The Approach to Inpatient Hyperglycemia

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Further Increases in the Prevalence of Diabetes Are Expected

Projected Number of Persons With Diagnosed Diabetes

Based on diabetes prevalence rates predicted from 1960-1980 trends from the National Health Interview Survey and predicted US Census Bureau’s population projections.

Rising Prevalence

“We are getting older, less active, heavier, and eating foods much higher in fat.”
Prevalence of IGT and DM in Nondiabetic Men with CAD Referred for Coronary Angiography

<table>
<thead>
<tr>
<th>CAD by angio</th>
<th>None</th>
<th>1 VD</th>
<th>2 VD</th>
<th>3 VD</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=363</td>
<td>61</td>
<td>113</td>
<td>116</td>
<td>73</td>
</tr>
<tr>
<td>NGT N (%)</td>
<td>36(59)</td>
<td>65(58)</td>
<td>43(37)</td>
<td>29(40)</td>
</tr>
<tr>
<td>IGT</td>
<td>22(36)</td>
<td>35(31)</td>
<td>55(47)*#</td>
<td>19(26)*</td>
</tr>
<tr>
<td>Diabetes</td>
<td>3(5)</td>
<td>13(12)</td>
<td>18(16)</td>
<td>23(34)*#</td>
</tr>
</tbody>
</table>

*p<0.05 vs groups 1-3, # p<0.05 vs 2 & 3. Kowalska I Diabetes Care 2001; 24:897

Question #1

What evidence is there that high glucose matters in the hospital situation?

Effects of FPG on Mortality in PCI Patients

1612 potential PCI patients divided into 4 groups based on baseline (fasting) glucose levels
- CDM – clinically diagnosed diabetics (24%)
- ADA-DM – met criteria for DM, FG > 126 (18%)
- Impaired FG - 110-125 (19%)
- Normal FG < 110 (39%)

Patients with impaired glucose were older, female, with more than 3-vessel disease.
**Effect of Glycemic Status on Mortality**

- **NFG**
  - Mortality: 2.5%
  - P-trend <0.001
- **IFG**
  - Mortality: 6.6%
- **ADA-DM**
  - Mortality: 9.5%
  - P-trend <0.001
- **CDM**
  - Mortality: 11.2%

**Question #2**

Does good inpatient glucose control make a difference?

**BARRIERS TO INSULIN THERAPY**

*Cardiovascular Risk Reduction After MI Reduced by Insulin Therapy in the DIGAMI Study*

- **All Subjects** (N = 620)
  - Risk reduction: 28%
  - P = .011
- **Low-risk and Not Previously on Insulin** (N = 272)
  - Risk reduction: 51%
  - P = .0004
  - IV Insulin 48 hours, then 4 injections daily

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*Multiple authors. J Am Heart J 2003;146:351.*

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**Post-CABG Mortality by Diabetic Status**


**Effect of Intensive Insulin Therapy in ICU Patients**

- Intensive therapy - 765 patients received insulin when BG > 110 mg/dL, maintain BG 80-110 mg/dL
- Conventional therapy – 783 patients received insulin when BG > 215 mg/dL, maintain BG 180-200 mg/dL

(Vanden Berghe et al. NEJM 2001;345:1359)

**Impact of Intensive Insulin Therapy on Clinical Outcomes**

<table>
<thead>
<tr>
<th></th>
<th>Conventional Therapy N = 783</th>
<th>Intensive Therapy N = 765</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death during ICU</td>
<td>8.0%</td>
<td>4.6%</td>
<td>&lt;0.04</td>
</tr>
<tr>
<td>ICU &gt; 5 days</td>
<td>20.2</td>
<td>10.6</td>
<td>0.005</td>
</tr>
<tr>
<td>History of db</td>
<td>16.0</td>
<td>9.6</td>
<td></td>
</tr>
<tr>
<td>No history of db</td>
<td>20.6</td>
<td>10.7</td>
<td></td>
</tr>
<tr>
<td>In-hosp death all</td>
<td>10.9</td>
<td>7.2</td>
<td>0.001</td>
</tr>
<tr>
<td>Those in ICU &gt;5d</td>
<td>26.3</td>
<td>16.8</td>
<td>0.001</td>
</tr>
</tbody>
</table>

(Vanden Berghe et al. NEJM 2001;345:1359)
Problems with Van Den Berghe's Study

- 60% patients were post-cardiac surgery
- The drip protocol is open-ended and depended on nurses training
- Has not been replicated
- Effect is seen in patients in the unit 5 days or longer
- Hypoglycemia higher with goal BG< 110mg/dl

How about more recent studies?

NICE-Sugar (Normoglycemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation) in Critically Ill Patients

The NEW ENGLAND JOURNAL of MEDICINE
6,104 patients were randomized: 3,054 were assigned to undergo intensive control and 3,050 to undergo conventional control.

- Within 24 hours after admission to ICU, adults underwent either intensive glucose control (81 to 108 mg/dl) or conventional glucose control (<180 mg/dl).
- Primary end point as death from any cause within 90 days after randomization.
- 829 patients (27.5%) in the intensive-control group and 751 (24.9%) in the conventional-control group died (OR for intensive control, 1.14; 95% confidence interval, 1.02 to 1.28; P=0.02).
- Severe hypoglycemia (BG 40 mg/dl) complicated 6.8% in the intensive-control group and 0.5% in the conventional-control group (P=0.001).
Intensive Insulin Therapy and Pentastarch Resuscitation in Severe Sepsis

537 patients with severe sepsis were randomized to undergo intensive glycemic control or conventional control.

- Mean morning BG lower in intensive therapy group (112 mg/dl) vs conventional therapy group (151 mg/dl)
- At 28 days, no difference in rate of death or the mean score for organ failure.
- Rate of severe hypoglycemia (<40 mg/dl) 17% vs 4.1%, p<0.001 and rate of severe adverse events 10.9% vs 5.2%, p=0.01


Intensive Insulin Therapy, Death and Hypoglycemia

In a recent metaanalysis of 26 trials (n=13,567) the pooled relative risk of death with intensive insulin therapy was 0.93.

Half of the trials reported hypoglycemia with a pooled RR of 6.0.

Surgical patients appears to do better than other critical care settings.

Griesdale DE et al. CMAJ 2009; 180: 821-827

Intensive Insulin Therapy and Mortality Among Critically Ill Patients

Question #3
How should hyperglycemia in critically ill patients be treated?

Standards of Medical Care in Diabetes-2010: American Diabetes Association

- Scheduled subcutaneous insulin with basal, nutritional, and correctional components is the preferred method in noncritically ill patients
- Glucose monitoring required in patients whose treatment increases the risk of hyperglycemia
- Establish a plan for hypoglycemia
- Obtain an HbA1c test on admission

Diabetes Care 2010; 33: Suppl 1. 511

Standards of Medical Care in Diabetes-2010: American Diabetes Association

- Identify patients with diabetes in the medical record
- Write an order for blood glucose monitoring

Critically ill patients:
- Insulin therapy should be initiated for treatment of persistent hyperglycemia at 180 mg/dL. Range of 140-180 mg/dL is recommended for the majority of patients
- Use an IV insulin protocol that is efficacious and avoids hypoglycemia

Non-critically ill patients:
- No clear evidence of blood glucose goals. If on insulin, premeal BG should be <140 mg/dL, with random <180 mg/dL. Individualize dependent upon glycemic history and co-morbidities.

Diabetes Care 2010; 33: Suppl 1. 511
Recommendations for Managing Patients With Diabetes in the Hospital Setting

2. Diabetes Care. 2009;31(suppl 1):S1-S110

- **Antihyperglycemic Therapy**
  - **Insulin**
    - Recommended
  - **OADs**
    - Not Generally Recommended

- **IV Insulin**
  - Critically ill patients in the ICU

- **SC Insulin**
  - Non-critically ill patients

Standards of Medical Care in Diabetes-2010: American Diabetes Association

- Three broad categories of patients
  - Medical history of diabetes
  - Unrecognized diabetes
  - Hospital related hyperglycemia

Diabetes Care 2010; 33: Suppl 1, S11

The Bad Old Days........

Plasma Glucose (mg/dL)

<table>
<thead>
<tr>
<th>Time of Day</th>
<th>Glucose</th>
</tr>
</thead>
<tbody>
<tr>
<td>0600</td>
<td>0</td>
</tr>
<tr>
<td>1200</td>
<td>0</td>
</tr>
<tr>
<td>1800</td>
<td>0</td>
</tr>
<tr>
<td>2400</td>
<td>0</td>
</tr>
<tr>
<td>0600</td>
<td>0</td>
</tr>
</tbody>
</table>
Ideal Basal/Bolus Insulin Absorption Pattern (US)


Plasma Insulin (µU/mL)

Ideal Basal/Bolus Insulin Absorption Pattern (UK)


Insulin Therapy in Hospital

Hospital should decide
- Who is involved in refining protocols
  - Ideally nurse-led with physician input for problems
  - When to call the endos
- Can (dare) you give IV insulin on the wards?
- Thresholds for starting insulin
  - Fasting vs post-prandial (1 vs 2 hr)
- Criteria for IV vs s/c insulin therapy
- Blood glucose targets (ie 140 mg/dL premeal, <180 mg/dL peak post meal)
- Strategy for conversion to s/c insulin
- When to call MD if BG <70 or >360 mg/dL
Starting Basal-Bolus From Scratch

Calculate Starting Total Daily Dose (TDD):
- Previous Total Daily Insulin Units Used or
- 0.4 units/kg (Type 1 DM) (0.3 units/kg if GFR 15-29, 0.2 units/kg if <15)
- 0.8 units/kg (Type 2 DM) (0.6-0.4 units/kg for reduced GFR)

This is very conservative and actual needs may turn out to be substantially more

Basal Insulin = 40-50% TDD
- Give All of Calculated Glargine Dose Q 24h ➔ Evening or HS Recommended
  Or
  Detemir BID (likely to be 50%-100% higher dose than glargine)
  NPH Q 12h
Goal: FBS And Pre-Meal Glucose <140 mg/dl

Starting Basal-Bolus From Scratch

Bolus Doses = 50-60% TDD
Dose Has 2 Components :
- Prandial Dose
- Correction Factor (CF) Dose For Glucose >150 mg/dL Before the Meal (“Catch Up” Portion)

Goal: 2h Post-Prandial <180 mg/dl
Best given after meal to be sure patient actually ate; If less than full meal consumed, adjust the meal portion of the bolus dose accordingly. However if 2 hr BG >180, record but do not rebolus

Insulin Sensitivity

- High
  - Need a low dose of insulin (< 40 units of insulin per day)
  - Type 1 diabetes
  - Lean Type 2 diabetes
  - Renal, adrenal failure
  - Stp pancreatectomy
  - NPO patients
- Moderate
  - Most Type 2 diabetes or patients using 40 – 80 units of insulin per day.
- Low
  - Need higher doses of insulin (> 80 units per day)
  - Obese type 2 diabetes
  - Sepsis
  - Glucocorticoid use (PPG > FPG correction)
Some Indications for Insulin Infusion to Treat Hyperglycemia

- Diabetic ketoacidosis and nonketotic hyperosmolar state
- Postoperative period following heart surgery
- General preoperative, intraoperative, and postoperative care
- MI or cardiogenic shock
- Stroke
- High-dose glucocorticoid therapy
- NPO status in type 1 diabetes
- Critically ill surgical patient requiring mechanical ventilation
- Dose-finding strategy, anticipatory to initiation or reinitiating of subcutaneous insulin therapy in type 1 or type 2 diabetes
- Diabetic sepsis

Intravenous Insulin Infusion Protocols

- Portland
- Leuven
- Yale
- Luther Mideifort Health System
- Wisconsin
- University of Washington
- Pennsylvania State University

IV Insulin Infusion in the Adult ICU Patient

- Start when BG >180 mg/dL
- Patients without H/O diabetes
  - D/c drip if BG stable for 4h and infusion <1U/h
  - Use correction factor only for 24h
  - If requires >10 U CF insulin, start 10 U glargine next day
  - If requires <10 U CF insulin, consider oral agent
  - Obtain HbA1c
- If no enteral feeding, requires 5 g glucose/h + 20 mEq/L K+
  - Move to greater IV insulin algorithm if BG 180-240 mg/dL, but does not decrease by >30 mg/dL
  - Move to lesser IV insulin algorithm if BG <140 mg/dL
**Patient Monitoring**

- Hourly BG if critically ill
- If BG in range for 4h, check BG every 2 h for 4 h, then every 4 h
- If consecutive BGs >200, check every h

**Transition From IV to S/C Insulin**

*Use TDD calculation as earlier or*

- Extrapolate last stable drip dose to 24 hours (TDD) (use 75-80% total dose)
- Give 40-50% as glargine, detemir or NPH
- Or multiply current insulin infusion rate (U/h) x 20
- Titrate glargine to achieve FPG 80-120 mg/dL
- Use 2 U increments if TDD glargine <100 U. If >100 U consider 10 U initial increment
- Give 50-60% as S/A insulin in divided doses when able to eat (1 unit/g CHO)
- Overtap S/C and IV insulin to reduce hyperglycemia escape (give basal insulin at least 3-4 h before S/C IV)
- If <2 h, give 10% calculated glargine dose as S/A analog
- Can use both IV and S/C insulin together for a time
- Do not switch to oral agents alone unless very low doses required in T2 DM (<10 units/day)
- Follow up required for patients initiated on insulin
- Need adequate calorie intake

**Question #4**

How do I treat high premeal glucose values?
**Correction Factor Dose, Added To Prandial Dose**

<table>
<thead>
<tr>
<th>Low Dose</th>
<th>Medium Dose</th>
<th>High Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total Insulin Dose</strong></td>
<td><strong>Total Insulin Dose</strong></td>
<td><strong>Total Insulin Dose</strong></td>
</tr>
<tr>
<td>&lt;40 units/day</td>
<td>40-80 units/day</td>
<td>&gt;80 units/day</td>
</tr>
<tr>
<td>Premeal BG</td>
<td>Additional Insulin</td>
<td>Premeal BG</td>
</tr>
<tr>
<td>120-170</td>
<td>1 unit</td>
<td>120-170</td>
</tr>
<tr>
<td>171-220</td>
<td>2 units</td>
<td>171-220</td>
</tr>
<tr>
<td>221-270</td>
<td>3 units</td>
<td>221-270</td>
</tr>
<tr>
<td>&gt;270</td>
<td>4 units</td>
<td>&gt;270</td>
</tr>
</tbody>
</table>

**Question #5**

Can oral agents be restarted at discharge?

**INSULIN TACTICS: Basal Insulin + Oral Agents**

- **Sulfonylurea/meglitinides/gliptins**
  - Provide post-prandial glucose control (avoid glyburide)
  - Attenuate hypoglycemia

- **Metformin**
  - Attenuates weight gain
  - Withdrawal associated with deterioration of glycemic control
  - Caution in elderly/renal impairment

- **Thiazolidinediones**
  - Caution due to CCF risk
  - Augment beta cell function
  - Anti-inflammatory
Addition of Biphasic, Prandial or Basal Insulin to Oral Therapy in Type 2 Diabetes: Which is Best?

Holman R et al; NEJM 2007; 357:1716

The Early “Portable” Insulin Infusion Device

Question #6

What happens after discharge?
Standards of Medical Care in Diabetes-2010:
American Diabetes Association: Discharge Planning

- Check level of understanding
- SMBG
- Definition, recognition, treatment and prevention of hyperglycemia and hypoglycemia
- Identification of health care providers
- Information on eating patterns
- When and how to take blood glucose lowering meds
- Sick day management
- Proper use and disposal of insulin syringes
- 1 month follow up appointments