Intensive Insulin Therapy and the Artificial Pancreas in Critical Care
Pitfalls, Practicalities, and Performance

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A (Now) Well Known Story

- **Hyperglycaemia is prevalent in critical care**
  - Impaired insulin production + Increased insulin resistance = High BG
  - Average blood glucose values > 180mg/dL are not uncommon
  - All due to the stress of the patient’s condition

- **Tight control → better outcomes:**
  - Reduced mortality ~17-43% (6.1-7.75 mmol/L) [van den Berghe, Krinsley]
  - Costly treatments & tests (mech. ventilation, transfusions, … ) are also reduced
  - $2000/day saved regardless of mortality outcome [van den Berghe, Krinsley]

- **However, how best to attack the problem?**
  - How to manage highly insulin resistant patients (usually high APACHE score)?
  - How to provide better safety from hypoglycaemia?
  - Initial results have been very hard to repeat to outcome
  - Model-based methods may offer an opportunity to better design and compare
Between a rock and a hard place: Pitfalls or just a hard problem?

- **Hypoglycaemia?**
  - Risk of neurological damage?
  - Fear of hypoglycaemia?
    - Lack of ‘buy-in’ by physicians and nursing staff

- **Hyperglycaemia?**
  - Patients evolve rapidly
  - High insulin resistance and insulin requirements
  - Insulin effect saturation
  - Infrequent measurement ← or → Burden

- Not doing anything …? Too hard?

There are actually very few “true” pitfalls of IIT
The Many Practicalities of IIT

• No standard protocols ➞ variability of care

• Protocol transparency is usually minimal – big complex charts or mysterious computer programs

• No standard metrics to assess safety & performance

• Clinical burden?
  – Limited nursing resource?
  – Education, training
  – ICU layout?

• Compliance is thus an issue and can have the greater effect than a (good) protocol

• Who benefits? Which patients and which units?

How to satisfy or meet all these issues and still succeed?
Hypoglycaemia → ~0-32% Solution

Table 1. Studies Reporting Protocols and Practical Aspects of Intensive Insulin Therapy

<table>
<thead>
<tr>
<th>Authors</th>
<th>Reference</th>
<th>Publication Year</th>
<th>Study Design</th>
<th>Number of Patients</th>
<th>Persons Involved in IIT</th>
<th>Threshold of IIT (BGC, mg/dl)</th>
<th>Incidence of Severe Hypoglycaemia</th>
<th>Conclusions by Author Regarding Safety</th>
</tr>
</thead>
<tbody>
<tr>
<td>Krinsley et al.</td>
<td>[6,41]</td>
<td>2004/2005</td>
<td>Before–after cohort</td>
<td>1,600</td>
<td></td>
<td>Less than 140</td>
<td>&quot;Not changed&quot;</td>
<td>Safe</td>
</tr>
<tr>
<td>Canji et al.</td>
<td>[21]</td>
<td>2004</td>
<td>Before–after cohort</td>
<td>100</td>
<td>Nurses</td>
<td>80–110</td>
<td>16%</td>
<td>Safe</td>
</tr>
<tr>
<td>Grey et al.</td>
<td>[42]</td>
<td>2004</td>
<td>Randomized controlled trial</td>
<td>61</td>
<td></td>
<td>80–120</td>
<td>32%</td>
<td>Safe</td>
</tr>
<tr>
<td>Zimmerman et al.</td>
<td>[43]</td>
<td>2004</td>
<td>Prospective cohort</td>
<td>342</td>
<td>Nurses</td>
<td>80–150</td>
<td>7%</td>
<td>Safe</td>
</tr>
<tr>
<td>Laver et al.</td>
<td>[44]</td>
<td>2004</td>
<td>Prospective cohort</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Safe</td>
</tr>
<tr>
<td>Goldberg et al.</td>
<td>[45]</td>
<td>2004</td>
<td>Prospective cohort</td>
<td>118</td>
<td>Nurses</td>
<td>100–140</td>
<td>0.2%</td>
<td>Safe</td>
</tr>
<tr>
<td>Goldberg et al.</td>
<td>[46]</td>
<td>2004</td>
<td>Prospective cohort</td>
<td>52</td>
<td>Nurses</td>
<td>100–140</td>
<td>0.3%</td>
<td>Safe</td>
</tr>
<tr>
<td>Ku et al.</td>
<td>[47]</td>
<td>2005</td>
<td>Before–after cohort</td>
<td>156</td>
<td>Nurses</td>
<td></td>
<td></td>
<td>Safe</td>
</tr>
<tr>
<td>Thomas et al.</td>
<td>[48]</td>
<td>2005</td>
<td>Before–after cohort</td>
<td>891</td>
<td></td>
<td></td>
<td></td>
<td>Safe</td>
</tr>
<tr>
<td>Chant et al.</td>
<td>[49]</td>
<td>2005</td>
<td>Before–after cohort</td>
<td>86</td>
<td>Nurses</td>
<td>90–140</td>
<td>0.2%–0.4%</td>
<td>Safe</td>
</tr>
<tr>
<td>Bland et al.</td>
<td>[50]</td>
<td>2005</td>
<td>Randomized controlled trial</td>
<td>10</td>
<td>Nurses</td>
<td></td>
<td>&quot;Rare&quot;</td>
<td>Safe</td>
</tr>
<tr>
<td>Moeniralam et al.</td>
<td>[51]</td>
<td>2005</td>
<td>Before–after cohort</td>
<td>7,327</td>
<td>Nurses and physicians</td>
<td>80–140</td>
<td>3.3%–4.0%</td>
<td>Safe</td>
</tr>
<tr>
<td>Taylor et al.</td>
<td>[22]</td>
<td>2006</td>
<td>Before–after cohort</td>
<td>281</td>
<td>Physicians and nurses</td>
<td>120–150, 80–110</td>
<td>1.1%–3.4%</td>
<td>Safe</td>
</tr>
</tbody>
</table>

NB: VISEP sunk with 12% - van den Berghe et al 4-25%

Hypoglycaemia?

Review

Hyperglycemia During Critical Illness

Stanley A. Nasraway, Jr, MD, FCCM

A universal concern with intensive insulin therapy has been that of the magnitude and consequences of hypoglycemia. A number of studies have conservatively defined hypoglycemia as a value of <40–60 mg/dL [2.2–3.3 mmol/L]. superscript 2, 16–18 Using this standard, the incidence of hypoglycemia using a protocol-driven continuous insulin regimen is reportedly in the range from 4.0% to 6.9%. In no trial has there been any reported observation of a hypoglycemic event that was severe or irreversible to the patient.

A recurrent and concerning issue for protocol implementation was that glucose readings were not drawn every 30 mins when the blood glucose fell >20 mg/dL within the range of 80–150 mg/dL, responsible for 84.3% of protocol violations. This specification was added at the second revision in an attempt to prevent significant decreases in blood glucose that were unanticipated from trends in glucose values.

The most important element to the implementation of an intensive insulin regimen is the acceptance and cooperation of the nursing staff. This proved to be most difficult from the results of nursing surveys (Table 5). The survey administered at 6 months exposed a loss of autonomy from personal care while gaining a labor-intensive, complex protocol that 50% deemed detrimental to their patients. Numerous meetings were held to enhance the protocol, and subsequent surveys are planned to ensure continuous quality improvement.

The limitations experienced by the implementation of our protocol. This study did not seek to validate the efficacy of intensive insulin therapy. We studied only septic patients, with no data to generalize to an entire MICU population, and brittle hypoglycemia may be less a problem in other patient groups.

Our Approach – Balance

Rising Glucose

- Nutritional Inputs
  - Endogenous Glucose Production

Falling Glucose

- Exogenous Insulin
  - Endogenous Insulin
  - Non-insulin Removal

• Measure as little as possible (1-2 hours for very critically ill cohort)
• Simple, transparent protocols/methods
• Do simple things, consistently and well, and in moderation
Basic Development

- Insulin-nutrition model
  *Simple model with saturable dynamics*

- Single patient trials

- Simulated patient trials using an cortically ill cohort

- Clinical Audit
  - 394 patients
  - July 2007

- Clinical Practice Improvement
  - Implemented Aug 2005

- Develop simple BALANCED insulin & nutrition protocol
  - “SPRINT”
Virtual Trials

Short Proof of Concept

Computerised Trials

Implemented as SPRINT
**Semi-Automated Feedback Control**

Nursing Staff

Measured data

Decision Support System

Identify and utilise patient specific parameters to optimise therapy

Control IV Insulin and Nutrition

Patient management

Measured data

Decision Support System

Identify and utilise patient specific parameters to optimise therapy

Control IV Insulin and Nutrition

Patient management

Control IV Insulin and Nutrition

Minimal time & training – Minimal interruption – Easy to understand

→ Transparent
The Cohorts: Before/After Study

### Total patients

<table>
<thead>
<tr>
<th></th>
<th>Retrospective</th>
<th>SPRINT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total patients</td>
<td>516</td>
<td>394</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>65 [53 - 74]</td>
<td>65 [50 – 74]</td>
</tr>
<tr>
<td>% Male</td>
<td>60.1%</td>
<td>62.9%</td>
</tr>
<tr>
<td>APACHE II score</td>
<td>19 [15 - 24]</td>
<td>18 [14 – 24]</td>
</tr>
<tr>
<td>APACHE II risk of death</td>
<td>24.1% [11.2% - 45.3%]</td>
<td>25.7% [13.3% - 48.1%]</td>
</tr>
</tbody>
</table>

**Admission:** 2 BG > 144 mg/dL or 1 BG > 180 mg/dL

No exclusions

- Retrospective before-after study – 1.2 yr SPRINT vs 2.5 yr past
- ROD is higher for SPRINT  
  - Different case mix with retrospective cohort having much more cardiovascular surgery than recently (non-clinical causes)
- Otherwise statistically similar  
  - Retrospective more cardiovascular surgery so ROD likely lower again  
  - More similar for LoS > 2 days
Cumulative Distribution of BG

GlucoCard™ measurements (Arkray Inc) from venous cannula – whole blood measurements

Blood Glucose [mg/dl]

Proportion of measurements

28% in 72-110 band
60% in 72-110 band
Were Virtual Trials Effective?

- SPRINT was Monte Carlo simulated first in to show efficacy
- Clinical & virtual results are almost identical
- Other protocols were simulated and shown for comparison

Virtual trials in a Monte Carlo format (for robustness to sensor and other errors) are useful to validate models and optimise protocols
Percentage time in 4-6.1 mmol/L band grouped by APACHE II score and starting BG

Measurements grouped by APACHE II score:

- Pre-SPRINT
- SPRINT

Grouped by starting BG:

- Typical entry levels
- DKA and “special” short stay patients

Blood glucose at initiation of treatment [mg/dL]
Nutrition and Insulin Concerns

Focuses on increasing feed as possible using “moderate” insulin

Avg feed rate exceeded @ 2.8 days

- 1279 kcal/day → 110g/day CHO
- In optimal middle tertile for ROD from Krishnan et al, 2005 study
- Nutrition is only useful if it is utilised

Mean Insulin of 2.9 U/hr most of time in days 1-5

SPRINT stopped at 2U/hr and ~1300+ kcal/day

Matches recent results where tight control via IIT decreased insulin required over days 2-7 and thus allows increased nutrition (Langouche et al, 2007)
Lowest Recorded BG = 1.6 mmol/L

Not so real

Lowest of 28k measurements

Likely real

Lowest of 28k measurements
Of hypos and “funny” sensors ...

• Approximately 1.5-2% of all measurements may be “funny”
  – Sudden changes over 36 - 54 mg/dL/hour followed by reverse an hour later after a control input change by SPRINT

• 24 total hypo’s ≤ 40 mg/dL (Glucocard, Arkray Inc) and 14 (58%) have relatively very high rates of change

• Number where the average rate of change (down and up) was:
  – > 36 mg/dL/hour = 14 (~48+% change per 1 hour)
  – > 54 mg/dL/hour = 8 (~58+% change per 1 hour)
  – > 72 mg/dL/hour = 2 (~65+% change per 1 hour)

• Leaving 10 likely very real hypo’s (0.036% of measures) on 8 patients (2%)

• Compare to 128 (0.44%) in ~30k measurements in Mackenzie et al (2006) and reported rates that are higher.

## Overall SPRINT Glycaemic Control

<table>
<thead>
<tr>
<th>Overall cohort data</th>
<th>Retrospective</th>
<th>SPRINT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>516</td>
<td>394</td>
</tr>
<tr>
<td>Hours of control</td>
<td>62,769</td>
<td>47,290</td>
</tr>
<tr>
<td>Total BG measurements</td>
<td>15,618</td>
<td>29,983</td>
</tr>
<tr>
<td>BG mean (lognormal)</td>
<td>131</td>
<td>108</td>
</tr>
<tr>
<td>BG standard deviation (lognormal)</td>
<td>43</td>
<td>27</td>
</tr>
<tr>
<td>Percentage of measurements between:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>72 – 110 mg/dL</td>
<td>31.5%</td>
<td>59.2%</td>
</tr>
<tr>
<td>72 – 126 mg/dL</td>
<td>50.3%</td>
<td>79.1%</td>
</tr>
<tr>
<td>72 – 140 mg/dL</td>
<td>62.9%</td>
<td>86.5%</td>
</tr>
<tr>
<td>Percentage of measurements less than:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>72 mg/dL</td>
<td>3.6%</td>
<td>3.9%</td>
</tr>
<tr>
<td>40 mg/dL</td>
<td>0.2%</td>
<td>0.1%</td>
</tr>
<tr>
<td>Mean insulin usage</td>
<td>1.0</td>
<td>2.9</td>
</tr>
<tr>
<td>Mean nutrition rate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>During periods of feeding</td>
<td>1611</td>
<td>1279</td>
</tr>
<tr>
<td>Entire duration of SPRINT usage</td>
<td>-</td>
<td>1055</td>
</tr>
<tr>
<td>Mean % of goal feed</td>
<td>-</td>
<td>66%</td>
</tr>
</tbody>
</table>

*Units: hours, mg/dL, %, U/hr, kcal/day*
**Per-Patient** cumulative BG distribution: median, IQR & 90% CI

→ Each individual patient’s BG cumulative distribution underneath

NOTE: only included patients with at least 20 measurements
The First 48 Hours – All Patients

Red line = median
Box = IQR
Whisker = 1.5*IQR
Red crosses = outliers

Time since initiation of SPRINT (hours)

BG (mg/dL)
SPRINT Glycaemic Control Per Patient

<table>
<thead>
<tr>
<th>Per-patient data</th>
<th>Retrospective</th>
<th>SPRINT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hours of control</td>
<td>57 [25 – 162]</td>
<td>53 [19 – 147]</td>
</tr>
<tr>
<td>Number of BG measurements</td>
<td>17 [8 – 40]</td>
<td>37 [16 – 97]</td>
</tr>
<tr>
<td>BG mean (lognormal)</td>
<td>135 [121 – 151]</td>
<td>108 [99 – 119]</td>
</tr>
<tr>
<td>BG standard deviation (lognormal)</td>
<td>29 [22 – 43]</td>
<td>23 [18 – 32]</td>
</tr>
<tr>
<td>Percentage of patients &lt; 126 mmol/L</td>
<td>82%</td>
<td>99%</td>
</tr>
<tr>
<td>Percentage of patients &lt; 110 mmol/L</td>
<td>73%</td>
<td>96%</td>
</tr>
<tr>
<td>Insulin usage</td>
<td>0.9 [0.1 – 1.6]</td>
<td>2.6 [2.1 – 3.3]</td>
</tr>
<tr>
<td>Nutrition rate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>During periods of feeding</td>
<td>724 [0 – 1596]</td>
<td>938 [0 – 1304]</td>
</tr>
<tr>
<td>Entire duration of SPRINT usage</td>
<td>-</td>
<td>708 [0 – 1174]</td>
</tr>
<tr>
<td>% of goal feed</td>
<td>-</td>
<td>50% [0% - 71%]</td>
</tr>
</tbody>
</table>

- Tighter per patient std deviation – indicates each patient is tighter than the cohort to their patient specific mean
- Variability (std deviation) is 20% lower/tighter than retrospective
- Nutrition is actually higher (due to tighter control and less shutoff?)
- Feed shutoff for other clinical reasons can skew results
- Effectively all patients are brought under 7 mmol/L and 96% under 6.1 mmol/L
ICU Mortality: SPRINT/Pre-SPRINT

LOS ≥ 1 day  |  LOS ≥ 2 days  |  LOS ≥ 3 days  |  LOS ≥ 4 days  |  LOS ≥ 5 days

P=0.265   |  P=0.150   |  P=0.059   |  P=0.058   |  P=0.036

The horizontal line shows the mortality for the retro cohort. The green line is the total mortality of SPRINT patients against total number of patients treated on the protocol.

NB: You likely survive or not in LOS < 2 days on merits of initial condition!
**Hospital Mortality: SPRINT/Pre-SPRINT**

- LOS ≥ 1 day
- LOS ≥ 2 days
- LOS ≥ 3 days
- LOS ≥ 4 days
- LOS ≥ 5 days

- \( P=0.244 \)
- \( P=0.077 \)
- \( P=0.023 \)
- \( P=0.012 \)
- \( P=0.010 \)

The horizontal line shows the mortality for the retro cohort. The green line is the total mortality of SPRINT patients against total number of patients treated on the protocol.

**NB:** You likely survive or not in LOS < 2 days on merits of initial condition!
Nursing Feedback at 2 Months

Survey completed by 26 Christchurch Hospital ICU Nurses

**Bottom line**: Intuitive and easy for staff to use.

ICU staff workload reduced

Compliance over 97% (dose)
In Summary: There are no pitfalls...

- It’s just a problem with our expectations and the practicalities:
  - Desired performance of IIT vs practicalities of implementation
  - Nutritional requirements in critical illness and cohort
  - Full reporting: per patient and cohort to allow better assessment of performance

- It’s a question of balance
  - Of therapy choices, practicalities, workload, patient types
  - Matching utilisation to supply (in all these things!)
Acknowledgements

Intensive Care Nursing Staff, Christchurch Hospital
Questions for the QA?