Glucose Management in Critically Ill Patients

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OBJECTIVES

• Understand the impact of glycemic control on clinical outcomes for critically ill surgical and medical patients
• Review current guidelines and glycemic targets for critically ill patients
• Implement strategies for safe and effective glycemic control during the ICU stay and on transition out of the ICU

THE IMPACT OF HYPERGLYCEMIA IN CRITICALLY ILL PATIENTS
HOSPITAL MORTALITY RATE AND MEAN GLUCOSE LEVELS IN CRITICALLY ILL PATIENTS

- 16,871 patients with acute myocardial infarction
- Mean Glucose of Survivors: 137.9
- Mean Glucose of Nonsurvivors: 172.0
- p < 0.0001

Hyperglycemia and Mortality in Critically Ill

- Mortality risk from hyperglycemia is greater in patients without a diagnosis of diabetes.
- Patients with diabetes: n = 78,142
- Patients without diabetes: n = 180,898

Hyperglycemia and Mortality in Acute Myocardial Infarction

16,871 patients with acute myocardial infarction

- Association Between Mean BG and In-Hospital Mortality after Multivariable Adjustment (Reference: Mean BG 100 to <110)
- No Diabetes
- All Diabetes
- Diabetes

Mikhail Kosiborod et al., Circulation. 2008;117:1018-1027
HYPERGLYCEMIA INCREASES MORTALITY IN CABG PATIENTS

Mortality Increases With Increases in Average Glucose Levels

- Illness related “stress” – counter regulatory hormones and cytokines cause insulin resistance
- Undiagnosed diabetes mellitus
- Medications: steroids, immunosuppressants, sympathomimetics, anesthetic agents, octreotide
- Parenteral and enteral nutrition
- Physical Inactivity
- Inappropriate insulin use e.g. Sliding scale insulin
LINK BETWEEN HYPERGLYCEMIA AND POOR OUTCOMES: POTENTIAL MECHANISMS

Metabolic stress response
- Stress hormones and peptides
  - Glucose
  - Insulin
- FFA
- Ketones
- Lactate
- Reactive O₂ species
- Transcription factors
- Secondary mediators

Immune dysfunction
- Infection dissemination
- Organ dysfunction

Prehospital stay
- Disability
- Death


Nonmetabolic Insulin Action

Insulin → FFA → TNF-α → NF-kB (inhibitor κB)
- eNOS
- NO
- ICAM-1
- VCAM-1
- E-selectin
- Adhesion molecules

TNF-α → phosphorilation → NF-κB
- Transcription to the nucleus
- Proinflammatory genes
- TNF-α → IL-6 → IL-8, MCP-1
- Monocyte/Macrophage

MMPs → CRP
- APPS
- SAA
- INOS
- NO
- CRP
- Adhesion molecules

Outcomes of treating hyperglycemia in the critically ill patients
DIGAMI-1: INSULIN THERAPY IMPROVES MORTALITY IN PATIENTS WITH DM AND AMI

DIGAMI = Diabetes and Insulin-Glucose Infusion in Acute Myocardial Infarction.

PORTLAND DIABETES PROJECT: REDUCTION IN MORTALITY


PORTLAND DIABETES PROJECT: REDUCTION IN DEEP STETERNAL WOUND INFECTION RATES

SQI = subcutaneous insulin. CII = continuous insulin infusion.

Anthony Furnary MD
1999 CCNM
INTENSIVE INSULIN THERAPY (IIT) IN CRITICALLY ILL (SURGICAL) PATIENTS


*Infectious complications were not statistically significant

BENEFITS OF TIGHT GLYCEMIC CONTROL: OBSERVATIONAL STUDIES AND EARLY INTERVENTION TRIALS

<table>
<thead>
<tr>
<th>Study</th>
<th>Setting</th>
<th>Population</th>
<th>Clinical Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Furnary, 1999</td>
<td>ICU</td>
<td>DM undergoing open heart surgery</td>
<td>65% ↓ infection</td>
</tr>
<tr>
<td>Furnary, 2003</td>
<td>ICU</td>
<td>DM undergoing CABG</td>
<td>57% ↓ mortality</td>
</tr>
<tr>
<td>Krisley, 2004</td>
<td>Med/surg ICU</td>
<td>Mixed, no Cardiac</td>
<td>29% ↓ mortality</td>
</tr>
<tr>
<td>Malmberg, 1995</td>
<td>CCU</td>
<td>Mixed</td>
<td>28% ↓ mortality</td>
</tr>
<tr>
<td>Van den Bergh, 2001*</td>
<td>Surgical ICU</td>
<td>Mixed with CABG</td>
<td>42% ↓ mortality</td>
</tr>
<tr>
<td>Lazar, 2004</td>
<td>OR &amp; ICU</td>
<td>CABG and DM</td>
<td>66% ↑ AFB post op survival 2 yr</td>
</tr>
</tbody>
</table>

*RCT, randomized clinical trial

DIGAMI 2 – A NEGATIVE STUDY

- 1253 T2 DM patients with AMI
- Randomized to 3 groups
- #1 – iv insulin + glucose ≥ 24 hours followed by MDI SC insulin
- #2 – iv insulin + glucose ≥ 24 ho followed by usual care
- #3 – Usual Care by physician
- No differences in mortality

- Deficiencies:
  1. Only 50% recruitment
  2. Underpowered analysis
  3. Target glucose levels NOT met

IIT IN MEDICAL ICU PATIENTS

- Not statistically significant
- P = 0.02
INTENSIVE GLUCOSE MANAGEMENT IN RCTS SHOWING NO BENEFIT

<table>
<thead>
<tr>
<th>Trial</th>
<th>N</th>
<th>Setting</th>
<th>Primary Outcome</th>
<th>ARR</th>
<th>RR</th>
<th>Odds Ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Van den Berghe 2001</td>
<td>1220</td>
<td>MICU</td>
<td>Hospital mortality</td>
<td>2.7%</td>
<td>7.0%</td>
<td>0.64* (0.84-1.00)</td>
<td>N.S.</td>
</tr>
<tr>
<td>HIC 2006</td>
<td>240</td>
<td>CCU AMI</td>
<td>6-m mortality</td>
<td>-1.8%*</td>
<td>-30%*</td>
<td>NR</td>
<td>N.S.</td>
</tr>
<tr>
<td>Glucoseol 2007</td>
<td>1101</td>
<td>ICU</td>
<td>ICU mortality</td>
<td>-1.5%</td>
<td>-10%</td>
<td>1.15* (0.84-1.44)</td>
<td>N.S.</td>
</tr>
<tr>
<td>VISP 2008</td>
<td>537</td>
<td>ICU</td>
<td>28-d mortality</td>
<td>1.3%</td>
<td>5.0%</td>
<td>0.87* (0.65-1.18)</td>
<td>N.S.</td>
</tr>
<tr>
<td>De La Rosa 2009</td>
<td>504</td>
<td>ICU</td>
<td>28-d mortality</td>
<td>-4.2%*</td>
<td>-13%*</td>
<td>NR</td>
<td>N.S.</td>
</tr>
<tr>
<td>NICE-SUGAR 2009</td>
<td>6104</td>
<td>ICU</td>
<td>3-mt 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>

NICE-SUGAR TRIAL: IDEAL TARGET IN ICU PATIENTS

- Intensive: Glucose 80-110 mg/dL
- Conventional: Glucose 140-180 mg/dL

- Average am glucose
  - 118 (IT) vs. 145 mg/dL

- Increased mortality in IT
  - 27.5% (IT) vs. 24.9%
  - OR for death = 1.4 (except in trauma and corticosteroid therapy)

- Hypoglycemia (BG < 40)
  - 4.8% (IT) vs. 5.5%

- No significant benefits in secondary outcomes

GLUCO-CABG: IDEAL TARGET IN CABG PATIENTS

- RCT, N=302 with 2 targets: 100-140 mg/dL vs 140-180 mg/dL
- Insulin infusion in ICU if glucose >140 mg/dL followed by SC insulin regimen during the entire hospital stay and for 90 days postop
- Composite postoperative complications: mortality, wound infection, pneumonia, bacteremia, respiratory failure, acute kidney injury and major cardiovascular events
  - In patients without diabetes, there were ~20% fewer postoperative complications
  - In patients with diabetes, no difference

Lujan et al at Diabetes Care 2010; 33:1465-1472
HEALTHCARE UTILIZATION AND COSTS

**DIGAMI 1**
- Gain in life-years: 0.94 years
- Cost per life-year gained: Euro 16,900
- Per Swedish standards, this is highly cost effective

**CABG Patients**
- Each 50 mg/dL BG increase was associated with:
  - Longer Post op days: 0.76 days
  - Higher hospital Charges: $2,824
  - Higher hospital costs: $1,769

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COSTS IN INTENSIVE CARE UNIT

**Leuven Study**
- Decreased ICU length of stay: 2.0 days
- Decreased ICU costs: 2,638 Euros/patient
- No difference in ward length of stay

**Stamford Study**
- Net decrease in costs: $1,580 per patient
- Decrease in ICU LOS: 0.3 median days (p=0.005)
- Decrease in Non-ICU days: 1 calendar day (p=0.54)

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COST SAVINGS IN PATIENTS TREATED WITH ITT-Triumph Study

Pre and post implementation of Intensive Insulin Protocols in ICU

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Change in Outcome (Decreased Patients Included)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. 13,129 (2003 to 2007)</td>
</tr>
<tr>
<td>Total LOS Costs</td>
<td>$7,580 (-$11,643, -$1,180)*</td>
</tr>
<tr>
<td>Direct Variable Costs</td>
<td>-$4,960 (-$6,995, -$8,950)*</td>
</tr>
<tr>
<td>Total ICU costs</td>
<td>-$3,918 (-$7,995, -$2,170)*</td>
</tr>
<tr>
<td>Direct variable ICU costs</td>
<td>-$3,215 (-$6,215, -$3,791)*</td>
</tr>
<tr>
<td>Total LOS</td>
<td>-0.35 (-1.156, .99)</td>
</tr>
<tr>
<td>ICU days</td>
<td>-1.80 (-2.78, -0.89)*</td>
</tr>
<tr>
<td>Mortality</td>
<td>-0.28 (-0.46, 0.0006)</td>
</tr>
<tr>
<td>Average glucose per patient day (mg/dL)</td>
<td>-9.18 (-12.49, -5.97)*</td>
</tr>
</tbody>
</table>

*Denotes significance at p < 0.05. Adjunct: two corrected bootstrap confidence intervals shown in parentheses. **Glucose reductions from 2004 to 2007 were significant (p < 0.05).
HYPOGLYCEMIA IN CRITICALLY ILL PATIENTS

Two centers; N= 4946
<22.4% of patients had hypoglycemia defined as glucose ≤ 81 mg/dL at least once
Mortality Rates:
- Hypoglycemia → 36.6%
- No hypoglycemia → 19.7%
Mortality increased with severity of hypoglycemia


HYPOGLYCEMIA

- Median time of hypoglycemia was over 3.5 hours
- Therapy at time of hypoglycemia:
  - 32.7% were receiving insulin
  - 67.3% were not (spontaneous)
- Insulin therapy was not a significant predictor of hospital mortality in a multivariate analysis
- Time to first episode of hypoglycemia and severity of hypoglycemia had significantly higher mortality


HYPOGLYCEMIA DUE TO INSULIN THERAPY

40 hospitals; 7820 acute myocardial infarction patients admitted with hypoglycemia
Subsequent hypoglycemia during hospitalization (< 60 mg/dL)

- Increased in hospital mortality if hypoglycemia occurred
- Hypoglycemia was associated with increased mortality in non insulin treated patients
  BUT NOT in patients treated with insulin

Koiborod M et al. JAMA. 2000;314:1556-1564
AACE/ADA/STS TARGET GLUCOSE LEVELS IN ICU PATIENTS

- 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 180 mg/dL
  - Lower glucose targets (110-140 mg/dL) may be appropriate in selected patients (Cardiothoracic surgery)
  - Targets <110 mg/dL or >180 mg/dL are not recommended

<table>
<thead>
<tr>
<th>Not recommended</th>
<th>Acceptable</th>
<th>Recommended</th>
<th>Not recommended</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;110</td>
<td>110-140</td>
<td>140-180</td>
<td>&gt;180</td>
</tr>
</tbody>
</table>

Lazar, HL et al. The Society of Thoracic Surgeons Practice Guidelines Series: Blood Glucose Management After Adult Outpatient DM Meds: Metformin 1000mg bid, Glyburide 5mg bid

STRATEGIES TO ACHIEVE GLYCEMIC CONTROL IN CRITICALLY ILL PATIENTS

ADMISSION #1 – CHEST PAIN

- 68 year old male admitted with chest pain and found to have AMI and CHF
- Type 2 DM for 14 years, HTN, Hyperlipidemia, Gout
- Outpatient DM Meds: Metformin 1000mg bid, Glyburide 5mg bid
- Exam: Lungs w/ rales, 2+ LE edema
- Labs: Admission glucose 316 mg/dL, HgbA1c 9.3%, creatinine 2.5, LFTs: 2.5 x normal
- Echo shows LVEF 25%
- Admitted to CCU after cardiac catheterization with glucose now 250 mg/dL

How should we treat this patient?
1. Continue metformin and increase the dose of glyburide to 10 mg bid
2. Start SLIDING SCALE subcutaneous insulin Q4-6 hours
3. Start insulin infusion with a glucose target of 110-140 mg/dL
4. Start insulin infusion with a glucose target of 140-180 mg/dL
**INDICATIONS FOR INTRAVENOUS INSULIN THERAPY: SUMMARY**

- Diabetic ketoacidosis
- Nonketotic hyperosmolar state
- Critical care illness (surgical, medical)
- Postcardiac surgery
- Myocardial infarction or cardiogenic shock
- NPO status in Type 1 diabetes
- Labor and Delivery

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**ADMISSION #1 – CONTINUED**

- Over the next 24 hours, the glucose control improved into the desired target and he is medically optimized
- He now has proceeds to surgery and has a 3 vessel CABG
- Postop, he is admitted to the surgical ICU on epinephrine and vasopressin drips for hypotension
- His initial glucose in the ICU is 251 mg/dl

How do we manage his glucose?

1. **SLIDING SCALE insulin Q 4-6 hours**
2. Start long and short acting insulin for basal-bolus insulin therapy
3. Start Insulin Infusion with a glucose target of 110-140 mg/dl
4. Start Insulin Infusion with a glucose target of 140-180 mg/dl

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**ADMISSION #1 – CONTINUED**

- Over the next 24 hours, the glucose control reaches target range
- Pressors are weaned off and he is extubated
- A diet is ordered and plans are started to transfer to the floor

What do we do next?

1. Restart metformin and increase glyburide dose to 10mg bid
2. Turn off insulin infusion and immediately start SLIDING SCALE insulin Q 4-6 hours
3. Transition to a long + short acting insulin for basal-bolus insulin therapy
DANGERS OF SLIDING-SCALE INSULIN REGIMENS

- Reactive to after hyperglycemia—provides supplemental insulin after hyperglycemia occurs
- No basal (long term) insulin coverage:
  - **Will cause DKA in patients with Type 1 diabetes**
- Does not consider nutritional changes or diurnal insulin requirements
- Non physiologic dosing that results in:
  - Increased incidence of hyperglycemic and hypoglycemic episodes


ROLLECOASTER EFFECT OF SLIDING-SCALE INSULIN

- Reactive to after hyperglycemia—provides supplemental insulin after hyperglycemia occurs
- Does not consider nutritional changes or diurnal insulin requirements
- Non physiologic dosing that results in:
  - Increased incidence of hyperglycemic and hypoglycemic episodes

KEY CONCEPTS OF INSULIN THERAPY

- **Basal** insulin
  - Controls hepatic glucose production
- **Food (prandial)** insulin
  - Based on meal carbohydrate content
- **Correction (supplemental)** insulin
  - Treats acute elevation in blood glucose
CONVERSION FROM IV TO SC INSULIN

- Use approx. 50-70% of stable 24 hour IV insulin requirements (if not 24 hours, can extrapolate over a recent stable period)
  - 70 units x 0.7 = 49 units (total 24 hour SC insulin dose)

- For glargine/detemir + lispro/aspart regimen:
  - 50% Basal: 49 x 0.5 = 25 units
  - 50% Nutritional divided QAC: 8 units
  - Use a corrective algorithm in addition to scheduled prandial

- For NPH + lispro/aspart regimen:
  - 2/3 NPH - divided into two doses: 49 x 2/3 = 16 units before
    breakfast and bedtime
  - 1/3 Nutritional, divided QAC = 5 units before each meal
  - Always discontinue the insulin drip two hours after the first long
    acting subcutaneous insulin dose.

CAUTIONS IN INSULIN DOSING...

- Changing steroid doses
- Changing pressor requirement over past 24 hours
- Changing renal function (rapidly decreasing urine output or GFR)
- Nutrition changes
- Improving infectious status
- Hypoglycemic Events

ADMISSION #2: FEVER

- 66 year old female admitted with fever of 103 F, SOB and hypotension.
- Intubated and started on pressors and admitted to Medical ICU
- Found to have a multilobar pneumonia with SIRS
- No history of Type 2 Diabetes but has HTN, Hyperlipidemia, CAD, COPD
- Labs: Glucose= 225 mg/dL, repeat accuchek 253 mg/dL HgbA1c = 5.9% Creatinine = 1.8 AST/ALT = normal

How should we treat this patient?
1. No therapy needed as this is acute hyperglycemia and not diabetes
2. Start SLIDING SCALE subcutaneous insulin Q4-6 hours
3. Start Insulin Infusion with a glucose target of 110-140 mg/dL
4. Start Insulin Infusion with a glucose target of 140-180 mg/dL
ADMISSION #2: CONTINUED

- Patient was managed on insulin infusion and reached the target
- Over the next 48 hours, patient is supported with mechanical ventilation, Norepinephrine, stress dose hydrocortisone, iv antibiotics
- Still not improved and TPN is started due to ileus
- Insulin infusion has been titrated up to 5-7 units/hr and she is requiring >140 units of IV insulin per 24 hours
- Labs: Cr = 2.6, LFTS now 3x normal

What is the next step?
1. Continue iv insulin infusion as is
2. Transition to basal bolus subcutaneous insulin regimen
3. Add NPH or Lantus in addition to iv insulin
4. Add Regular insulin into the TPN formula

ADMISSION # 2 - ADDING INSULIN IN TPN

- Insulin is more effective when added to the TPN than when delivered in another infusion
- Delay in preparation of TPN, often 12-24 hours later requires planning
- Be conservative, add only 20-50% of previous 24 hour iv insulin requirements needs to be delivered via TPN
- Watch for clinical and medication changes and change insulin in TPN in advance to avoid hypoglycemia.

GLP-1 RECEPTOR ANTAGONIST THERAPY IN CRITICALLY ILL PATIENTS

**Advantages:**
- Glucose dependent insulin stimulation prevents hypoglycemia
- Glucagon inhibition may be useful in the maladaptation of the stress response
- Suppression of hepatic glucose
- Increased tissue insulin sensitivity
- Potential cardiovascular benefits with improved cardiac function, reduced infarct size
- Less nursing time to monitor glucose and administer insulin

**Disadvantages:**
- Small, limited studies investigating use in critically ill patients
- Usually compared to placebo, not insulin
- High incidence of GI side effects
- Rescue insulin therapy often needed
- Long term effects unknown
- More studies needed


Labs: Cr = 2.6, LFTS now 3x normal
THANK YOU FOR YOUR ATTENTION!