Ventilation

\[ P = 0.03 \]

Cumulative Hazard

Intensive treatment

Conventional treatment

Days

Time to Discharge from the ICU

![Graph showing the comparison between intensive treatment and conventional treatment on the time to discharge from the ICU. The graph indicates a statistically significant difference (P=0.04) with intensive treatment leading to earlier discharge.](image_url)
Time to Discharge from the Hospital

## Comparative Rates of Hypoglycemia

<table>
<thead>
<tr>
<th>Hypoglycemia</th>
<th>Conventional</th>
<th>Intensive</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall incidence</td>
<td>3.1%</td>
<td>18.7%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Patients experiencing 2 or more episodes</td>
<td>0.8%</td>
<td>3.9%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Blood glucose during episodes</td>
<td>31±8</td>
<td>32±5</td>
<td>NS</td>
</tr>
<tr>
<td>Incidence in patients with long ICU stay</td>
<td>3.9%</td>
<td>25.1%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Limitations of the Two Leuven Studies

• Both the surgical and medical ICU studies were single center reducing generalizability.

• By necessity, both were unblinded potentially resulting in biases.

• Both studies were underpowered (acknowledged by the authors) resulting in wide confidence intervals.

• The “favorable” effects on morbidity were secondary endpoints with “significant” findings just barely below the threshold for statistically significance.
A large, carefully performed randomized controlled trial needed to answer the critical question of appropriate glucose targets for critically ill patients.
Eligibility:
Patients expected to require treatment in the ICU for 3 or more consecutive days

N=6104

Intensive control group
(target BG: 81-108 mg/dL)

n=3054

Conventional control group
(target BG: ≤180 mg/dL)

n=3050

• Multicenter, open-label, randomized, controlled trial
• Primary Endpoint: 90-day all-cause mortality
• 42 Centers in Australia, New Zealand, and Canada

## NICE-SUGAR: Insulin Therapy and Glucose

<table>
<thead>
<tr>
<th>Variable</th>
<th>Conventional</th>
<th>Intensive</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin use</td>
<td>69.0%</td>
<td>97.2%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean daily dose</td>
<td>16.9 units</td>
<td>50.0 units</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Morning FBG</td>
<td>145 mg/dL</td>
<td>118 mg/dL</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Time-weighted glucose</td>
<td>144 mg/dL</td>
<td>115 mg/dL</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypoglycemia (glucose &lt; 40 mg/dL)</td>
<td>0.5%</td>
<td>6.8%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

NICE-SUGAR: Primary Endpoint 90 Day Mortality

Odds ratio = 1.14
95% CI - 1.02 to 1.28
P = 0.02

Conventional glucose control
Mortality 27.5%

Intensive glucose control
Mortality 24.9%

# NICE-SUGAR Study: Other Outcomes

<table>
<thead>
<tr>
<th>Outcome Measure</th>
<th>Intensive Control Group</th>
<th>Conventional Control Group</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>28-Day mortality</td>
<td>22.3%</td>
<td>20.8%</td>
<td>.17</td>
</tr>
<tr>
<td>90-Day mortality</td>
<td>27.5%</td>
<td>24.9%</td>
<td>.02</td>
</tr>
<tr>
<td>Dialysis</td>
<td>15.4%</td>
<td>14.5%</td>
<td>.34</td>
</tr>
<tr>
<td>Bloodstream infections</td>
<td>12.8%</td>
<td>12.4%</td>
<td>.57</td>
</tr>
</tbody>
</table>

NICE-SUGAR Study: Conclusions

• Intensive glucose control did not offer benefits to critically ill patients.

• Glucose target <180 mg/dL (144 mg/dL achieved) resulted in lower 90-day mortality than 81-108 mg/dL.

• Increased hypoglycemic events observed with lower glucose targets.

• ADA and AACE position: “Good glucose management, through establishing patient-specific glycemic targets and individualizing care, are important objectives for patients in the hospital setting.”

Use of Intensive Insulin Therapy for the Management of Glycemic Control in Hospitalized Patients: A Clinical Practice Guideline From the American College of Physicians

Amir Qaseem, MD, PhD, MHA; Linda L. Humphrey, MD, MPH; Roger Chou, MD; Vincenza Snow, MD; and Paul Shekelle, MD, PhD, for the Clinical Guidelines Committee of the American College of Physicians*

Description: The American College of Physicians (ACP) developed this guideline to present the evidence for the link between the use of intensive insulin therapy to achieve different glycemic targets and health outcomes in hospitalized patients with or without diabetes mellitus.

Methods: Published literature on this topic was identified by using MEDLINE and the Cochrane Library. Additional articles were obtained from systematic reviews and the reference lists of pertinent studies, reviews, and editorials, as well as by consulting experts; unpublished studies on ClinicalTrials.gov were also identified. The literature search included studies published from 1950 through March 2009. Searches were limited to English-language publications. The primary outcomes of interest were short-term mortality and hypoglycemia. This guideline grades the evidence and recommendations by using the ACP clinical practice guidelines grading system.

Recommendation 1: ACP recommends not using intensive insulin therapy to strictly control blood glucose in non-surgical intensive care unit (SICU)/medical intensive care unit (MICU) patients with or without diabetes mellitus (Grade: strong recommendation, moderate-quality evidence).

Recommendation 2: ACP recommends not using intensive insulin therapy to normalize blood glucose in SICU/MICU patients with or without diabetes mellitus (Grade: strong recommendation, high-quality evidence).

Recommendation 3: ACP recommends a target blood glucose level of 7.8 to 11.1 mmol/L (140 to 200 mg/dL) if insulin therapy is used in SICU/MICU patients (Grade: weak recommendation, moderate-quality evidence).

Ann Intern Med. 2011;154:260-267. For author affiliations, see end of text.
American College of Physicians 2011 Guideline

- ACP recommends not using intensive insulin therapy to strictly control blood glucose in non-SICU or non-MICU patients with or without diabetes.

- ACP recommends not using intensive insulin therapy to normalize blood glucose in SICU or MICU patients with or without diabetes.

- ACP recommends a target blood glucose level of 140 to 200 mg if insulin therapy is used in SICU or MICU patients.
## Randomized Controlled Trials of Intensive Glucose Management in Critical Care Showing No Benefit

<table>
<thead>
<tr>
<th>Trial</th>
<th>N</th>
<th>Setting</th>
<th>Blood Glucose* Target</th>
<th>Primary Outcome</th>
<th>RRR†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Van den Berghe 2006¹</td>
<td>1200</td>
<td>MICU</td>
<td>80-110</td>
<td>180-200</td>
<td>7.0%¶</td>
</tr>
<tr>
<td>Glucontrol 2007²</td>
<td>1101</td>
<td>ICU</td>
<td>80-110</td>
<td>140-180</td>
<td>-10%¶</td>
</tr>
<tr>
<td>Gandhi 2007³</td>
<td>399</td>
<td>Operating Room</td>
<td>80-110</td>
<td>&lt;200</td>
<td>4.3%¶</td>
</tr>
<tr>
<td>VISEP 2008⁴</td>
<td>537</td>
<td>ICU</td>
<td>80-110</td>
<td>180-200</td>
<td>5.0%‡¶</td>
</tr>
<tr>
<td>De La Rosa 2008⁵</td>
<td>504</td>
<td>SICU/MICU</td>
<td>80-110</td>
<td>180-200</td>
<td>-13%¶</td>
</tr>
<tr>
<td>NICE-SUGAR 2009⁶</td>
<td>6104</td>
<td>ICU</td>
<td>81-108</td>
<td>≤180</td>
<td>-10.6§</td>
</tr>
</tbody>
</table>

*Blood glucose in mg/dL; †RRR=Relative risk reduction, intensive group vs conventional group; ‡Personal communication;
Dr. Frank Brunkhorst; § P<.05; ¶Not significant (P>.05).

Recommendations for ICU Glycemic Control

• Treat most patients with critical illness and hyperglycemia (glucose >180 mg/dL) with insulin infusions

• Target a blood glucose of 140-180 mg/dL avoiding levels <140 or >180 mg/dL

• Strictly avoid long acting insulins such as glargine which have catastrophic complications in the ICU

• Future research: Can a closed loop system achieve better outcomes by allowing more stable glucose control?
INTENSIVE INSULIN THERAPY IN CRITICALLY ILL PATIENTS

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Background  Hyperglycemia and insulin resistance are common in critically ill patients, even if they have not previously had diabetes. Whether the normalization of blood glucose levels with insulin therapy improves the prognosis for such patients is not known.

Methods  We performed a prospective, randomized, controlled study involving adults admitted to our surgical intensive care unit who were receiving mechanical ventilation. On admission, patients were randomly assigned to receive intensive insulin therapy (maintenance of blood glucose at a level between 80 and 110 mg per deciliter) or conventional treatment (insulin

CRITICALLY ill patients who require intensive care for more than five days have a 20 percent risk of death and substantial morbidity. Critical-illness polyneuropathy and skeletal-muscle wasting prolong the need for mechanical ventilation. Moreover, increased susceptibility to severe infections and failure of vital organs amplify the risk of an adverse outcome.

Hyperglycemia associated with insulin resistance is common in critically ill patients, even those who have not previously had diabetes. It has been reported that pronounced hyperglycemia may lead to com-
Intensive Insulin Therapy in the Medical ICU

Greet Van den Berghe, M.D., Ph.D., Alexander Wilmer, M.D., Ph.D., Greet Hermans, M.D., Wouter Meersseman, M.D., Pieter J. Wouters, M.Sc., Ilse Milants, R.N., Eric Van Wijngaerden, M.D., Ph.D., Herman Bobbaers, M.D., Ph.D., and Roger Bouillon, M.D., Ph.D.

ABSTRACT

BACKGROUND
Intensive insulin therapy reduces morbidity and mortality in patients in surgical intensive care units (ICUs), but its role in patients in medical ICUs is unknown.

METHODS
In a prospective, randomized, controlled study of adult patients admitted to our medical ICU, we studied patients who were considered to need intensive care for at least three days. On admission, patients were randomly assigned to strict normalization of blood glucose levels (80 to 110 mg per deciliter [4.4 to 6.1 mmol per liter])...
Intensive versus Conventional Glucose Control in Critically Ill Patients

The NICE-SUGAR Study Investigators*

ABSTRACT

BACKGROUND
The optimal target range for blood glucose in critically ill patients remains unclear.

METHODS
Within 24 hours after admission to an intensive care unit (ICU), adults who were expected to require treatment in the ICU on 3 or more consecutive days were randomly assigned to undergo either intensive glucose control, with a target blood glucose range of 81 to 108 mg per deciliter (4.5 to 6.0 mmol per liter), or conventional glucose control, with a target of 180 mg or less per deciliter (10.0 mmol or less per liter). We defined the primary end point as death from any cause within 90
Standards of Medical Care in Diabetes—2012

Diabetes mellitus is a chronic illness that requires continuing medical care and ongoing patient self-management education and support to prevent acute complications and to reduce the risk of long-term complications. Diabetes care is complex and requires that many issues, beyond glycemic control, be addressed. A large body of evidence exists that supports a range of interventions to improve diabetes outcomes.

These standards of care are intended to provide clinicians, patients, researchers, payers, and other interested individuals with the components of diabetes care, general treatment goals, and tools to evaluate the quality of care. While individual preferences, comorbidities, and other patient factors may require modification of goals, targets that are desirable for most patients with diabetes are provided. Specifically titled sections of the standards address children with diabetes, pregnant women, and people with prediabetes. These new evidence. For the current revision, committee members systematically searched Medline for human studies related to each subsection and published since 1 January 2010. Recommendations (bulleted at the beginning of each subsection and also listed in the “Executive Summary: Standards of Medical Care in Diabetes—2012”) were revised based on new evidence or, in some cases, to clarify the prior recommendation or match the strength of the wording to the strength of the evidence. A table linking the changes in recommendations to new evidence can be reviewed at http://professional.diabetes.org/CPSR_Search.aspx. Subsequently, as is the case for all Position Statements, the standards of care were reviewed and approved by the Executive Committee of ADA’s Board of Directors, which includes health care professionals, scientists, and lay people.

Feedback from the larger clinical community was valuable for the 2012 revision of the standards. Readers who wish to

- Type 1 diabetes (results from β-cell destruction, usually leading to absolute insulin deficiency)
- Type 2 diabetes (results from a progressive insulin secretory defect on the background of insulin resistance)
- Other specific types of diabetes due to other causes, e.g., genetic defects in β-cell function, genetic defects in insulin action, diseases of the exocrine pancreas (such as cystic fibrosis), and drug- or chemical-induced (such as in the treatment of HIV/AIDS or after organ transplantation)
- Gestational diabetes mellitus (GDM) (diabetes diagnosed during pregnancy that is not clearly overt diabetes)

Some patients cannot be clearly classified as having type 1 or type 2 diabetes. Clinical presentation and disease progression vary considerably in both types of diabetes. Occasionally, patients who otherwise have type 2 diabetes may present with ketoacidosis. Similarly, patients with