Management of Hospital Hyperglycemia

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Outline

- Clinical Case
- Briefly review data linking hyperglycemia and its management to clinical outcomes
- Management options
- Summary
- Questions
Clinical Case

A 48 year old obese male is admitted with a severe pneumonia requiring IV antibiotics. His admission labs are remarkable for a random glucose of 268 mg/dl. He gives no previous history of diabetes.

Hyperglycemia: FBG > 126 mg/dl or RBG > 200 mg/dl

Does this patient have diabetes mellitus or stress hyperglycemia?

Is this hyperglycemia harmful or it can be ignored?

How should he be managed?
Hospital Hyperglycemia

Types

Known Diabetes
Diabetes diagnosed and treated before admission

Newly Diagnosed Diabetes
Fasting glucose >126 mg/dl, or random glucose >200 mg/dl during hospital stay. HbA1c >6.5

Stress Hyperglycemia
Fasting glucose >126 mg/dl or random glucose >200 mg/dl during hospital stay that reverts to normal in a few days. HbA1c <6.5

Steroid Induced

Nutritional: TPN/TFs associated
Stress Hyperglycemia
(Transient hyperglycemia Associated with acute illness)

- Fasting blood glucose >126 mg/dl, Random glucose >200 mg/dl
- Term usually applied to patients with no previous history of diabetes
- Patients with previously well controlled diabetes with deterioration of glycemic control on admission
- Related to stress of an acute illness
- Secondary to the action of
  Stress hormones; Glucagon
  Catecholamines
  Cortisol
  Growth Hormone
  Cytokines; IL 1
  TNF-A
- Tends to resolve with resolution of acute stress
- In the past believed to be a benign adaptive response
- Plenty of data supporting poor outcomes
HYPERGLYCEMIA: AN INDEPENDENT MARKER OF IN-HOSPITAL MORTALITY IN PATIENTS WITH UNDIAGNOSED DIABETES

*Hyperglycemia: Fasting BG ≥ 126 mg/dl or Random BG ≥ 200 mg/dl X 2

<table>
<thead>
<tr>
<th>Status</th>
<th>Glucose Level</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normoglycemia</td>
<td>Glu=108 mg/dl</td>
<td>1.7%</td>
</tr>
<tr>
<td>Known Diabetes</td>
<td>Glu=230 mg/dl</td>
<td>3.0%</td>
</tr>
<tr>
<td>New Hyperglycemia</td>
<td>Glu=189 mg/dl</td>
<td>16%</td>
</tr>
</tbody>
</table>

Umpierrez G et al, J Clin Endocrinol Metabol 87:978, 2002
Association Between Hyperglycemia and Increased Mortality in a Heterogeneous Population of Critically Ill Patients


N= 1826

Hospital Morality Rate and Mean Glucose Value

Mortality

Glucose

80-99 100-119 120-139 140-159 160-179 180-199 200-249 250-299 ≥300

9.6 12.2 15.1 18.8 28.4 29.4 37.5 32.9 42.5

N= 1826

Effect of Admission Hyperglycemia* on Mortality in Patients with Acute Myocardial Infarction


180 Day Mortality

<table>
<thead>
<tr>
<th>Status</th>
<th>N</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Euglycemic Patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>without Diabetes</td>
<td>779</td>
<td>14.1%</td>
</tr>
<tr>
<td>Hyperglycemic Patients</td>
<td></td>
<td>47.7%</td>
</tr>
<tr>
<td>without Diabetes</td>
<td></td>
<td>26.7%</td>
</tr>
<tr>
<td>with Diabetes</td>
<td></td>
<td>29.8%</td>
</tr>
</tbody>
</table>
Impaired Glucose Metabolism Predicts Mortality After a Myocardial Infarction


Mortality (11-16 Months)

- **Gp 1 (Glu <100mg/dl)**: 9.0%
- **Gp 2 (Glu 100-150 mg/dl)**: 13.0%
- **Gp 3 (Glu 150-200 mg/dl)**: 30%
- **Gp 4 (Glu >200 mg/dl)**: 44%

*P* < 0.005

*n* = 336
Mortality of DM Patients Undergoing CABG

The Relation Between Hyperglycemia and Outcomes in 2471 Patients Admitted to the Hospital With Community Acquired Pneumonia


Non-ICU Patients With CAP

- In-Hospital Mortality
  - Glucose <200 mg/dl: 9%
  - Glucose >200 mg/dl: 13%
  - P = 0.03

- Complications
  - Glucose <200 mg/dl: 22%
  - Glucose >200 mg/dl: 29%
  - P = 0.07

Complications: ACS, CHF and Nosocomial infections other than lungs
Hyperglycemia leads to

- Glycosuria, volume depletion and electrolyte fluxes
- Increased platelet aggregation and thrombosis
- Increase in cytokines and inflammation
- Diminished neutrophil adherence, chemotaxis, phagocytosis, and extravasation
- Non-enzymatic glycosylation of immunoglobulins
- Defective collagen synthesis and poor wound healing

IV Insulin Therapy Significantly Decreases Postoperative Mortality

(Endocr Pract. 2004; 10[Suppl 2]:21-33)

Cardiac Surgical Patients Mortality

- Mean Glucose 213: SC 5.3%, IV Insulin 2.5%
- Mean Glucose 177: SC 5%, IV Insulin 3.0%

P < 0.0001

Cardiovascular Mortality 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

Intensive Insulin Therapy in Critically Ill Patients Improves Survival

# Intensive Insulin Therapy in Critically Ill Patients

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Target Glucose</th>
<th>Mean Glucose</th>
<th>Hypoglycemia</th>
<th>Mortality</th>
<th>Target Glucose</th>
<th>Mean Glucose</th>
<th>Hypoglycemia</th>
<th>Mortality</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leuven SICU '01</td>
<td>1548</td>
<td>180-200</td>
<td>153</td>
<td>6 (0.8%)</td>
<td>63 (8.0%)</td>
<td>80-110</td>
<td>103</td>
<td>39 (5.1%)</td>
<td>35 (4.6%)</td>
<td>&lt;0.04</td>
</tr>
<tr>
<td>Leuven MICU '06</td>
<td>1200</td>
<td>180-200</td>
<td>153</td>
<td>19 (3.1%)</td>
<td>162 (26.8%)</td>
<td>80-110</td>
<td>111</td>
<td>111 (18.7%)</td>
<td>144 (24.2%)</td>
<td>0.31</td>
</tr>
<tr>
<td>Glucontrol '04</td>
<td>1101</td>
<td>140-180</td>
<td>144</td>
<td>13 (2.7%)</td>
<td>83 (15.3%)</td>
<td>80-110</td>
<td>117</td>
<td>44 (8.7%)</td>
<td>92 (17.2%)</td>
<td>0.410</td>
</tr>
<tr>
<td>VI SEP '08</td>
<td>537</td>
<td>180-200</td>
<td>151</td>
<td>12 (4.1%)</td>
<td>75 (26%)</td>
<td>80-110</td>
<td>112</td>
<td>42 (17%)</td>
<td>61 (24.7%)</td>
<td>0.74</td>
</tr>
<tr>
<td>Colombia '08</td>
<td>504</td>
<td>180-200</td>
<td>148</td>
<td>2 (0.8%)</td>
<td>71 (31.2%)</td>
<td>80-110</td>
<td>117</td>
<td>21 (8.3%)</td>
<td>84 (33.1%)</td>
<td>NS</td>
</tr>
<tr>
<td>Saudi Arabia '08</td>
<td>523</td>
<td>180-200</td>
<td>171</td>
<td>8 (3.1%)</td>
<td>44 (17.1%)</td>
<td>80-110</td>
<td>115</td>
<td>76 (28.6%)</td>
<td>36 (13.5%)</td>
<td>0.70</td>
</tr>
<tr>
<td>NICE SUGAR</td>
<td>6104</td>
<td>140-180</td>
<td>145</td>
<td>15 (0.5%)</td>
<td>751 (24.9%)</td>
<td>80-110</td>
<td>118</td>
<td>206 (6.8%)</td>
<td>829 (27.5%)</td>
<td>0.02</td>
</tr>
</tbody>
</table>
Take Home Points from the ICU Studies

Do not neglect glycemic control in critically ill patients, as studies have compared tight (80-110 mg/dl) with good control (140-180 mg/dl) but not tight control with no/poor control (>200 mg/dl)
Revised ADA/AACE Inpatient Glucose Targets

- **ICU:** 140-180 mg/dl
- **Non-ICU:**
  - Pre-meal 100-140 mg/dl
  - Post-meal <180 mg/dl
Oral Anti-Diabetic Agents

Impractical for managing inpatient hyperglycemia;

- Delayed action profile
- Limited ability to treat more pronounced hyperglycemia
- Contraindicated in renal, hepatic and cardiac dysfunction
- Hypoglycemia
Sliding Scale Insulin

- Ineffective and not recommended as a sole therapy
- Reactive approach to blood sugar control and delays insulin delivery until hyperglycemia develops
- Does not deliver basal insulin which is an essential part of an insulin regimen
- Promotes large swings in glucose control
Randomized Study of Basal-Bolus Insulin Therapy in the Inpatient Management of Patients with Type 2 Diabetes (RABBIT 2 Trial)

**Blood Glucose Levels During Insulin Treatment**

Umpierrez, Diabetes Care 30: 2007
Blood Glucose Levels in Patients Who Failed SSRI: Transition to Basal Bolus Insulin

Failure was defined as 3 consecutive BG values > 240 mg/dL during SSRI
Physiologic Serum Insulin Profile

<table>
<thead>
<tr>
<th>Time (Hours)</th>
<th>Breakfast</th>
<th>Lunch</th>
<th>Dinner</th>
</tr>
</thead>
<tbody>
<tr>
<td>4:00</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8:00</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12:00</td>
<td></td>
<td>50</td>
<td>120</td>
</tr>
<tr>
<td>16:00</td>
<td></td>
<td>75</td>
<td>150</td>
</tr>
<tr>
<td>20:00</td>
<td></td>
<td>100</td>
<td>175</td>
</tr>
<tr>
<td>24:00</td>
<td></td>
<td>125</td>
<td>190</td>
</tr>
<tr>
<td>4:00</td>
<td></td>
<td></td>
<td>200</td>
</tr>
</tbody>
</table>

Plasma insulin (µU/ml)
Available Insulin Preparations

- **Rapid acting:** Insulin lispro, aspart or glulisine
- **Short acting:** Regular Insulin
- **Intermediate acting:** NPH
- **Long acting:** Insulin detemir, Insulin glargine

Adapted from Nolte (2009)
Basal/Bolus Treatment Program with Long and Rapid Acting Analogs

Aspart, Lispro or Glulisine

Glargine or Detemir
Methods of Insulin Administration

- MDI (multiple daily injections)
- CSI I (continuous subcutaneous insulin infusion)
- CIII (continuous intravenous insulin infusion)
- Added to TPN
Multiple Daily Injections (MDIs)

- Requires basal insulin (NPH, glargine or detemir) injected once or twice daily.

- Requires premeal, bolus insulin with a rapid acting insulin analog (lispro, aspart or glulisine) and plan for adjusting insulin for varying food intake.

- Requires correction scale for high blood glucose.
Determining **Initial** Insulin Needs

**Weight Based**

- Determine Total Daily Insulin (TDI)
- Multiply weight in Kg X 0.3 u/Kg for Type 1 and 0.5 u/Kg for Type 2 DM

For a 100 Kg person with type 2 DM, the TDI will be 

\[(100 \times 0.5) = 50\] units daily

- Half of the TDI is basal and rest of the half is bolus
- \[50/2 = 25\] units
Basal Insulin

Glargine (Lantus) 25 units QD

Detemir (Levemir) 25 units QD or 12-13 units BID

NPH (Humulin N or Novolin N) 12-13 units BID
Bolus Insulin

Has two components - Meal carb coverage
- Correction or SSI

Lispro (Humalog)

Aspart (Novolog)

Glulisine (Apidra)

Regular (Humulin R or Novolin R)
Bolus Insulin (Scheduled Pre-meal)

2 Choices

i) Rule of 500: (Insulin to Carbohydrate ratio; I to C)
   
   \[
   \frac{500}{TDI} \\
   \frac{500}{50} = 10 \text{ grams} \\
   \]

   1 unit of insulin covers 10 gm CHO

ii) Divide 25 units into three meals
   
   \[
   \frac{25}{3} = 8 \\
   
   8 \text{ units insulin (fixed dose) before each meal}
   \]
Carbohydrate Content of Selected Food Items

1 carbohydrate serving (1 carb) = 15 gm

<table>
<thead>
<tr>
<th>Food Item</th>
<th>Carbohydrate Content (gm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apple (medium)</td>
<td>21</td>
</tr>
<tr>
<td>Apple pie (1 slice)</td>
<td>58</td>
</tr>
<tr>
<td>Bagel (plain)</td>
<td>38</td>
</tr>
<tr>
<td>Banana (medium)</td>
<td>27</td>
</tr>
<tr>
<td>Bread (1 slice)</td>
<td>12</td>
</tr>
<tr>
<td>Corn flakes 1 cup</td>
<td>25</td>
</tr>
<tr>
<td>Doughnut (plain)</td>
<td>23</td>
</tr>
<tr>
<td>Ice cream (1/2 cup)</td>
<td>16</td>
</tr>
<tr>
<td>OJ (1 carton; 8 oz)</td>
<td>26</td>
</tr>
<tr>
<td>Pasta (1/2 cup)</td>
<td>18</td>
</tr>
<tr>
<td>Milk (1 cup)</td>
<td>12</td>
</tr>
</tbody>
</table>
Reading Labels

Nutrition Facts

Serving Size 1 cup (228g)
Servings Per Container 2

Amount Per Serving

<table>
<thead>
<tr>
<th>Nutrients</th>
<th>Amount</th>
<th>% Daily Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calories</td>
<td>250</td>
<td>11%</td>
</tr>
<tr>
<td>Total Fat</td>
<td>12g</td>
<td>18%</td>
</tr>
<tr>
<td>Saturated Fat</td>
<td>3g</td>
<td>15%</td>
</tr>
<tr>
<td>Trans Fat</td>
<td>3g</td>
<td>1%</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>30mg</td>
<td>10%</td>
</tr>
<tr>
<td>Sodium</td>
<td>470mg</td>
<td>20%</td>
</tr>
<tr>
<td>Potassium</td>
<td>700mg</td>
<td>20%</td>
</tr>
<tr>
<td>Total Carbohydrate</td>
<td>31g</td>
<td>10%</td>
</tr>
<tr>
<td>Dietary Fiber</td>
<td>0g</td>
<td>0%</td>
</tr>
<tr>
<td>Sugars</td>
<td>5g</td>
<td></td>
</tr>
<tr>
<td>Protein</td>
<td>5g</td>
<td>4%</td>
</tr>
</tbody>
</table>

vitamin A           | 4%       |
Vitamin C           | 2%       |
Calcium             | 20%      |
Iron                | 1%       |

* Percent Daily Values are based on a 2,000 calorie diet. Your Daily Values may be higher or lower depending on your calorie needs.
**Blueberry, prepared from recipe**

**Serving Size**: 1 pancake, 6" dia (2.7 oz)

<table>
<thead>
<tr>
<th>Nutrition Facts</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Calories 171</td>
<td>(715 kJ)</td>
<td></td>
</tr>
<tr>
<td>Calories from fat 64</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Fat 7.1g</td>
<td>11%</td>
<td></td>
</tr>
<tr>
<td>Sat. Fat 1.5g</td>
<td>8%</td>
<td></td>
</tr>
<tr>
<td>Cholesterol 43mg</td>
<td>14%</td>
<td></td>
</tr>
<tr>
<td>Sodium 317mg</td>
<td>13%</td>
<td></td>
</tr>
<tr>
<td>Total Carbs. 22.3g</td>
<td>7%</td>
<td></td>
</tr>
<tr>
<td>Protein 4.7g</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium 158.6mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Potassium 106.3mg</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

[Compare Foods]
Normal Blood Glucose Profile

Graph Showing The Effect Of Glucose (reference food) On Blood Glucose Level

- Blood Sugar Levels
- 1 Hour
- 2 Hours
- Glucose (reference food)
Bolus Insulin (Correctional/SSI) Sensitivity

Rule of 1700

1700/TDI

1700/50=34, rounded to 35

1 unit of insulin lowers this patients BG by 35 mg/dl.
## Daily Insulin Adjustments

<table>
<thead>
<tr>
<th></th>
<th>AM</th>
<th>Noon</th>
<th>PM</th>
<th>HS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before</td>
<td>223</td>
<td>278</td>
<td>252</td>
<td>305</td>
</tr>
<tr>
<td>Insulin</td>
<td>198</td>
<td>265</td>
<td>311</td>
<td>328</td>
</tr>
<tr>
<td>After</td>
<td>169</td>
<td>214</td>
<td>231</td>
<td>253</td>
</tr>
<tr>
<td>Insulin</td>
<td>171</td>
<td>187</td>
<td>191</td>
<td>209</td>
</tr>
</tbody>
</table>
Daily Insulin Adjustments (cont’d)

Increase basal insulin by 20%

Glargine from 25 units → 30 units

Recalculate bolus insulin from new basal insulin dose

Total daily insulin → 30+30= 60 units
I to C ratio: 500/60= 8.3 gms, or 1 u per 8 gm carbs or 2 u/c
Sensitivity/Correction: 1700/60= 28.3, or 1 u per 30 mg/dl
Managing patients already on insulin

Patients in good to fair control (A1c <8.0%)

May continue with patient’s home insulin regimen, if PO

If NPO

- Decrease basal insulin by 20-30% (glargine, detemir), or 50% (NPH). Monitor FBG, adjust basal insulin
- Hold scheduled meal insulin
- Calculate correctional insulin from new basal insulin dose and use Q 4 hourly
Managing patients already on insulin

**Patients in poor control (A1c > 8.0%)**
If BGs 200s to 300s, titrate basal insulin up, recalculate meal and correction insulin from new TDI

<table>
<thead>
<tr>
<th></th>
<th>AM</th>
<th>Noon</th>
<th>PM</th>
<th>HS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>223</td>
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<td>252</td>
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</tr>
<tr>
<td>200</td>
<td>198</td>
<td>265</td>
<td>311</td>
<td>328</td>
</tr>
</tbody>
</table>

Patient on glargine 30 units already, and aspart 5 u TID.

A 20% increase will be glargine 36 units daily
TDI → 72 units
Carb coverage: 500/72 → 1 u per 7 gms or 2 u per carb
Correction: 1700/72 → 1 u per 24

If BGs 400s, use insulin drip. Cover meals with s/c insulin while patient on insulin drip.
Indications for IV Insulin Infusion (Drip)

- DKA or NKHS
- Extreme Hyperglycemia
- Critical Illness (ICU)
- NPO (uncertainty of duration of npo)
- Major surgery
- TPN (At initiation)
- TFs (At initiation)
- High dose Steroids

Always cover meals with s/c short acting insulin while patients on the insulin drip to prevent food related increase in insulin drip rates
### Continuous Intravenous Insulin Infusion

<table>
<thead>
<tr>
<th>Date:</th>
<th>11/06</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time:</td>
<td>05:54</td>
</tr>
<tr>
<td>Glucose (mg/dl)</td>
<td></td>
</tr>
<tr>
<td>Random glucose</td>
<td>118</td>
</tr>
<tr>
<td>Punctuate Site</td>
<td>Finger</td>
</tr>
<tr>
<td>Glucose (mg/dl)</td>
<td>118</td>
</tr>
<tr>
<td>Insulin U/Unit</td>
<td>1 Unit/L</td>
</tr>
<tr>
<td>Rate (u/hr)</td>
<td>1 u/hr</td>
</tr>
<tr>
<td>Carbohydrates</td>
<td></td>
</tr>
<tr>
<td>Carbohydrate Intake</td>
<td></td>
</tr>
</tbody>
</table>
Inpatient Special Circumstances

Transitioning from intravenous insulin infusion to subcutaneous insulin

- Determine 24 hour IV total insulin received and calculate 80% of this. This will be Total Daily Insulin (TDI)
- If patient NPO, give all 80% as basal insulin (Glargine or Detemir)
- If patient taking PO, then best to determine basal insulin needs from overnight insulin drip rates
- Calculate prandial insulin with rule of 500, and correction with rule of 1700
IV Insulin to S/C Conversion

- 3.4 u/4 hours = 20.4 units / 24 hours
- Take 80% of 20 units = 16 units. This is the basal insulin
- If 16 units is the basal insulin, then TDI =32 units
- Meal Insulin to Carb ratio= 500/32 = 15.6 gms
- Correction Insulin= 1700/32 = 53 mg/dl, may use pre-built medium intensity SSI
Inpatient Special Circumstances

TPN

Hyperglycemia resulting from TPN may be treated with;

Adding insulin to the TPN (ideal)

Continuous Intravenous Insulin Infusion
(at least initially)

S/C long acting insulin (least desirable)
TPN Composition
Adding Insulin to TPN

Assess total carbohydrate in the TPN (e.g; 22.5% in 1 liter = 225 gm)

Assess insulin to carbohydrate ratio from TDI (e.g; 1 u/10 gms or 1.5 u/carb)

Divide 225 gm/10 = 22.5 units insulin

Add regular insulin 22.5 units to each TPN bag

Calculate insulin to carbohydrate in grams ratio; 22.5/225 = 0.1 u/gm dextrose

Give this ratio to the pharmacist to be maintained for any TPN dextrose Δs

Increase in daily increments 0.025-0.05 U/gm until desired glucose levels
Inpatient Special Circumstances

TUBE FEEDS

Ideally start with insulin infusion until desired TF rate reached
Add up 24 hour drip rates, take 80% of it;
If TFs continuous, switch insulin to once/twice daily basal Insulin.
If TFs nocturnal, use NPH.

Determine the amount of carbohydrate in the tube feed formula
e.g; 150 gms per liter
Determine insulin to carbohydrate ratio, e.g; 1 u per 10 gm carbs.
Divide 150 gms/10= 15 units. This is the basal insulin dose.
If patient already on certain basal insulin, add the above 15 units to the existing basal insulin dose to cover the tube feeds
Available Insulin Preparations

- **Rapid acting:** Insulin lispro, aspart or glulisine
- **Short acting:** Regular Insulin
- **Intermediate acting:** NPH
- **Long acting:** Insulin detemir, Insulin glargine

Adapted from Nolte (2009)
Inpatient Special Circumstances

High Dose Steroids

Start with insulin infusion initially.

Once stable insulin drip rates achieved with BGs in target, switch to s/c insulin

Always cover meals with s/c short acting insulin while patients on the insulin drip to prevent food related increase in insulin drip rates
Summary

- Hospital hyperglycemia is harmful and leads to poor outcomes
- Insulin is a preferred agent to treat hospital hyperglycemia, oral agents are discouraged
- In the ICU, use IV insulin infusion. Studies support relaxed targets but do not recommend poor or no control
- Always give basal insulin (Glargine, Levemir, NPH) 1-2 hours before stopping insulin drips
- Insulin should not be used as sliding scale alone, and instead as either basal/bolus therapy or IV infusion form
- Insulin may be added to TPN as needed to provide more stable control
- Steroid Induced and nutritional hyperglycemia is best treated with IV insulin initially
- Always get HbA1c on hyperglycemic patients