Intensive Insulin Therapy – What is the Role in 2012?

CRITICAL CARE POT POURI
Intensive Insulin Therapy – What is *Our* Role in 2013?

CRITICAL CARE POT POURI
Disclosures

- adviser of Medtronic (cont), Roche, GlySure (cont.), Edwards (cont.) and Optiscan
- institution received restricted grants from Medtronic (cont.) and Optiscan
- received speakers fee from Roche
Agenda

• glucose
• history
• targets
• needs
Hyperglycemia and Hypoglycemia are Associated with Outcome

Bagshaw S. Crit Care Med 2009; 37:463
Blood Glucose Variability is Associated with Outcome

Krinsley J. *Crit Care Med* 2008; 53:3008
Cumulative Impact of Disturbances in Three Domains

<table>
<thead>
<tr>
<th>Event</th>
<th>OR [95%–CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoglycemia</td>
<td>2.5 [2.0 – 3.1]</td>
</tr>
<tr>
<td>Hypoglycemia + Hyperglycemia</td>
<td>4.8 [3.4 – 6.8]</td>
</tr>
<tr>
<td>Hypoglycemia + Hyperglycemia + Glucose Variability</td>
<td>6.0 [3.9 – 9.2]</td>
</tr>
</tbody>
</table>

Mackenzie I. *Intensive Care Med* 2011; **37**:382
Neuronal Death is Triggered by Glucose Reperfusion

Table 1
Blood glucose concentration during HG and GR

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Fasting (before insulin)</th>
<th>Arterial glucose concentration (mM)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>HG (isoelectric EEG)</td>
</tr>
<tr>
<td>5–10 mM</td>
<td>4.24 ± 0.32 (n = 7)</td>
<td>0.38 ± 0.02</td>
</tr>
<tr>
<td>10–15 mM</td>
<td>4.25 ± 0.19 (n = 7)</td>
<td>0.38 ± 0.02</td>
</tr>
</tbody>
</table>

Data represent arterial glucose concentrations (mM) in each of the 3 target GR ranges, in WT rats with and without tempol treatment, and in SOD-1 Tg rats. Data are mean ± SEM. AP < 0.05 versus the GR 5–10 mM group; BP < 0.01 versus the GR 5–10 mM group.
Agenda

- glucose
- history
- targets
- needs
Intensive Insulin Therapy Benefits Surgical ICU–patients

van den Berghe G. NEJM 2000; 345:1359
Intensive Insulin Therapy Benefits Medical ICU–patients

van den Berghe G. *NEJM* 2006; **354**:449
Intensive Insulin Therapy Benefits PICU–patients

<table>
<thead>
<tr>
<th></th>
<th>Conventional insulin group (N=351)</th>
<th>Intensive insulin group (N=349)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of PICU deaths</td>
<td>20 (57%)</td>
<td>9 (2-6%)</td>
<td>0.038</td>
</tr>
<tr>
<td>Causes of PICU death (n)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiogenic (non-recovery of initial vitium or intractable shock)</td>
<td>7</td>
<td>8</td>
<td>0.024</td>
</tr>
<tr>
<td>Neurological complications or deterioration</td>
<td>8*</td>
<td>1†</td>
<td></td>
</tr>
<tr>
<td>Pulmonary (intractable ARDS or terminal weaning failure)</td>
<td>5†</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Odds ratio PICU mortality (95% CI) (uncorrected)</td>
<td>0.44 (0.19-0.97)</td>
<td>--</td>
<td>0.043</td>
</tr>
<tr>
<td>Odds ratio PICU mortality (95% CI) (corrected for baseline risks)</td>
<td>0.28 (0.09-0.79)</td>
<td>--</td>
<td>0.016</td>
</tr>
<tr>
<td>30-day PICU mortality</td>
<td>18 (51%)</td>
<td>8 (2-3)</td>
<td>0.047</td>
</tr>
<tr>
<td>Odds ratio 30-day mortality (95% CI) (uncorrected)</td>
<td>0.43 (0.19-1.01)</td>
<td>--</td>
<td>0.053</td>
</tr>
<tr>
<td>Odds ratio 30-day mortality (95% CI) (corrected for baseline risks)</td>
<td>0.23 (0.07-0.74)</td>
<td>--</td>
<td>0.014</td>
</tr>
</tbody>
</table>

* Eight neurological causes of death, of which four were in the upon-admission category complicated/high-risk surgery or trauma, two in the upon-admission category cardiac surgery, one in the upon-admission category neurological medical disorders, and one in the upon-admission category other medical disorders. The admission Glasgow coma scale was 15/15 in five of these eight patients, 6/15 in one, and 3/15 in two. One neurological cause of death in the upon-admission category cardiac surgery. The admission Glasgow coma scale of this patient was 3/15. Five pulmonary causes of death, of which one was in the upon-admission category cardiac surgery, two in the upon-admission category infectious medical, and two in the upon-admission category other medical. §Corrected for baseline age group, weight, sex, diagnostic category, malignancy, ventilation, extracorporeal membrane oxygenation/assist, glucose, PEO2>1 (indicated in table 1).

Table 3: Mortality in the two treatment groups

Vlasselaers D. Lancet 2009; 373:547
Randomized Controlled Trials of Intensive Insulin Therapy

<table>
<thead>
<tr>
<th>Study</th>
<th>Control Arm</th>
<th>Intensive Arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>van den Berghe 2001</td>
<td>40%, 33 [17 - 56] IU/day</td>
<td></td>
</tr>
<tr>
<td>van den Berghe 2006</td>
<td>70%, 10 [0 - 38] IU/day</td>
<td></td>
</tr>
<tr>
<td>Arabi 2008</td>
<td>75%, 31 ± 42 IU/day</td>
<td></td>
</tr>
<tr>
<td>de la Rosa 2008</td>
<td>47%, 13 ± 33 IU/day</td>
<td></td>
</tr>
<tr>
<td>Brunkhorst 2008</td>
<td>74%, 5 [0 - 22] IU/day</td>
<td></td>
</tr>
<tr>
<td>Finfer 2009</td>
<td>67%, 17 ± 29 IU/day</td>
<td></td>
</tr>
<tr>
<td>Preiser 2009</td>
<td>66%, 0.3 [0 - 1.3] IU/hour</td>
<td></td>
</tr>
</tbody>
</table>

Blood Glucose Level (mg/dL)
Increased Risk of Severe Hypoglycemia

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Patients</th>
<th>SH</th>
</tr>
</thead>
<tbody>
<tr>
<td>van den Berghe <em>et al.</em></td>
<td>2001</td>
<td>surgical</td>
<td>1 vs. 5%</td>
</tr>
<tr>
<td>van den Berghe <em>et al.</em></td>
<td>2006</td>
<td>medical</td>
<td>3 vs. 19%</td>
</tr>
<tr>
<td>Arabi <em>et al.</em></td>
<td>2008</td>
<td>mixed</td>
<td>3 vs. 29%</td>
</tr>
<tr>
<td>de la Rosa <em>et al.</em></td>
<td>2008</td>
<td>mixed</td>
<td>2 vs. 9%</td>
</tr>
<tr>
<td>Brunkhorst <em>et al.</em></td>
<td>2008</td>
<td>mixed</td>
<td>4 vs. 17%</td>
</tr>
<tr>
<td>Finfer <em>et al.</em></td>
<td>2009</td>
<td>mixed</td>
<td>1 vs. 7%</td>
</tr>
<tr>
<td>Preiser <em>et al.</em></td>
<td>2009</td>
<td>mixed</td>
<td>3 vs. 9%</td>
</tr>
</tbody>
</table>
Even Mild Hypoglycemia is Associated with Mortality

Krinsley J. *Crit Care* 2011; *15*:R173
<table>
<thead>
<tr>
<th>Blood Glucose Measurement</th>
<th>Blood Glucose Measurement</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>what?</strong></td>
<td><strong>what?</strong></td>
</tr>
<tr>
<td>arterial blood*</td>
<td>whole blood*</td>
</tr>
<tr>
<td>central or peripheral</td>
<td>plasma or serum</td>
</tr>
<tr>
<td>venous blood</td>
<td></td>
</tr>
<tr>
<td>capillary</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood Glucose Measurement</td>
<td>Blood Glucose Measurement</td>
</tr>
<tr>
<td><strong>where and how?</strong></td>
<td><strong>accurateness?</strong></td>
</tr>
<tr>
<td>at bedside* – blood</td>
<td>calibrated* or non –</td>
</tr>
<tr>
<td>gas analyzer* or</td>
<td>calibrated devices</td>
</tr>
<tr>
<td>point-of-care device</td>
<td></td>
</tr>
<tr>
<td>central laboratory</td>
<td></td>
</tr>
</tbody>
</table>

**Delivery of Insulin**

**how?**
- subcutaneous infusion
- peripheral intravenous infusion
- central venous infusion*
- variations in delivery introduced by co-infusion

**Delivery of Insulin**

**how?**
- accurate syringe pumps*
- volumetric pumps
- other

**SGC algorithm: insulin dosing**

from **simple set of rules** to guidelines of increasing complexity
- accepting higher incidence of (mild) hypoglycemia*
- to fear for (severe) hypoglycemia
- accuracy (insulin change should neither be too big nor too small, or changed in the wrong direction)

**SGC algorithm: blood glucose measurement timing**

from measurements **at strict time points and in between if necessary** to a loose schedule or no schedule at all
- punctuality (blood glucose should be measured neither too early nor too late)

**Glucose administration**

continuous glucose infusion*
- balanced enteral feeding/parenteral feeding*

**SGC algorithm**

"closed loop"
- between blood glucose level and insulin infusion

**SGC algorithm**

decision support
- i.e., with computer or sliding scales, etc.

**SGC algorithm**

"expertise"-based*

**Training**

skill*
- motivation*

Schultz M. *Crit Care* 2010; 14:223
Hidden in the Leuven Guideline?

- nurse–based strategy
- skill
- accept lower blood glucose levels
- in case of severe hypoglycemia: prevent overcorrection
Implementing the Leuven Guideline – Outside Leuven –

Schultz M. *Minerva Anestesiol* 2012; 78:982
Implementing the Leuven Guideline – Outside Leuven –
Implementing the Leuven Guideline – Outside Leuven –

Table V.—Mortality in patients with and without severe hypoglycemia.

<table>
<thead>
<tr>
<th></th>
<th>Period–1</th>
<th>Period–2</th>
<th>Period–3</th>
<th>$P^a$</th>
<th>$P^b$</th>
<th>$P^c$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with severe hypoglycemia, N.</td>
<td>80</td>
<td>149</td>
<td>80</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients without severe hypoglycemia, N.</td>
<td>1241</td>
<td>1020</td>
<td>926</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICU mortality (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with severe hypoglycemia</td>
<td>32.5%</td>
<td>22.1%</td>
<td>26.3%</td>
<td>0.088</td>
<td>0.486</td>
<td>0.386</td>
</tr>
<tr>
<td>Patients without severe hypoglycemia</td>
<td>17.3%</td>
<td>18.2%</td>
<td>16.2%</td>
<td>0.573</td>
<td>0.235</td>
<td>0.488</td>
</tr>
<tr>
<td>Hospital mortality (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with severe hypoglycemia</td>
<td>47.5%</td>
<td>29.5%</td>
<td>37.5%</td>
<td>0.007</td>
<td>0.219</td>
<td>0.201</td>
</tr>
<tr>
<td>Patients without severe hypoglycemia</td>
<td>26.7%</td>
<td>27.2%</td>
<td>25.3%</td>
<td>0.796</td>
<td>0.345</td>
<td>0.462</td>
</tr>
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</table>

Period–1, before implementation of the new tight glucose control (TGC) guideline; period–2, physicians and nurses practiced TGC; period–3, exclusively nurses practiced TGC. $P^a$ indicates significance level of differences between period–1 and –2; $P^b$ indicates significance level of difference between period–2 and –3; $P^c$ indicates significance level of difference between period–1 and –3.
Preventing Variability after Hypoglycemia

Harmsen R. *Unpublished data*
Targets

- glucose
- history
- targets
- needs
Glucose Control may Include …

- prevent (mild?) hyperglycemia
- prevent (mild?) hypoglycemia
- prevent glycemic variability (after hypoglycemia?)
Intensive Insulin Therapy and Glycemic Variability

Meyfroidt G. *Crit Care Med* 2010; 38:1021
Agenda

- glucose
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- targets
- needs
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<td>venous blood capillary</td>
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<table>
<thead>
<tr>
<th>Delivery of Insulin</th>
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</tr>
</thead>
<tbody>
<tr>
<td>how?</td>
<td>how?</td>
</tr>
<tr>
<td>subcutaneous infusion</td>
<td>accurate syringe pumps*</td>
</tr>
<tr>
<td>peripheral intravenous</td>
<td>volumetric pumps</td>
</tr>
<tr>
<td>infusion*</td>
<td>other</td>
</tr>
<tr>
<td>central venous infusion*</td>
<td></td>
</tr>
<tr>
<td>variations in delivery</td>
<td></td>
</tr>
<tr>
<td>introduced by co–infusion</td>
<td></td>
</tr>
</tbody>
</table>

**SGC algorithm: insulin dosing**

- from **simple set of rules** to guidelines of increasing complexity
- accepting higher incidence of (mild) hypoglycemia* to fear for (severe) hypoglycemia
- accuracy (insulin change should neither be too big nor too small, or changed in the wrong direction)

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**Glucose administration**

- continuous glucose infusion*
- balanced enteral feeding/parenteral feeding*

**SGC algorithm**

- “closed loop” between blood glucose level and insulin infusion
- decision support i.e., with computer or sliding scales, etc.

**SGC algorithm**

- “expertise”–based*

**Training**

- skill*
- motivation*
Capillary versus Arterial Blood Glucose Monitoring

# Meter Trials Failed to Show Benefit

<table>
<thead>
<tr>
<th>Study</th>
<th>No</th>
<th>Benefit</th>
<th>System</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leuven I</td>
<td>1548</td>
<td>Yes</td>
<td>Portable Lab Analyzer</td>
</tr>
<tr>
<td>Leuven II</td>
<td>1200</td>
<td>No</td>
<td>Included Meters</td>
</tr>
<tr>
<td>VISEP</td>
<td>537</td>
<td>No</td>
<td>Included Meters</td>
</tr>
<tr>
<td>Glucontrol</td>
<td>1101</td>
<td>No</td>
<td>Included Meters</td>
</tr>
<tr>
<td>Leuven III</td>
<td>700</td>
<td>Yes</td>
<td>Portable Lab Analyzer</td>
</tr>
<tr>
<td>NICE–SUGAR</td>
<td>6104</td>
<td>No</td>
<td>Included Meters</td>
</tr>
</tbody>
</table>
**Blood Glucose Measurement**
- **what?**
  - arterial blood*
  - central or peripheral venous blood
  - capillary

- **where and how?**
  - at bedside* – blood gas analyzer* or point-of-care device
  - central laboratory

- **what?**
  - whole blood*
  - plasma or serum

- **accurateness?**
  - calibrated* or non – calibrated devices

---

**Delivery of Insulin**
- **how?**
  - subcutaneous infusion
  - peripheral intravenous infusion
  - central venous infusion*

  variations in delivery introduced by co–infusion

**Delivery of Insulin**
- **how?**
  - accurate syringe pumps*
  - volumetric pumps
  - other

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from **simple set of rules*** to guidelines of increasing complexity

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**SGC algorithm**

“expertise”–based*

---

**Training**

skill*

motivation*

---

Schultz M. *Crit Care* 2010; 14:223
Conventional BGL Monitoring Lacks Trending

- lack of immediate feedback
- lack of predictability
- no hypo/hyperglycemia alarms
- “… planning for intervention is an obvious superior approach compared to reacting to outdated data”

Miller M. J Diabetes Science & Techn 2007; 1:903
Conventional BGL Monitoring is Time–Consuming and Expensive

Figure 1. Perceived benefits of CGM in the ICU.

Miller M. J Diabetes Science & Techn 2007; 1:903
Potential Methods for Monitoring

- arterial or venous blood
- subcutaneous (interstitial)
Potential Methods for Monitoring

- venous
  - venous ex vivo
- arterial
- transdermal
- needle
- dialysis catheter
- optical sensor
- microdialysis
Optiscan – Optical

blood

venous

arterial

transdermal

interstitial

needle
dialysis catheter

venous ex vivo

optical

sensor

microdialysis
Glumetric – Optical

blood

venous

venous \textit{ex vivo}

arterial

transdermal

interstitial

needle

dialysis catheter

optical

sensor

microdialysis
Edwards – Sensor

- venous ex vivo
- arterial
- transdermal
- needle
- dialysis catheter
- optical
- microdialysis
GlySure – Sensor

blood

venous

venous \textit{ex vivo}

arterial

transdermal

interstitial

needle

dialysis catheter

optical

sensor

microdialysis
Dipylon – Microdialysis

- venous ex vivo
- arterial
- transdermal
- interstitial
- needle
- dialysis catheter
- optical
- sensor
- microdialysis
EchoTherapeutics – Transdermal

- blood
  - venous
    - venous *ex vivo*
    - arterial
    - transdermal
    - interstitial
  - dialysis catheter
  - needle
- optical
  - sensor
  - microdialysis
Medtronic – Sensor

- venous ex vivo
- arterial
- transdermal
- interstitial
- needle
- dialysis catheter

Blood

Optical

Sensor

Microdialysis
Menarini Diagnostics – Microdialysis

- Blood
  - Venous ex vivo
  - Venous
  - Arterial
  - Transdermal
- Interstitial
- Needle
- Dialysis catheter
- Optical
  - Sensor
  - Microdialysis
Future Methods for Monitoring

**BLOOD**

- **Point Accuracy**: GOOD
- **Trend Accuracy**: GOOD
- **Complex/Invasive**: HIGH
- **Reading Delay**: SHORT
- **Reading Rate**: FREQUENT
- **Placement**: IV CATHETER
- **Transportability**: FAIR
- **Total Cost of Ownership**: HIGH
- **Alerts & Alarms**: GOOD

**INTERSTITIAL FLUID**

- **Point Accuracy**: FAIR AT BEST
- **Trend Accuracy**: FAIR
- **Complex/Invasive**: LOW
- **Reading Delay**: SHORT
- **Reading Rate**: VERY FREQUENT
- **Placement**: SUBCUTANEOUS
- **Transportability**: GOOD
- **Total Cost of Ownership**: FAIR
- **Alerts & Alarms**: GOOD

**Legend:**
- IV CATHETER
- GOOD
- FAIR
- HIGH
- SHORT
- FREQUENT
- VERY FREQUENT
Future Methods for Monitoring

Legend:
- Less complications
- Less complexity
- High accuracy
- Less accuracy
- More complexity
- More complications

Early Research  Development  Clinical Feasibility Studies  Release

GluMetrics
Edwards Lifesciences
GLUCOCLEAR
Dexcom
Medtronic
cma
OptiScan
DIRAMO

MJ|Schultz
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Normoglycemia

Hyperglycemia

Hypoglycemia

Increased glycemic variability

Increased or decreased glucose complexity

CGM may improve performance (i.e., prevention of hyperglycemia and hypoglycemia and may minimize glycemic variability)

CGM may have the potential to give insight into insulin resistance of individual patients

Schultz M. Crit Care 2012; in press
Conclusions

• glucose control *is* part of your practice
• intensive insulin therapy *or* prevention of dysglycemia
• from conventional monitoring *to* (almost) continuous monitoring