Inpatient Diabetes Management: The Slippery Slope of Sliding Scale Insulin

David Newman, MD
University of North Dakota School of Medicine
Sanford Health
Big Sky Conference 2017

Learning Objectives

Upon Completion of this conference, participants should be able to:

- Define various forms of insulin and their durations of action
- Describe the blood sugar targets in hospitalized patients
- Recognize the outcomes associated with hyperglycemia and hypoglycemia in the hospital
- Evaluate strategies to maintain euglycemia in the inpatient setting

Early Cohort Studies & Randomized Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Setting</th>
<th>Population</th>
<th>Clinical Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mainberg, 1995</td>
<td>ICU</td>
<td>Mixed</td>
<td>28% ↓ mortality After 1 year</td>
</tr>
<tr>
<td>Fumary, 1999</td>
<td>ICU</td>
<td>DM undergoing open heart surgery</td>
<td>65% ↓ infection</td>
</tr>
<tr>
<td>Fumary, 2003</td>
<td>ICU</td>
<td>DM undergoing CAGB</td>
<td>57% ↓ mortality</td>
</tr>
<tr>
<td>Lavo, 2004</td>
<td>OR and ICU</td>
<td>DM undergoing CAGB</td>
<td>60% ↓ A Fib post op survival 2 yr</td>
</tr>
<tr>
<td>Kimoto, 2004</td>
<td>Med/Surg ICU</td>
<td>Mixed, no Cardiac</td>
<td>29% ↓ mortality</td>
</tr>
<tr>
<td>Van den Bergh, 2004*</td>
<td>Surgical ICU</td>
<td>Mixed, with CAGB</td>
<td>34% ↓ mortality</td>
</tr>
<tr>
<td>Van den Bergh, 2004*</td>
<td>Medical ICU</td>
<td>Mixed</td>
<td>10% ↓ mortality</td>
</tr>
</tbody>
</table>

*RCT, randomized clinical trial.

General Inpatient medicine

- Intern: “Yeah, he also has diabetes, I think, he was insulin as an outpatient.”
- Dr. Wiisanen: “So what should we do about his blood sugars?”
- Intern: “Maybe start some insulin?”
Insulin Basics

- Basal: Long Duration
- Bolus: Rapid Acting, Short Duration
  - Sliding Scale – check whenever, give rapid acting insulin
  - Prandial – rapid acting given before meals based on meal size
  - Corrective (Supplemental) – rapid acting given before meals based on blood sugars

Insulin Analogues: Chemical Properties

- Human Insulin
  - Dimers and hexamers in solution
- Aspart
  - Limited self-aggregation
  - Monomers in solution
- Lispro
  - Limited self-aggregation
  - Monomers in solution
- Glulisine
  - Limited self-aggregation
  - Monomers in solution
- Glargine
  - Soluble at low pH
  - Precipitates at neutral (physiologic) pH
- Detemir:
  - Fatty acid tail (myristic acid) added to human insulin
  - Complexes with albumin
  - >20 hour action

Physiologic Insulin Secretion: 24-Hour Profile

Detemir: Way different

- Fatty acid tail (myristic acid) added to human insulin
- Complexes with albumin
  - >20 hour action
Neutral Protamine Hagedorn Insulin

Available Insulin Formulations

<table>
<thead>
<tr>
<th>Human Insulin</th>
<th>“Analog” Insulin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regular</td>
<td>Rapid acting</td>
</tr>
<tr>
<td>NPH</td>
<td>aspart (Novolog)</td>
</tr>
<tr>
<td>Mixed (70/30)</td>
<td>glulisine (Apidra)</td>
</tr>
<tr>
<td></td>
<td>lispro (Humalog)</td>
</tr>
</tbody>
</table>

Mixed
- Humalog 50/50, Humalog 75/25
- Novolog 70/30

Long acting
- glargine (Lantus, Basaglar)
- detemir (Levemir)

Action Profiles of Injected Modified Human Insulins and Insulin Analogues

- Aspart, glulisine, lispro 4–6 hours
- Regular 6–8 hours
- NPH 12–20 hours
- Giargine, detemir ~24 hours

Ideal Situation

- Cardiology: Post Call with Dr. Jessen
  - Intern: “He was well controlled on metformin and sitagliptan as an outpatient.”
  - Dr. Jessen: “We need to off load the RV to increase his EF to maximize his PMI!”
  - Intern: “I think we will start insulin and get an A1C”
  - Dr. Jessen: “What should his blood sugar be?”

Sliding-Scale Regular Insulin

- BD = 280
- BD = 257
- BD = 220

Concerns:
- Reactive approach: Hyperglycemia
- Insulin stacking: Hypoglycemia

Cardiology: Post Call with Dr. Jessen

- Intern: “He was well controlled on metformin and sitagliptan as an outpatient.”
- Dr. Jessen: “We need to off load the RV to increase his EF to maximize his PMI!”
- Intern: “I think we will start insulin and get an A1C”
- Dr. Jessen: “What should his blood sugar be?”
Clinical Guidelines for the Management of Hyperglycemia in Hospitalized Patients in a Non-Critical Care Setting

The Endocrine Society, European Endo Society, American Heart Association, American Diabetes Association, Society of Hospitalist Medicine, American Association of Diabetes Educators

Strength of Recommendations and Level of Evidence Supporting Hospital Glucose Suggestions.

Diagnosis & recognition of hyperglycemia and diabetes in the hospital setting

Glycemic Targets in Non-Critical Care Setting

A1C for Diagnosis of Diabetes in the Hospital
Recommendations for Managing Patients With Diabetes in the Hospital Setting

Antihyperglycemic Therapy

- **Insulin** Recommended
- **OADs** Not Generally Recommended

---

Insulin Therapy in patients with T2D

- **D/C oral antidiabetic drugs on admission**
- **Insulin naïve**: starting total daily dose (TDD):
  - 0.3 U/kg to 0.5 U/kg
  - Lower doses in the elderly and renal insufficiency
- **Previous insulin therapy**: reduce outpatient insulin dose by 20-25%
- Scheduled SQ insulin consists of basal or intermediate acting insulin in combination with prandial rapid-acting insulin

---

Rabbit 2 Trial: Changes in Glucose Levels With Basal-Bolus vs. Sliding Scale Insulin

<table>
<thead>
<tr>
<th>Days of Therapy</th>
<th>BG, mg/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>100</td>
</tr>
<tr>
<td>2</td>
<td>120</td>
</tr>
<tr>
<td>3</td>
<td>140</td>
</tr>
<tr>
<td>4</td>
<td>160</td>
</tr>
<tr>
<td>5</td>
<td>180</td>
</tr>
<tr>
<td>6</td>
<td>200</td>
</tr>
<tr>
<td>7</td>
<td>220</td>
</tr>
<tr>
<td>8</td>
<td>240</td>
</tr>
</tbody>
</table>

- **Sliding-scale regular insulin (SSRI)** was given 4 times daily
- **Basal-bolus regimen**: glargine was given once daily; glulisine was given before meals.

<table>
<thead>
<tr>
<th>Days of Therapy</th>
<th>BG, mg/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>100</td>
</tr>
<tr>
<td>2</td>
<td>120</td>
</tr>
<tr>
<td>3</td>
<td>140</td>
</tr>
<tr>
<td>4</td>
<td>160</td>
</tr>
<tr>
<td>5</td>
<td>180</td>
</tr>
<tr>
<td>6</td>
<td>200</td>
</tr>
<tr>
<td>7</td>
<td>220</td>
</tr>
<tr>
<td>8</td>
<td>240</td>
</tr>
</tbody>
</table>

- **BG < 60 mg/dL**: 3%
- **BG < 40 mg/dL**: none

---

DEAN Trial: Changes in Mean Daily Blood Glucose Concentration

<table>
<thead>
<tr>
<th>BG, mg/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
</tr>
<tr>
<td>120</td>
</tr>
<tr>
<td>140</td>
</tr>
<tr>
<td>160</td>
</tr>
<tr>
<td>180</td>
</tr>
<tr>
<td>200</td>
</tr>
<tr>
<td>220</td>
</tr>
<tr>
<td>240</td>
</tr>
</tbody>
</table>

- **NPH/Regular**: BG < 40 mg/dl: 1.6%
- BG < 60 mg/dl: 3%

---

Insulin Treatment in in Non-ICU Setting

**T2DM with BG > 140 mg/dl (7.7 mmol/l)**

- NPO
- Uncertain oral intake
- **Adequate Oral Intake**
- Basal insulin TDD: 0.4-0.5 U/Kg/day
  - ½ basal, ½ bolus
  - Adjust as needed

---

Do you need basal bolus in ALL patients?
**Basal Plus Correction vs. Basal Bolus**

**Basal plus supplements**
- Starting glargine*: 0.25 units/kg
- Correction with glulisine for BG >140 mg/dL per sliding scale

* Reduce TDD to 0.15 U/kg in patients ≥70 yrs and/or serum creatinine ≥2.0 mg/dL

**Basal Bolus Regimen**
- Starting TDD*: 0.5 U/kg
  - Glargine: 0.25 U/kg
  - Glulisine: 0.25 U/kg in three equally divided doses (AC)
- Correction with glulisine for BG >140 mg/dL per sliding scale

* Reduce TDD to 0.3 U/kg in patients ≥70 yrs and/or serum creatinine ≥2.0 mg/dL

---

**Basal-PLUS vs Basal Bolus: 300 medical & surgical non-ICU patients**

- Basal Plus: glargine once daily 0.25 U/kg plus glulisine supplements
- Basal Bolus: TDD: 0.5 U/kg/d Glargine 50% Glulisine 50%

---

**Glycemic control and frequency of treatment failures in patients treated with basal bolus and basal plus regimens**

- **Basal Bolus:**
  - Starting TDD: 0.5 U/kg/d
  - Glargine 50%
  - Glulisine 50%

---

**Basal-PLUS vs Basal Bolus: Medicine and Surgery Patients**

**Oncology rounds with Dr. Glatt**

- Intern: "So he is having his tumor surgically removed on Thursday."
- Dr. Glatt: "Did you read last week's Blood, JAMA, and NEJM?"
- Intern: "No. Nobody does that."
Adverse Events Stratified by Perioperative Hyperglycemia

Randomized study of basal bolus insulin therapy in the management of general surgery patients with T2DM (Rabbit Surgery)

Research Question:
In patients with T2DM on diet, oral agents or insulin treatment, does treatment with basal bolus regimen with glargine and glulisine is superior to SSRI?

Primary Outcomes:
- Differences between groups in mean daily BG
- Composite of hospital complications: wound infection, pneumonia, respiratory failure, acute renal failure, and bacteremia

Mean BG before meals and at bedtime during basal bolus and SSI therapy

Mean BG before meals and at bedtime during basal bolus and SSI therapy

Postoperative Complications

Endocrinology with Dr. Newman

- Dr. Newman: "What about their sugars?"
- Intern: "I did everything you said, and my patient's blood sugars still suck"
- Dr. Newman: "Work Harder"

Cost difference (log transformation) between SSI and Basal: $2105, 95% CI -$3303, $7000
Non-adjusted without adjustment, the mean cost difference is $3843 with 95% CI -$36090, $43776.
Tailoring Insulin Regimens

- Control any raised random reading by adjusting the dose of previously administered regular insulin.
- For example: a high post lunch reading will NOT be controlled by increasing the dose of next insulin (as in sliding scale), rather adjustment of the pre-lunch regular insulin on the next day will bring down raised reading to the required levels.

Dose Adjustments – Rabbit 2

<table>
<thead>
<tr>
<th>Fasting BG</th>
<th>Adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>100-140 mg/dl</td>
<td>No change</td>
</tr>
<tr>
<td>140-180 mg/dl</td>
<td>Increase TDD by 10% daily</td>
</tr>
<tr>
<td>&gt;180 mg/dl</td>
<td>Increase TDD by 20% daily</td>
</tr>
<tr>
<td>70-99 mg/dl</td>
<td>Decrease TDD by 10%</td>
</tr>
<tr>
<td>&lt;70 mg/dl</td>
<td>Decrease TDD by 20%</td>
</tr>
</tbody>
</table>

- Only increase insulin if not getting values less than 100 during the day
- Adjust for other factors (NPO, steroids, dialysis)

Non-ICU hypoglycemia – LOS

- Retrospective cohort study of 2,582 pts with DM. Hypoglycemia BG<50 mg/dl was seen in 7.7% admissions.
- Multivariate analysis; LOS increased by 2.5 days compared with the average for the disease for each additional day with a hypoglycemic episode (P<0.001).

Non-ICU hypoglycemia – Inhospital Mortality

- Retrospective cohort study of 2,582 DM pts on general ward. Hypoglycemia BG<50 mg/dl (7.7%). Mean hospital BG 168±48

Inpatient (Non ICU) Summary

- Stop oral drugs
- Use basal bolus therapy
- If previously on insulin, decrease outpatient regimen by 20%
- Starting insulin
  - 0.4 units per kg in most patients
  - Less if old or with kidney problems
  - More if sugars are over 200
  - Half basal and half bolus

Targets 140 to 180
**Intensive Care Unit**

- Intern: “And her blood sugars are high. I think we should start insulin.
- Dr. Myrmoe: “Sounds good.”
- Intern: “Do they need tight control?”
- Dr. Myrmoe: “Define tight”

---

**Intensive Glucose Management in RCT**

<table>
<thead>
<tr>
<th>Trial</th>
<th>N</th>
<th>Setting</th>
<th>Primary Outcome</th>
<th>ARR</th>
<th>RRR</th>
<th>Odds Ratio</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Van den Berghe 2006</td>
<td>1230</td>
<td>MICU</td>
<td>ICU mortality</td>
<td>-2.7%</td>
<td>7.0%</td>
<td>0.44 (0.84-1.06)</td>
<td>N.S.</td>
</tr>
<tr>
<td>Glucostat 2007</td>
<td>1101</td>
<td>ICU</td>
<td>ICU mortality</td>
<td>-1.5%</td>
<td>-10%</td>
<td>1.05 (0.81-1.34)</td>
<td>N.S.</td>
</tr>
<tr>
<td>Gliedt 2007</td>
<td>399</td>
<td>CPR</td>
<td>Composite</td>
<td>2%</td>
<td>4.3%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VISEP 2008</td>
<td>537</td>
<td>ICU</td>
<td>28-d mortality</td>
<td>1.3%</td>
<td>5.0%</td>
<td>0.89 (0.58-1.38)</td>
<td>N.S.</td>
</tr>
<tr>
<td>De La Rosa 2008</td>
<td>504</td>
<td>ICU</td>
<td>28-d mortality</td>
<td>-4.2%</td>
<td>-13%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NICE-SUGAR 2009</td>
<td>6104</td>
<td>ICU</td>
<td>3-mo mortality</td>
<td>-2.6%</td>
<td>-10.6</td>
<td>1.14 (1.02-1.28)</td>
<td>&lt; 0.05</td>
</tr>
</tbody>
</table>

* not significant


---

**Intensive Insulin Therapy and Hypoglycemic Events in Critically Ill Patients**

<table>
<thead>
<tr>
<th>Study</th>
<th>RT</th>
<th>Control</th>
<th>Risk ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Van den Berghe et al</td>
<td>30/14</td>
<td>6/930</td>
<td>6.03 (2.53-15.06)</td>
</tr>
<tr>
<td>Henderson et al</td>
<td>7352</td>
<td>1/285</td>
<td>7.67 (1.00-58.80)</td>
</tr>
<tr>
<td>Eber et al</td>
<td>1/7</td>
<td>1/76</td>
<td>1.00 (0.08-10.25)</td>
</tr>
<tr>
<td>Van den Berghe et al</td>
<td>2/535</td>
<td>1/120</td>
<td>5.94 (3.79-9.26)</td>
</tr>
<tr>
<td>Minola et al</td>
<td>5/50</td>
<td>0/533</td>
<td>11.69 (5.25-21.91)</td>
</tr>
<tr>
<td>Auerbach et al</td>
<td>27/102</td>
<td>6/1397</td>
<td>4.03 (1.95-8.36)</td>
</tr>
<tr>
<td>De La Rosa et al</td>
<td>21/254</td>
<td>2/2369</td>
<td>10.33 (2.45-45.61)</td>
</tr>
<tr>
<td>Dunn et al</td>
<td>14/50</td>
<td>1/1500</td>
<td>3.62 (0.66-19.31)</td>
</tr>
<tr>
<td>Okumen et al</td>
<td>17/10</td>
<td>1/95</td>
<td>1.15 (1.17-71.39)</td>
</tr>
<tr>
<td>Rezende et al</td>
<td>4/46</td>
<td>1/196</td>
<td>4.11 (2.7-6.0)</td>
</tr>
<tr>
<td>Lepkowski et al</td>
<td>4/35</td>
<td>1/317</td>
<td>2.07 (0.76-5.91)</td>
</tr>
<tr>
<td>Ando et al</td>
<td>7/264</td>
<td>15/2541</td>
<td>3.14 (4.32-18.03)</td>
</tr>
<tr>
<td>Macintyre et al</td>
<td>50/121</td>
<td>9/1119</td>
<td>5.46 (2.82-10.98)</td>
</tr>
<tr>
<td>NICE-SUGAR 2009</td>
<td>15/300</td>
<td>20/1500</td>
<td>1.70 (1.10-2.61)</td>
</tr>
<tr>
<td>Overall</td>
<td>544/1185</td>
<td>945/5728</td>
<td>5.99 (4.46-8.03)</td>
</tr>
</tbody>
</table>

Hazard Ratio for Death from Specific Causes According to the Occurrence of Moderate or Severe Hypoglycemia.

- ICU setting:
  - Starting threshold of no higher than 180 mg/dL
  - Once IV insulin is started, the glucose level should be maintained between 140 and 100 mg/dL.
  - Lower glucose targets (110-140 mg/dL) may be appropriate in selected patients.
  - Targets <110 mg/dL or >180 mg/dL are not recommended

---

**NICE-SUGAR Trial: Hypoglycemia and Mortality**

- Risk Ratio (95% CI)

---

**AACE/ADA Recommended Target Glucose Levels in ICU Patients**

- Starting threshold of no higher than 180 mg/dL
- Once IV insulin is started, the glucose level should be maintained between 140 and 100 mg/dL.
- Lower glucose targets (110-140 mg/dL) may be appropriate in selected patients.
- Targets <110 mg/dL or >180 mg/dL are not recommended.

---

**Recommended**

- Not recommended <110
- Acceptable 110-140
- Recommended 140-180
- Not recommended >180

---

General Medicine with Dr. Lien

- Intern: "Yeah, we found him a ride, so he can go home."
- Dr. Lien: "What about his diabetes"
- Intern: "He probably needs a meter."

Discharge Insulin Algorithm

<table>
<thead>
<tr>
<th>A1C &lt; 7%</th>
<th>A1C 7%-9%</th>
<th>A1C &gt; 9%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Re-start outpatient treatment regimen (OAD and/or insulin)</td>
<td>Re-start outpatient oral agents and D/C on glargine once daily at 50-80% of hospital dose</td>
<td>D/C on basal bolus at same hospital dose</td>
</tr>
<tr>
<td>Alternative: re-start oral agents and D/C on glargine once daily at 80% of hospital dose</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Discharge Treatment

Hospital Discharge Algorithm Based on Admission HbA1C for the Management of Patients with T2DM

Primary outcome:
- change in A1C at 4 wks and 12 wks after discharge

<table>
<thead>
<tr>
<th></th>
<th>All Patients</th>
<th>OAD</th>
<th>OAD + Glargine</th>
<th>Glargine+ Glulisine</th>
<th>Glargine</th>
</tr>
</thead>
<tbody>
<tr>
<td>p patients, n (%)</td>
<td>224</td>
<td>81 (36)</td>
<td>61 (27)</td>
<td>54 (24)</td>
<td>20 (9)</td>
</tr>
<tr>
<td>A1C Admission, %</td>
<td>8.7±1.5</td>
<td>6.9±1.1</td>
<td>9.2±1.9</td>
<td>11.1±2.3</td>
<td>8.2±2.2</td>
</tr>
<tr>
<td>A1C 4 Wks F/U, %</td>
<td>7.9±1.7*</td>
<td>7.0±1.4</td>
<td>8.0±1.4*</td>
<td>8.8±1.8*</td>
<td>7.7±1.7</td>
</tr>
<tr>
<td>A1C 12 Wks F/U, %</td>
<td>7.3±1.5*</td>
<td>6.6±1.1</td>
<td>7.3±1.6*</td>
<td>8.0±1.8*</td>
<td>6.7±0.8*</td>
</tr>
<tr>
<td>BG=10 mg/dl, n (%)</td>
<td>52 (23)</td>
<td>17 (22)</td>
<td>17 (30)</td>
<td>23 (44)</td>
<td>5 (25)</td>
</tr>
<tr>
<td>BG&lt;40 mg/dl, n (%)</td>
<td>7 (3)</td>
<td>3 (4)</td>
<td>0 (0)</td>
<td>1 (6)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>
* p<0.001 vs. Admission A1C; ψp=0.08

Special Situations

- Steroids
  - Need more insulin, especially mealtime
- Type 1 Diabetes
  - Don’t stop basal insulin!
- Insulin drips
  - Give basal insulin before stopping
- Insulin pumps
  - Call endocrine

Summary

- Targets almost always 140 to 180
- Use basal bolus therapy instead of sliding scale – bolus before eating!
- Be proactive instead of reactive
- Use discharge as an opportunity to tailor diabetes medications
- Treat the patient, not the disease

Thank you

- David.Newman@sanfordhealth.org