Objective:

a. Describe the physiological basis for hyperglycemia in the critically ill patient
b. List adverse outcomes associated with both hyperglycemia and hypoglycemia
c. Summarize how management of hyperglycemia in the intensive care unit has evolved over the last decade based on the available literature
d. Identify the appropriate level of glycemic control in the intensive care unit
I. Introduction

A. Hyperglycemia is a common finding amongst critically ill patients\textsuperscript{1,2}

i. True incidence of hyperglycemia in the hospitalized setting is unknown\textsuperscript{1}

   a. Incidence in the intensive care unit is much higher when compared to the general medicine population
   b. May be as high as 50% in adult critically ill patients\textsuperscript{3}

ii. Not all critically ill patients who develop hyperglycemia are diabetic\textsuperscript{3}

B. While increases in blood glucose represent a normal stress response, hyperglycemia has been associated with numerous adverse outcomes\textsuperscript{4}

i. Increased mortality in multiple disease states\textsuperscript{5-9}

ii. Increased risk of infections\textsuperscript{4,10,11}

iii. Prolonged duration of mechanical ventilation\textsuperscript{11,12}

C. Despite nearly a decade of research, the optimal level of glucose control in the critically ill is still a controversial topic

II. Definitions

A. Hospital-related hyperglycemia\textsuperscript{1,2}

   i. Fasting blood glucose $\geq 126$ mg/dL
   ii. Random blood glucose $\geq 200$ mg/dL
   iii. Occurs during hospitalization and reverts to normal after discharge

B. Hypoglycemia\textsuperscript{1,2,14}

   i. Severe

      a. $\leq 40$ mg/dL regardless of presence of symptoms
      b. $\leq 50$ mg/dL with symptoms of hypoglycemia

   ii. Mild

      a. $> 40$ but $< 60$ mg/dL
      b. Typically asymptomatic

III. Pathophysiology

A. Risk factors for development of hyperglycemia\textsuperscript{2,3}

   i. Preexisting diabetes
   ii. Infection
   iii. Sepsis/shock
   iv. Trauma
   v. Medications
   vi. Total parenteral nutrition

B. Stress-induced hyperglycemia\textsuperscript{3,4}

   i. “Fight or flight” response

   ii. Release of hormones during stressful situations (see table 1)

      a. Induction of skeletal muscle insulin resistance
      b. Increase in gluconeogenesis
      c. Increase in glycogenolysis
iii. Results in increased glucose in circulation (i.e., hyperglycemia)

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Hormone</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Epinephrine</td>
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<tr>
<td>Induces skeletal muscle insulin resistance</td>
<td>✓</td>
</tr>
<tr>
<td>Increases gluconeogenesis</td>
<td>✓</td>
</tr>
<tr>
<td>Increases glycogenolysis</td>
<td>✓</td>
</tr>
<tr>
<td>Increases lipolysis</td>
<td></td>
</tr>
<tr>
<td>Increases glucagon release</td>
<td></td>
</tr>
<tr>
<td>Direct β-cell suppression of insulin secretion</td>
<td>✓</td>
</tr>
</tbody>
</table>

iv. Hyperglycemia ensures the central nervous system is perfused with an adequate supply of glucose\(^3,4\)

   a. Astrocytes store energy in the form of glycogen
      1. Glycogen rapidly converted to glucose
   b. Astrocytes only store a few minutes’ supply of glycogen
   c. Brain dependent on a continuous supply of glucose
   d. Peripheral insulin resistance, coupled with increased gluconeogenesis and glycogenolysis, ensures an adequate supply of carbohydrates for glucose-dependent, insulin-insensitive cells of the brain

C. Pathophysiological pathways of hyperglycemia (Figure 1)

   i. Stress-response hormones increase glucose and decrease insulin sensitivity
   ii. Immune dysfunction
      a. Overall state of immunosuppression\(^1,10,11\)
         1. Hyperglycemia linked to phagocyte dysfunction
            a. Reduced adherence, chemotaxis, phagocytosis, and intracellular superoxide production
         2. Transient elevations in glucose reduce lymphocytes
b. Abundance of a food source leads to microorganism overgrowth

iii. Lipolysis and anaerobic respiration\(^1,4\)
   a. Insulin-sensitive tissues (e.g., skeletal muscle) suffer during stress-induced hyperglycemia
   b. Tissues in the periphery must utilize lipid-based energy sources or convert to anaerobic metabolism
   c. Leads to increased free fatty acids and lactic acidosis
   d. Production of free fatty acids may result in production of reactive oxygen species

iv. Increased production of reactive oxygen species (ROS)\(^1,3\)
   a. ROS have potential to cause direct cellular damage
      1. Apoptosis
      2. DNA/RNA damage
      3. Protein denaturation
   b. Cells exposed to a hyperglycemic environment \textit{in vitro} switch from nitric oxide production to ROS
   c. In addition to direct cellular damage, ROS generation causes activation of transcriptional factors and inflammatory mediators (e.g., TNF)

v. Physiological outcomes of stress-induced hyperglycemia\(^1,5\)
   a. Inflammation
   b. Cellular damage
   c. Ischemia/necrosis
   d. Acidosis
Figure 1. Pathophysiologic consequences of hyperglycemia

D. Pathophysiology of hypoglycemia
   i. Brain stores only limited supply of glucose in the form of glycogen
   ii. During hypoglycemia, the central nervous system (CNS) is the first system affected
   iii. Deprivation of glucose to the cells in the CNS results in anaerobic metabolism and ROS creation
      a. Ultimately results in cell death and tissue damage
   iv. Areas of cell death and ischemia may become foci for seizure activity
   v. If left untreated, will result in coma or brain death

IV. Adverse Effects Associated with Hyperglycemia

A. Increased mortality
   i. Burns
a. 7-fold increased risk of death observed in pediatric burn patients with $\geq 40\%$ of blood glucose levels $> 140$ mg/dL.$^5$

ii. Stroke
a. Animal models demonstrate hyperglycemia increases risk of cerebral edema, blood-brain barrier injury, and hemorrhagic transformation of infarct.$^6$
   b. Blood glucose $> 144$ mg/dL served as an independent predictor for poor outcomes and shorter survival.$^7$

iii. Myocardial infarction
a. Oxidative stress and superoxide free radical formation increase area of infarct.$^8$
   b. Capes et al. performed a systematic review which indicated a blood glucose $> 144$ mg/dL increases mortality 3.9-fold.$^8$

iv. Head trauma
a. Rovlias and Kotsou studied 267 patients with severe head trauma treated surgically for evacuation of an intracranial hematoma.$^9$
   1. Admission or post-operative blood glucose $> 200$ mg/dL was predictive of a poor outcome (persistent vegetative state or death)

B. Higher rate of infection$^{4,10,11}$
   i. Increased incidence of pulmonary, urinary tract, and deep wound infections in post-surgical patients with blood glucose levels $> 200$ mg/dL

C. Critical Illness Neuromuscular Abnormalities (CINMA)$^{12,13}$
   i. First described in critically ill patients who could not be weaned from mechanical ventilation
   ii. Weakened limb and respiratory muscles prolong the need for mechanical ventilation and extend hospitalization
      a. Hyperglycemia may promote formation of reactive oxygen species which, in turn, exert toxic effects on neurons
   iii. Stevens et al. conducted a systematic review of literature which evaluated intensive care patients for CINMA$^{13}$
      a. 46% of patients in the included studies had CINMA diagnosed by either clinical status or diagnostic techniques
      b. Predictors for CINMA included systemic inflammatory response syndrome/sepsis, hyperglycemia, catecholamine administration, and multiple organ failure

V. Adverse Effects Associated with Hypoglycemia

A. Neurological$^{14,15}$
   i. Symptoms are difficult to assess in critically ill patients$^{14,15}$
      a. Diaphoresis, agitation, and confusion
      b. Concomitant use of sedatives, analgesics, and/or neuroleptics may mask symptoms
   ii. Seizures and coma

B. Mortality
i. Brain death
ii. Single episode of hypoglycemia serves as a predictor for increased mortality\textsuperscript{16}
   a. 55.9% mortality among patients with at least one episode of severe hypoglycemia
   b. 39.5% mortality among control cohort
   c. Odds ratio 2.28; 95% CI, 1.41 – 3.70; P = 0.0008

VI. Background Literature in Diabetic Patients

A. Diabetes Mellitus Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI)\textsuperscript{17}
   i. Evaluated 602 patients with suspected acute myocardial infarction within the prior 24 hours who either had known diabetes or a blood glucose of $\geq$ 198 mg/dL on admission
   ii. Patients were randomized to either intensive insulin or standard- of-care
      a. Intensive treatment based on a coronary care insulin infusion protocol to maintain blood glucose between 126 and 196 mg/dL
      b. After at least 24 hours of intravenous insulin, subcutaneous insulin was initiated and continued for at least 3 months
      c. Standard-of-care patients received insulin only when treatment was deemed clinically necessary
   iii. Patients were followed for a mean of 344 days
      a. Reductions in blood glucose were significantly greater in the intensive group during hospitalization
      b. HbA1c was significantly lower in the intensive group at both 3 months and 1 year after randomization
      c. Length of stay was significantly longer in the intensive group compared to the control group (11.3 days vs. 9.5 days; P = 0.043)
      d. Mortality was significantly lower at 1 year
         1. In-hospital mortality: 11.1% vs. 9.1% (P >0.05)
         2. 3 months: 15.6% vs. 12.4% (P>0.05)
         3. 1 year: 26.1% vs. 18.6% (P = 0.0273)
      e. Hypoglycemia
         1. 15% of patients in intensive group experienced hypoglycemia during hospitalization
         2. Resulted in the discontinuation of subcutaneous insulin in 10% of patients
         3. No events of hypoglycemia in the control group
   iv. Authors’ conclusions
      a. Intensive insulin-glucose infusion with subsequent subcutaneous insulin resulted in significantly decreased 1 year mortality
      b. Intensive control resulted in more episodes of hypoglycemia, but these episodes did not result in any adverse effects
B. United Kingdom Prospective Diabetes Study (UKPDS) 33\textsuperscript{18}
  i. Compared the effects of intensive blood glucose control vs. conventional treatment on micro- and macrovascular complications of type 2 diabetes
  ii. Randomized 3867 newly diagnosed type 2 diabetic patients to receive either intensive therapy (metformin, sulfonylurea or insulin) or conventional therapy (diet)
    a. Intensive goal: fasting plasma glucose < 108 mg/dL
    b. Conventional goal: best achievable fasting glucose with diet alone; drug therapy initiated if symptoms of hyperglycemia or fasting glucose > 270 mg/dL
  iii. Patients were followed for 10 years
    a. HbA1c was reduced with intensive therapy (7% vs. 7.9%)
    b. Diabetes-related endpoints were reduced by 12% (p = 0.029)
      1. Mostly driven by a reduction in microvascular events
    c. Non-statistically significant reductions in diabetes-related and all-cause mortality
    d. Hypoglycemic events significantly greater in intensive group
      1. 36.5% in intensive group vs. 1.2% in conventional
  iv. Authors’ conclusion
    a. Intensive control reduced the risk of microvascular, but not macrovascular, diabetes-related events

C. Summary of background literature in diabetic patients
  i. Intensive glucose control in diabetic patients resulted in reduced mortality post-myocardial infarction and reduced diabetic microvascular complications
  ii. Hypoglycemia was observed more often with intensive control
  iii. Coupled with adverse events associated with hyperglycemia, literature in diabetic patients provides the rationale for evaluation of intensive glucose control in critically ill patients

VII. Glycemic Control in Critically Ill Patients

A. Van den Berghe I – Surgical ICU\textsuperscript{19}

<table>
<thead>
<tr>
<th>Objective</th>
<th>Intensive Insulin Therapy (IIT)</th>
<th>Conventional Insulin Therapy (CIT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design</td>
<td>To assess whether the normalization of blood glucose levels with insulin therapy improves morbidity and mortality compared to conventional blood glucose control</td>
<td></td>
</tr>
<tr>
<td>Population</td>
<td>Single-center (Leuven, Belgium) surgical ICU; Prospective, randomized, controlled</td>
<td></td>
</tr>
<tr>
<td>Methods</td>
<td>All adult patients admitted between February 2000 – January 2001</td>
<td></td>
</tr>
<tr>
<td>Laboratory</td>
<td>Blood glucose assessed at bedside q4 hours and qAM with daily labs</td>
<td></td>
</tr>
<tr>
<td>Glucose goal (mg/dL)</td>
<td>80 – 110</td>
<td>180 – 200</td>
</tr>
<tr>
<td>Insulin initiated (mg/dL)</td>
<td>&gt; 110</td>
<td>&gt; 215</td>
</tr>
<tr>
<td>ICU discharge</td>
<td>All patients converted to CIT once discharged from ICU</td>
<td></td>
</tr>
<tr>
<td>Outcomes</td>
<td>Primary: ICU all-cause mortality</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Secondary: In-hospital mortality, length of ICU stay, prolonged duration of mechanical ventilation, critical-</td>
<td></td>
</tr>
</tbody>
</table>
Glycemic Control in the ICU

illness neuromuscular abnormalities, need for dialysis, and bacteremia during ICU stay

Statistics

- Planned enrollment of 2500 patients
- 3 month planned interim analyses for prematurely stopping study (Two-sided alpha < 0.01)
- Analyzed on intention to treat basis (Adjusted with Lan-Demets method for multiple t-tests)

Results

- N = 1548
- Study stopped prematurely (after fourth interim analysis)

<table>
<thead>
<tr>
<th></th>
<th>IIT (n=765)</th>
<th>CIT (n=783)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLYCEMIC CONTROL</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Mean morning glucose (mg/dL)</td>
<td>103 ± 19</td>
<td>153 ± 33</td>
<td></td>
</tr>
<tr>
<td>Severe hypoglycemia</td>
<td>39 (5.1%)</td>
<td>6 (0.77%)</td>
<td></td>
</tr>
<tr>
<td>MORTALITY</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICU (Primary Endpoint)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intent-to-treat (adjusted)</td>
<td>35 (4.6%)</td>
<td>63 (8.0%)</td>
<td>&lt; 0.04</td>
</tr>
<tr>
<td>Patients in ICU ≤ 5 days</td>
<td>13 (1.7%)</td>
<td>14 (1.8%)</td>
<td>0.9</td>
</tr>
<tr>
<td>Patients in ICU &gt; 5 days</td>
<td>22/208 (10.6%)</td>
<td>49/243 (20.2%)</td>
<td>0.005</td>
</tr>
<tr>
<td>In-Hospital</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intent-to-treat</td>
<td>55 (7.2%)</td>
<td>85 (10.9%)</td>
<td>0.01</td>
</tr>
<tr>
<td>MORBIDITY</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median ICU stay (days)</td>
<td>3 (2-6)</td>
<td>3 (2-9)</td>
<td>0.2</td>
</tr>
<tr>
<td>ICU stay &gt; 14 days</td>
<td>87 (11.4%)</td>
<td>123 (15.7%)</td>
<td>0.01</td>
</tr>
<tr>
<td>Mechanical Ventilation &gt; 14 days</td>
<td>57 (7.5%)</td>
<td>93 (11.9%)</td>
<td>0.003</td>
</tr>
<tr>
<td>CINMA</td>
<td>45/157 (28.7%)</td>
<td>107/206 (51.9%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Dialysis</td>
<td>37 (4.8%)</td>
<td>64 (8.2%)</td>
<td>0.007</td>
</tr>
<tr>
<td>Bacteremia during ICU stay</td>
<td>32 (4.2%)</td>
<td>61 (7.8%)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Authors’ Conclusions

- IIT reduced mortality and morbidity when compared to CIT in critically ill surgical patients
- Benefits of IIT were attributed to patients who required > 5 days of ICU care

Critiques

- Nutrition
  - First 24 hours – all patients received 200-300 grams IV glucose
  - No breakdown of TPN vs. TPN + enteral vs. enteral nutrition
  - Single-center – regional differences may diminish generalizability
  - Higher rates of hypoglycemia with IIT
  - Since treatment was not blinded, were effects related to increased care?
  - Does stopping the trial early artificially inflate the benefits?

B. Effect of an Intensive Glucose Management Protocol on the Mortality of Critically Ill Adult Patients

i. Compared outcomes before (retrospective) and after (prospective) initiation of an intensive insulin protocol
   a. 800 patients in each arm
   b. Single-center (Stamford Hospital), mixed medical/surgical ICU

ii. Study protocol
   a. Goal blood glucose < 140 mg/dL
   b. Intermittent subcutaneous insulin utilized unless 2 consecutive blood glucose measurements exceeded 200 mg/dL
      1. If 2 consecutive exceeded 200 mg/dL, an insulin infusion was initiated
c. Protocol dictates how much insulin to administer based on patient’s blood glucose level

iii. Results
   a. Blood glucose levels significantly reduced (P < 0.001)
      1. 152.3 ± 93.4 mg/dL (retro.) vs. 130.7 ± 55.1 mg/dL (pro.)
      2. 56.3% decrease in blood glucose values > 200 mg/dL
   b. Rates of hypoglycemia low
      1. Severe: 0.34% (retro.) vs. 0.35% (pro.); P = 0.89
      2. Mild: 0.54% vs. 1.02%; P = 0.02
   c. Hospital mortality
      1. 20.9% (retro.) vs. 14.8% (pro.); P = 0.002
      2. Most noticeable reductions in patients with sepsis or neurological diagnosis
   d. Average length of ICU stay decreased by about half a day with intensive protocol

iv. Author’s Conclusions
   a. Patients treated with intensive insulin protocol benefited from 29.3% reduction in mortality and a shorter length of ICU stay

C. Management of Diabetes and Hyperglycemia in Hospitals – 2004 ADA Statement
   i. Endorses findings of Van den Berghe et al. 2001 study in surgical ICU
   ii. Grade A evidence
   iii. “Intensive insulin therapy with intravenous insulin, with the goal of maintaining blood glucose 80-110 mg/dL, reduces morbidity and mortality among critically ill patients in the surgical ICU”

D. Van den Berghe II – Medical ICU

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### Intensive Insulin Therapy in the Medical ICU

<table>
<thead>
<tr>
<th>Objective</th>
<th>To assess whether the benefits of intensive insulin therapy in the surgical ICU could be reproduced in the medical ICU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design</td>
<td>• Single-center (Leuven, Belgium) MICU; Prospective, randomized, controlled</td>
</tr>
</tbody>
</table>
| Population| • 1200 patients expected to require at least 3 days in MICU between March 2002 – May 2005
   • No SICU patients; no patients on PO nutrition                                                              |
| Methods   | Intensive Insulin Therapy (IIT) | Conventional Insulin Therapy (CIT) |
| Laboratory| Blood glucose assessed at bedside q4 hours and qAM with daily labs |
| Glucose goal (mg/dL) | 80 – 110 | 180 – 200 |
| Insulin initiated (mg/dL) | > 110 | > 215 |
| ICU Discharge | All patients converted to CIT once discharged from ICU |

| Outcomes | • Primary
   • In-hospital all-cause mortality
   • Secondary |
• ICU all-cause mortality, 28- and 90-day mortality, length of stay, duration of mechanical ventilation, acute kidney injury (doubling of serum creatinine from admission), bacteremia

Statistics
• Planned enrollment: 1200 patients requiring ≥ 3 days in MICU; 80% power; alpha < 0.05
• Separate analyses for intent to treat and ≥ 3 days

Results
• Hypoglycemia
  • IIT was independent predictor of hypoglycemic event (HR 7.5; 95% CI, 4.5-12.5; P < 0.001)
  • Mortality increased with hypoglycemia

<table>
<thead>
<tr>
<th>MORTALITY</th>
<th>IIT</th>
<th>CIT</th>
<th>HR</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>In-hospital</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intent-to-treat</td>
<td>222/595 (37.3%)</td>
<td>242/605 (40%)</td>
<td>0.94</td>
<td>0.84 – 1.06</td>
<td>0.31</td>
</tr>
<tr>
<td>≥ 3 days in ICU</td>
<td>166/386 (43%)</td>
<td>200/381 (52.5%)</td>
<td>0.84</td>
<td>0.73 – 0.97</td>
<td>0.02</td>
</tr>
<tr>
<td>ICU</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intent-to-treat</td>
<td>144/595 (24.2%)</td>
<td>162/605 (26.8%)</td>
<td></td>
<td></td>
<td>0.31</td>
</tr>
<tr>
<td>≥ 3 days in ICU</td>
<td>121/386 (31.3%)</td>
<td>145/381 (38.1%)</td>
<td></td>
<td></td>
<td>0.05</td>
</tr>
<tr>
<td>28-day</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intent-to-treat</td>
<td>178/595 (29.9%)</td>
<td>182/605 (30%)</td>
<td></td>
<td></td>
<td>0.95</td>
</tr>
<tr>
<td>≥ 3 days in ICU</td>
<td>133/386 (34.5%)</td>
<td>149/381 (39.1%)</td>
<td></td>
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<td>0.18</td>
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<tr>
<td>90-day</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intent-to-treat</td>
<td>214/595 (35.9%)</td>
<td>228/605 (37.7%)</td>
<td></td>
<td></td>
<td>0.53</td>
</tr>
<tr>
<td>≥ 3 days in ICU</td>
<td>163/386 (42.2%)</td>
<td>187/381 (49.1%)</td>
<td></td>
<td></td>
<td>0.06</td>
</tr>
</tbody>
</table>

| MORBIDITY |     |     |     |         |         |
| In-Hospital Length of Stay |     |     |     |         |         |
| Intent-to-treat | Shorter in IIT group | 1.16 | 1.00 – 1.35 | 0.05 |
| ≥ 3 days in ICU | Shorter in IIT group | 1.58 | 1.28 – 1.95 | < 0.001 |
| ICU Length of Stay |     |     |     |         |         |
| Intent-to-treat | Shorter in IIT group | 1.15 | 1.01 – 1.32 | 0.04 |
| ≥ 3 days in ICU | Shorter in IIT group | 1.34 | 1.28 – 1.95 | < 0.001 |
| Duration of Mechanical Ventilation |     |     |     |         |         |
| Intent-to-treat | Shorter in IIT group | 1.21 | 1.02 – 1.44 | 0.03 |
| ≥ 3 days in ICU | Shorter in IIT group | 1.43 | 1.16 -1.75 | < 0.001 |
| Acute Kidney Injury |     |     |     |         |         |
| Intent-to-treat | 5.9% | 8.9% |       |         | 0.04 |
| ≥ 3 days in ICU | 8.3% | 12.6% |       |         | 0.05 |
| Bacteremia | 8% | 7% |       |         | 0.5 |

Authors’ Conclusions
• Intensive control decreased morbidity, but had no effect on in-hospital mortality in a medical ICU
• In patients who required at least 3 days of ICU care, intensive control reduced morbidity and mortality

Critiques
• No way to predict which patient will require ≥ 3 days in MICU
• Nutrition – enteral route accounted for < 50% median caloric intake until day 7-9
• Higher rates of hypoglycemia diminishes potential benefits

E. Impact of Tight Glucose Control by Intensive Insulin Therapy on ICU Mortality and the Rate of Hypoglycemia: Final Results of the GLUCONTROL Study22,23

1. Published in abstract form only
2. Prospective, randomized, controlled, multicenter study conducted in 7 European nations
3. Enrolled adult patients admitted to either medical or surgical ICU
4. Comparators
   a. Group A: Blood glucose goal 80-110 mg/dL
   b. Group B: Blood glucose goal 140-180 mg/dL
5. Outcomes
   a. Primary: ICU mortality
b. Secondary: In-hospital and 28-day mortality, length of stay, rate of hypoglycemia, infection, and organ failure

vi. Study stopped prematurely
   a. Safety concerns over high rate of hypoglycemia
   b. High rate of unintended protocol violations

vii. Results
   a. N = 1,011
   b. Median blood glucose (mg/dL)
      2. Group B: 147 (128-165)
   c. Hypoglycemia: 9.8% (A) vs. 2.7% (B); P < 0.0001
   d. ICU mortality: 16.7% (A) vs. 15.2% (B); NS

viii. Authors’ conclusions
   a. Tighter blood glucose control did not confer a mortality benefit but did increase the risk of hypoglycemia 4-fold
   b. Death in the ICU was significantly associated with hypoglycemia

F. Intensive Insulin Therapy and Pentastarch Resuscitation in Severe Sepsis – VISEP

   i. Randomized, multicenter, open-label, 2x2 factorial trial to evaluate the benefit of intensive insulin therapy and 10% pentastarch
   ii. Enrolled adult sepsis and septic shock patients in 18 German MICUs
   iii. Comparators
      a. Intensive insulin therapy (IIT): Blood glucose goal 80-110 mg/dL
      b. Conventional insulin therapy (CIT): Goal 180-200 mg/dL
   iv. Outcomes
      a. Primary: All-cause 28-day mortality and sequential organ failure assessment (SOFA) scores
      b. Secondary: Length of ICU stay, 90 day mortality, duration of mechanical ventilation/vasopressors
      c. Safety: Rate of severe hypoglycemia
   v. Study stopped prematurely secondary to high rates of hypoglycemia
   vi. Results
      a. N = 488
      b. Hypoglycemia: 12.1% (IIT) vs. 2.1% (CIT); P < 0.001
         1. Episodes associated with IIT were more likely to be classified as life-threatening and require prolonged hospitalization
         2. Hypoglycemia identified as an independent risk factor for all-cause mortality
      c. Mean blood glucose: 112 mg/dL (IIT) vs. 151 mg/dL (CIT)
      d. 28-day and 90-day mortality: No statistical difference
         1. 28-day: 24.7% (IIT) vs. 26% (CIT); P = 0.74
         2. 90-day: 39.7% (IIT) vs. 35.4% (CIT); P = 0.31
   vii. Authors’ conclusions
a. Intensive insulin therapy has no measurable, consistent benefit in the medical ICU
b. IIT results in higher rate of hypoglycemia, which was independently associated with poor outcomes

G. NICE-SUGAR – Medical and Surgical ICU\textsuperscript{25}
Objectives
Does intensive insulin therapy reduce 90-day mortality when compared to conventional blood glucose control?

Design
- Multicenter (42 hospitals) in Canada and Australia; Parallel-group, randomized, controlled

Population
- Adult patients expected to require at least 3 days of ICU care between Dec. 2004 and Nov. 2008

Methods

<table>
<thead>
<tr>
<th>Laboratory</th>
<th>Intensive Insulin Therapy (IIT)</th>
<th>Conventional Insulin Therapy (CIT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose goal (mg/dL)</td>
<td>81 – 108</td>
<td>&lt; 180</td>
</tr>
<tr>
<td>Insulin initiated (mg/dL)</td>
<td>&gt; 108</td>
<td>&gt; 180</td>
</tr>
<tr>
<td>Insulin dose</td>
<td>Treatment guided by algorithm accessed via secure website</td>
<td></td>
</tr>
<tr>
<td>ICU Discharge</td>
<td>All patients converted to CIT goal once discharged from ICU</td>
<td></td>
</tr>
</tbody>
</table>

Outcomes

<table>
<thead>
<tr>
<th>GLYCEMIC CONTROL</th>
<th>IIT (n=3010)</th>
<th>CIT (n=3012)</th>
<th>OR</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean AM glucose (mg/dL)</td>
<td>115 ± 18</td>
<td>144 ± 23</td>
<td>1.14</td>
<td>1.02 – 1.28</td>
<td>0.02</td>
</tr>
<tr>
<td>Severe hypoglycemia</td>
<td>206/3016 (6.8%)</td>
<td>15/3014 (0.5%)</td>
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</table>

<table>
<thead>
<tr>
<th>MORTALITY</th>
</tr>
</thead>
<tbody>
<tr>
<td>90-day (Primary outcome)</td>
</tr>
<tr>
<td>Intent-to-treat</td>
</tr>
<tr>
<td>Adjusted</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>28-day (Tertiary outcome)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intent-to-treat</td>
</tr>
<tr>
<td>Median Survival Time</td>
</tr>
<tr>
<td>Cause-Specific Death</td>
</tr>
<tr>
<td>Overall</td>
</tr>
<tr>
<td>Cardiovascular</td>
</tr>
<tr>
<td>Place of Death</td>
</tr>
<tr>
<td>ICU</td>
</tr>
<tr>
<td>Hospital (post-ICU)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>MORBIDITY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length of Stay (median)</td>
</tr>
<tr>
<td>ICU</td>
</tr>
<tr>
<td>Hospital</td>
</tr>
</tbody>
</table>

| Duration of Mechanical Ventilation (days) |
|-----------------|---------------|-------------|
| Intent-to-treat | 6.6 ± 6.6 | 6.6 ± 6.5 | 0.56 |
| Dialysis | 465 (15.4%) | 438 (14.5%) | 0.34 |

<table>
<thead>
<tr>
<th>Bacteremia</th>
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<tbody>
<tr>
<td>Intent-to-treat</td>
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</table>

Statistics
- Planned enrollment: 6100 (90% power; Two-sided alpha < 0.05); Intention-to-treat analysis

Results
- N = 6104 (IIT 3054 CIT 3050)
- Treatment discontinuation: IIT 10% vs. CIT 7.4% (Physician request: 115 (3.8%) vs. 48 (1.6%)
- 99.5% adherence to study algorithm

Authors’ Conclusions
- Intensive insulin therapy with a goal of normoglycemia increased mortality among critically ill adults
- Based on the results of this trial, the goal of treatment should be < 180 mg/dL

Critiques
- Is a 90-day mortality reflective of 6 days worth of IIT?
- Most “scientific” treatment algorithm
- Large proportion of IIT patients not at goal
- Nutrition: IIT 70% vs. CIT 71.4% enteral nutrition
- NNH with IIT was 38
VIII. Why Are There Discordant Findings?

A. Differences between three major studies\(^{19,21,25}\)
   i. Treatment goals similar
   ii. Patient populations
      a. In Van den Berghe I, > 60% of patients were admitted after cardiac surgery
      b. Subsequent studies with MICU patients included more septic shock/hemodynamically unstable patients
      c. IIT in septic shock/hemodynamically unstable patients may have added more insult to injury

B. Nutrition
   i. Patients in Van den Berghe I administered high dose glucose (200-300 grams over the first 24 hours)\(^{19}\)
      a. Insulin therapy may have been treating an iatrogenic effect
      b. Glucose may have protected patients from hypoglycemic events
   ii. Total parenteral nutrition vs. enteral nutrition vs. combination
      a. Patients in the two Van den Berghe trials had high rates of TPN use\(^{19,21}\)
      b. In Van den Berghe II, at least 50% of patients still on TPN at day 7\(^{21}\)
      c. TPN is associated with hyperglycemia, in addition to other complications\(^{26,27}\)
      d. TPN is not the standard of care – if no contraindications, enteral nutrition should be attempted as soon as possible\(^{27}\)

C. Stopping trials early for benefit
   i. Van den Bergh I study stopped after interim analysis shows superiority of intensive insulin therapy\(^{19}\)
   ii. 2005 Systematic Review conducted by Montor et al.\(^{28}\)
      a. Trials stopped early tended to over-inflate the true results
      b. May catch the treatment effect at a “random high”
      c. Exaggerated therapeutic benefits
   iii. Experience with CHARM program\(^{29}\)
      a. Fourth interim analysis revealed relative risk reduction (24%) that crossed predefined stopping boundary (\(P < 0.001\))
      b. Safety board voted to continue trial
      c. When trial carried out to intended completion, risk reduction was attenuated to 9% (\(P = 0.055\))

D. Single-center vs. Multi-center
   i. Single-center studies may reflect characteristics of study population or treatment center that are not generalizable to other populations
   ii. Multi-center trials are recommended before adoption of interventions for critically ill\(^{30}\)
   iii. Experience with induction of hypothermia following traumatic brain injury\(^{31,32}\)
      a. Single-center trial shows benefit that cannot be replicated in a larger, multi-center trial
IX. Other Related Issues

A. Measuring blood glucose with point-of-care devices\textsuperscript{33,34}
B. Amount of exogenous insulin administered or level of glucose control\textsuperscript{35}
C. Variability in blood glucose control may independently drive mortality\textsuperscript{36}

X. Current Areas of Research/Future Studies

A. Continuous blood glucose monitoring\textsuperscript{37}
B. Additional studies on intensive control\textsuperscript{38}

XI. Conclusions and Recommendations

A. Optimal level of blood glucose control in critically ill is still unknown
B. Based on the available literature:
   i. Intensive control does not appear advantageous and may lead to increased morbidity and mortality
   ii. “Lax” control (i.e., > 180 mg/dL) may increase the risk of hyperglycemia-associated adverse events and mortality
   iii. Patients should be managed using a strict algorithm-based approach to avoid high rates of hypoglycemia and large shifts in blood glucose
   iv. Goal of < 140 mg/dL appears to offer a “happy medium”
      a. Krinsley et al. found that an algorithm-based approach with a goal blood glucose of < 140 mg/dL provided mortality benefit with low levels of hypoglycemia
      b. Ensures that providers still “care” about the blood glucose, but may not necessarily have to micromanage it
      c. Goal < 140 mg/dL will reduce the number of hypoglycemic episodes
      d. Current recommendations in national guidelines
         1. ADA recommends < 140 mg/dL\textsuperscript{2}
         2. Surviving Sepsis Guidelines recommend < 150 mg/dL\textsuperscript{39}
References


