Learning Objectives

1. Recognize the pathophysiological changes of patients with stress hyperglycemia and diabetes in the hospital.
2. Discuss several studies which relate to the implications of hyperglycemia in the hospital regarding critically ill and medical-surgical patients.
3. Discuss the current blood glucose guidelines for critically ill and medical-surgical patients in the hospital.
Hospital Cost of Diabetes in USA

- Total estimated cost of diagnosed diabetes in 2012 is
  - $245 billion
  - $176 billion in direct medical costs
  - $69 billion in reduced productivity
- Components of medical expenditures
  - Hospital inpatient care (43%)
  - Prescription meds to Rx complications of DM (18%)
  - Antidiabetic agents and diabetes supplies (12%)
  - Physician office visits (9%)
  - Nursing/residential facility stays (8%)
- 41% increase from previous estimate of $174 billion (in 2007 dollars)


Stress Hyperglycemia Exacerbates Illness

Hyperglycemia and Poor Hospital Outcome

Insulin Requirements in Health and Illness


Critically Ill Patients

Mean Glucose Value (mg/dL)

N=1826 ICU patients.

Hyperglycemia and Mortality in the Medical Intensive Care Unit

Note: modest increase BG after ICU admission was associated with substantial increase in hospital mortality.
Intensive Insulin Therapy in Critically Ill Surgical Patients: The Leuven Study

Randomized controlled trial: 1,548 pts admitted to a surgical ICU. Pts were assigned to receive either:

- **Conventional therapy**: IV insulin if BG > 215 mg/dL
  - Target BG levels: 180-200 mg/dL
  - Mean daily BG: 153 mg/dL
- **Intensive therapy**: IV insulin if BG > 110 mg/dL
  - Target BG levels: 80-110 mg/dL
  - Mean daily BG: 103 mg/dL

Van-Den Berge et al, NEJM 345:1359, 2001

Intensive Insulin Therapy in Critically Ill Patients

<table>
<thead>
<tr>
<th>Condition</th>
<th>Relative Risk reduction (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>42%*</td>
</tr>
<tr>
<td>Bacteremia</td>
<td>46%*</td>
</tr>
<tr>
<td>Prolonged (&gt;10 d) antibiotics</td>
<td>36%*</td>
</tr>
<tr>
<td>Prolonged (&gt;14 d) ventilation</td>
<td>38%*</td>
</tr>
<tr>
<td>Dialysis</td>
<td>41%*</td>
</tr>
<tr>
<td>Prolonged (&gt;14 d) ICU Stay</td>
<td>28%*</td>
</tr>
</tbody>
</table>

* P < 0.01

Van-Den Berge et al, NEJM 345:1359, 2001
Survival Increased due to IIT (including non diabetic patients) for Patients with a BG goal of 80-110 mg/dL who remained in ICU > 5 days


- Randomized, controlled trial in Australia, New Zealand, Canada, US
- 6104 adult medical and surgical patients admitted to the ICU
  - Intensive- IV insulin started if BS > 108: goal 81-108
  - Conventional- IV insulin started only if BS > 180: goal 144-180
- 20% of patients were diabetic
- Primary endpoint: all-cause 90-day mortality

Intensive Insulin Therapy: NICE-SUGAR (2009)

- Intensive group
  - Actual glucose: 115 +/- 18 mg/dL
  - Patients with BS < 40: 6.8%
- Conventional group
  - Actual glucose: 144 +/- 23 mg/dL
  - Patients with BS < 40: 0.5%

The NICE-SUGAR Study Investigators. NEJM 2009;360:1283-97

The Nice-Sugar Study Investigators. NEJM 2009;360:1283-1297
Intensive Insulin Therapy: NICE-SUGAR (2009)

Mortality:
Intensive: n=829 (27.5%)
Conventional: n=751 (24.9%)
P=0.03

The Nice-Sugar Study Investigators. NEJM. 2009; 360: 1283-1297

Discussion:
• "In this large, international, randomized trial, we found that intensive glucose control increased mortality among adults in the ICU: a blood glucose target of 180 mg/dL or less resulted in lower mortality than did a target of 81 to 108 mg/dL."

The Nice-Sugar Study Investigators. NEJM. 2009; 360: 1283-1297

Why were the results of the Leuven SICU not reproduced?
• Single center vs multicenter studies
• Variability in duration of hyperglycemia before the start of the insulin protocol
• Variability in the type of insulin protocol
• Parenteral hyperalimentation the rule in Leuven study and enteral nutrition the rule in NICE SUGAR
Pooled Meta-analysis of 26 trials: Relative Risk of Death with Intensive Insulin Therapy

The pooled relative risk of death with IIT was 0.93 compared with conventional therapy (95% CI 0.83-1.04).


Severe Hypoglycemia in ICU Is More Likely With Intensive Insulin Therapy Than Conventional Glycemic Control: A Meta-analysis

Overall severe hypoglycemia RR 5.99 (4.47-8.03)


Summary of Most Current Professional Societies’ Guidelines for Glycemic Control

Point of Care Testing Blood Glucose in Critical Illness

Factors to Consider When Using Devices in ICU Glucose Measurement

• Accuracy
• Speed of results
• Cost per test
• Sample volumes


Arterial, Capillary or Venous Blood

• Arterial blood has higher glucose levels compared with venous
  • 5-10 mg/dL higher than capillary and venous concentrations

Patient Conditions that Increase Risk of Errors

- CKD results in greater risk of hypoglycemia and anemia
- Hct <20% (may falsely raise BG in POC BG meters that do not detect Hct)
- End-stage liver disease and malnutrition add to glycemic instability
- Sepsis heightens risk of hypoglycemia

Inferences and Limitations of POC Devices: Clinical

- Interference from endogenous substances
  - Triglycerides, bilirubin, uric acid
- Conditions: Dehydration, hypoxia, DKA/HHS, hypotension, shock, capillary hypo-perfusion, heart failure, finger edema
- Hematocrit outside range: ~<10% or > 60%
- Interference from other sugars: maltose-containing infusions
  - Glucose dehydrogenase pyrroloquinoline quinone (GDH-PQQ) reagents

Point of Care Devices

- International Organization for Standardization guideline (ISO 15197, 2003)
  - BG ≥ 75 mg/dL, 95% need to be within ±20% of the “reference” value (lab and/or POC BG)
  - BG < 75 mg/dL, 95% need to be within ±15 mg/dL.
    - 1 out of 20 tests may have poor accuracy
    - meter will be approved


Point of Care Devices

- International Organization for Standardization guideline: 2014 FDA Draft
  - BG ≥ 70 mg/dL, 99% need to be within ± 10% of the “reference” value (lab analyzed BG)
    - The other 1% must not exceed ± 20%
  - BG < 70 mg/dL, 99% need to be within ± 7 mg/dL
    - The other 1% cannot exceed ± 15 mg/dL

FDA Draft Recommendations for Hospital POC BG Meters

<table>
<thead>
<tr>
<th>Comparison of 2003 ISO 15197 standard and 2014 FDA draft recommendations for hospital POC BG meters</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard</td>
<td>BG ≥ 70 mg/dL, ≤ 179 mg/dL, in 2003</td>
</tr>
<tr>
<td>Lab glucose example</td>
<td>15 min.</td>
</tr>
<tr>
<td>2003 ISO/POC BD</td>
<td>95%</td>
</tr>
<tr>
<td>20-64 mg/dL</td>
<td>95%</td>
</tr>
<tr>
<td>65-119 mg/dL</td>
<td>95%</td>
</tr>
<tr>
<td>120-179 mg/dL</td>
<td>95%</td>
</tr>
<tr>
<td>180-239 mg/dL</td>
<td>95%</td>
</tr>
<tr>
<td>240 mg/dL</td>
<td>95%</td>
</tr>
<tr>
<td>2014 FDA Draft recommendations</td>
<td>95%</td>
</tr>
<tr>
<td>BG &gt; 70 mg/dL</td>
<td>90%</td>
</tr>
<tr>
<td>BG &lt; 70 mg/dL</td>
<td>90%</td>
</tr>
</tbody>
</table>

Wired vs Wireless POC Glucose Meters

<table>
<thead>
<tr>
<th>Wired POC meters</th>
<th>Wireless POC meters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Need to dock meter</td>
<td>Meter docking not required</td>
</tr>
<tr>
<td>Less durable</td>
<td>Durability increased</td>
</tr>
<tr>
<td>Slower work flow</td>
<td>Improves work flow</td>
</tr>
<tr>
<td>Increased sources of errors</td>
<td>Real-time BG reporting, less errors</td>
</tr>
<tr>
<td>Not accessible without docking stations</td>
<td>Access from anywhere with a wireless network</td>
</tr>
<tr>
<td>Results, 6-240 s</td>
<td>Results, 5 s</td>
</tr>
</tbody>
</table>

Glycemic Targets in Non-Critical Care Setting

Premeal BG target of <140 mg/dl (7.8 mmol/L) and random BG <180 mg/dl (10 mmol/L) for the majority of patients.

Glycemic targets be modified according to clinical status.
- Patients with terminal illness, a higher target range (BG <180-200 mg/dl) may be reasonable.

For avoidance of hypoglycemia, diabetic therapy be reassessed when BG<100 mg/dl (5.5 mmol/L).

American College of Physicians recommended a BG target < 200 mg/dl (11.1 mmol/L), Ann Intern Med. 2012


Use of Oral Diabetes Agents in Hospitalized Patients

• 3 primary categories of oral agents:
  • Secretagogues: sulfonylureas and meglitinides
    - Long action and predisposition to hypoglycemia
  • Biguanides
    - Lactic acidosis (rare), however hospitalized pts at risk for hypoxia, hypoperfusion and renal insufficiency
    - Side effects: nausea, diarrhea and decreased appetite
  • Thiazolidinediones
    - Increase intravascular volume, concern for CHF and hemodynamic changes
• OHA have significant limitations for inpatient use
• OHA provide little flexibility for titration
• Insulin when used properly may have many advantages in the hospital setting

DPP-4 Therapy in Hospitalized Patients

**Study Type:** Multicenter, prospective, open-label randomized clinical trial

**Patient Population:** Patients with T2D admitted to general medicine and surgery services at 3 hospitals: Emory University, Grady, and University of Michigan

**Treatment Groups***

- Group 1. Sitagliptin once daily (n=30)
- Group 2. Sitagliptin plus glargine insulin once daily (n=30)
- Group 3. Basal bolus regimen with glargine once daily and lispro before meals (n=30)

* All groups received supplemental doses of lispro for BG > 140 mg/dl before meals


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Mean Daily BG During Treatment

![Mean Daily BG During Treatment Graph](image)


Mean BG before Meals and at Bedtime during Treatment

![Mean BG before Meals and at Bedtime during Treatment Graph](image)

Data is mean ± SE
Conclusions

- Treatment with sitagliptin alone or in combination with basal insulin is safe and effective for the management of hyperglycemia in general medicine and surgery patients with T2DM.

Exenatide for Hyperglycemia in CICU

- Prospective, single-center, open-label, nonrandomized pilot study
- 40 patients admitted to the CICU with BG 140-400 mg/dL
- All patients received IV exenatide as a bolus followed by a fixed dose infusion for up to 48 hours
- Exenatide effectiveness benchmarked to two historical insulin infusion cohorts, one (INT) with BG target 90-119 mg/dL (n=84) and the other (MOD) with a target of 100-140 mg/dL (n=71)
Median Glucose Values over Time

Target glucose levels were 100-140 mg/dL for both the exenatide and modified control (MOD) arms, and 90-119 mg/dL for the intensive control group (INT).


Conclusions

- Steady state glucose values were similar between the exenatide (132 mg/dL) and the MOD groups (127 mg/dL), but lower in the INT group (105 mg/dL).
- Median time to steady state was 2.0 hrs in the exenatide group compared to 12.0 hours in the MOD group and 3.0 hours in the INT group.
- No episodes of severe hypoglycemia (<50 mg/dL) occurred in patients who received exenatide.
- Nausea was reported by 16 patients and vomiting by 2 patients.
- Summary: IV exenatide is effective in lowering glucose levels in CICU patients, but its use may be limited by nausea.


Randomized Basal Bolus versus Sliding Scale Regular Insulin Therapy in Patients with Type 2 Diabetes (RABBIT-2 Trial)

Study Type: Prospective, randomized, open-label trial

Patient Population: 130 subjects with DM2
- Oral hypoglycemic agents or diet therapy,
- Insulin naive

Study Sites: Grady Memorial Hospital, Atlanta
- Jackson Memorial Hospital, Miami

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

![Graph showing glucose levels over days of therapy for Admit 1, Sliding scale, Basal-bolus, and BG, mg/dL from 100 to 240.]

- P<.05.
- Sliding scale regular insulin (SSRI) was given 4 times daily
- Basal-bolus regimen: glargine was given once daily; glulisine was given before meals.
- 0.4 U/kg/d x BG between 140-200 mg/dL.
- 0.5 U/kg/d x BG between 201-400 mg/dL


Basal–Bolus Insulin Regimen in Non-critically Ill Patients

- **Treatment success**
  - BG target of <140 mg/dL was achieved in 59% of patients on Basal-bolus (Lantus® + Apidra®) and 38% of patients (SSRI)

- **Treatment failure**
  - One out of 9 patients using SSRI remained with BG >240 mg/dL and switched to Basal-Bolus (Lantus® + Apidra®)


Rabbit-2: Conclusion

- Basal/bolus insulin regimen with glargine once daily and glulisine before meals is a better insulin regimen than SSRI in the management of type 2 diabetics in the non-ICU setting
- SSRI as a single insulin regimen should not be used for the management of patients with type 2 diabetes

Rabbit Surgery (Randomized Study of Basal Bolus Insulin Therapy in the Inpatient Management of Patients with T2DM Undergoing General Surgery): Research Design and Methods

- **Study Type:** Multi-center, prospective, open-label randomized clinical trial
- **Patient Population:** Patients with known T2DM admitted to general surgery services
- **Study Sites:** Grady Memorial Hospital, Veterans Affairs Medical Center and Emory University Hospital, Atlanta, GA
- **Treatment Groups:**
  - Group 1: basal bolus regimen (n=104)
  - Group 2: sliding scale regular insulin (n=107)


Glucose Levels During Basal Bolus and SSI Therapy

- **Graph:**
  - Basal Bolus vs. Sliding Scale Insulin
  - Duration of Treatment (days)
  - Blood Glucose (mg/dl)

- **Statistical Notes:**
  - * p: <0.001
  - † p: 0.01
  - ‡ p: 0.02

Postoperative Complications

- **Graph:**
  - Glargine+Glulisine vs. Sliding Scale Insulin

- **Statistical Notes:**
  - P=0.003
  - P=0.05
  - P=0.02
  - P=0.10

- **Composite of hospital complications:** wound infection, pneumonia, respiratory failure, acute renal failure, and bacteremia.

**DEAN Trial: Changes in Mean Daily Blood Glucose Concentration**

- **Detemir + aspart**
- **NPH + regular**

Data are means ± SEM.

Baseline-bolus regimen: detemir was given once daily, and aspart was given before meals.

NPH/regular regimen: NPH and regular insulin were given twice daily, two-thirds in AM, one-third in PM.


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**Basal Plus Trial: Basal + 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 before meals
  - 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.

Discharge Insulin Algorithm

- **A1C < 7%**
  - Re-start outpatient treatment regimen (OAD and/or insulin)

- **A1C 7%-9%**
  - Re-start outpatient oral agents and D/C on glargine once daily at 50% of hospital dose

- **A1C >9%**
  - D/C on basal bolus at same hospital dose.
  - Alternative: re-start oral agents and D/C on glargine once daily at 80% of hospital dose

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Change in HbA1C after Discharge

- **Admission**: 8.67±2.5
- **4 Weeks**: 7.86±1.7
- **12 Weeks**: 7.26±1.5

Data are mean ±SD
* p<0.001 from admission

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Basal-PLUS vs Basal Bolus: 375 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%

Patients treated with diet, oral agents or with low-dose insulin ≤ 0.4 U/Kg/Day

Conclusion

- Measurement of HbA1c is a useful tool to assess metabolic control and to design treatment regimen at the time of hospital discharge.

- The proposed HbA1c-based hospital discharge algorithm is an effective and safe regimen for the management of general medicine and surgical patients with T2DM.

- This study included frequent contacts not common for all post-discharge patients, thus future randomized trials are need to confirm the efficacy of the proposed HbA1c based discharge algorithm in general medicine and surgery with type 2 diabetes.

Carbohydrate Counting Diet

**How to order a diabetic diet**

There are 3 levels of the carbohydrate (CHO) counting diet:
- Level 1 is 5 to 1600 kcal.
- Level 2 is 1700-2000 kcal.
- Level 3 is 2 to 2100 kcal.

The average female needs about 1700-1800 kcal.
The average male needs about 2000 kcal.

* It is appropriate to order a COMBINED Cardiac Fitness (CF) diet with the CHO counting diet to provide lower fat, lower sodium foods.

Example of a Diet Order:
Level 2, CF
Discharge Planning

- Be proactive! Start early (2-3 days before)
- What can this patient handle at home, assisted living, rehabilitation, or skilled nursing facilities
- Consider side effects, drug intolerances, comorbidities, costs
- Rx’s, supplies, appointments
- Medication reconciliation
- “Survival skills”
- Outpatient follow up with primary care provider, endocrinologist or diabetes educator within 1 month of discharge is key for all patients having hyperglycemia in the hospital

Overcoming the Barriers to Optimal Glycemic Control in the Hospital

- Achievable goals
- Teamwork
- Optimal glycemic control
Thank you