Hyperglycemia/Hypoglycemia and Glycemic Variability in the Hospital

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University of Michigan

COI: F. Pasquel

External Industry Relationships *

<table>
<thead>
<tr>
<th>Company Name(s)</th>
<th>Role</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMJ Open Diabetes &amp; Care</td>
<td>Social Media Editor</td>
</tr>
<tr>
<td>Merck</td>
<td>Consultant activities</td>
</tr>
<tr>
<td>Boehringer Ingelheim</td>
<td>Consultant activities</td>
</tr>
</tbody>
</table>

Hyperglycemia/Hypoglycemia and Glycemic Variability

Hyperglycemia

Hypoglycemia

Outcomes

Glycemic variability

DCCT: Absolute Risk of Sustained Retinopathy Progression by Mean A1c

![Graph showing the relationship between A1c and rate of progression of retinopathy](Image)


Different complications (eye, kidney, nerve, blood vessels) arise from limited number of triggers perturbing a limited number of metabolic pathways.

How does glycemic variability contribute to complications?

![Diagram showing the relationship between glycemic variability and complications](Image)

Brownlee M. Nature 2001;414:813-20)

AADE 2017
Inhospital Hyperglycemia

- Hyperglycemia is an independent risk factor for clinical outcomes in critically-ill patients.
- Higher glucose values, in patients with and without diabetes, is associated with greater risk for mortality and hospital complications.

Hyperglycemia and Mortality in the MICU


Hospital Mortality by BG Levels during TPN

Overall in-hospital mortality was 27.2%

Hypoglycemia

Hypoglycemia in T2DM

- The primary cause of hypoglycemia in T2DM is diabetes medication—sulfonylureas and insulin.
- The risk of hypoglycemia is increased in older patients, those with longer diabetes duration, lesser insulin reserve and with strict glycemic control.
- Hypoglycemia has substantial clinical impact, in terms of mortality, morbidity and quality of life.
- The cost implications of severe episodes—high direct hospital costs and indirect costs.
- Hypoglycemia and fear of hypoglycemia limit the ability to achieve and maintain optimal glycemic control.
- Newer therapies, may carry a lower risk of hypoglycemia.

Factors that may increase risk of hypoglycemia during therapy

- Behavioral factors
- missed or irregular meals, exercise
- Impaired drug clearance
- renal impairment, hepatic failure, hypothyroidism
- Impaired counterregulatory capacity
- Addison’s, growth hormone deficiency, hypopituitarism
- Decreased endogenous glucose production
- liver failure, alcohol
- Concurrent medications
- Decreased renal excretion of SUs - aspirin, allopurinol
- Displacement of SUs from albumin - aspirin, warfarin, trimethoprim

Risk of Hypoglycemia Associated with Medications in T2DM

<table>
<thead>
<tr>
<th>Medication</th>
<th>Route</th>
<th>Risk of Hypoglycemia %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>Oral</td>
<td>0.3 (1) Similar to placebo</td>
</tr>
<tr>
<td>Sulfonylureas</td>
<td>Oral</td>
<td>18% to 30% per year</td>
</tr>
<tr>
<td>Glinides</td>
<td>Oral</td>
<td>5-10%</td>
</tr>
<tr>
<td>TZDs</td>
<td>Oral</td>
<td>&lt; 3% Similar to placebo</td>
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<tr>
<td>α-glucosidase inhibitors</td>
<td>Oral</td>
<td>&lt; 3% Similar to placebo</td>
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<tr>
<td>DPP-IV Inhibitors</td>
<td>Oral</td>
<td>&lt; 3% Similar to placebo</td>
</tr>
<tr>
<td>Colesevelam</td>
<td>Oral</td>
<td>Similar to placebo</td>
</tr>
<tr>
<td>Bromocriptine mesylate</td>
<td>Oral</td>
<td>0.2-0.4</td>
</tr>
</tbody>
</table>


Intensive Insulin Therapy and Hypoglycemic Events in Critically Ill Patients

<table>
<thead>
<tr>
<th>Study</th>
<th>IIT Control</th>
<th>Risk ratio (95% CI)</th>
<th>No. Events/Total No. Patients</th>
<th>Hypoglycemic Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Van den Berghe et al</td>
<td>39/278</td>
<td>6.65 (2.83-15.05)</td>
<td>7/200</td>
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Overall 654/6138 98/6209 5.99 (4.47-8.03)


Effect of intensive glucose lowering treatment on hypoglycemic events

Compared with the standard treatment group, the risk of severe hypoglycemia was more than twice as high in the intensive treatment group (2.33, 1.62 to 3.36). Absolute five year risk increases in severe hypoglycemia ranged from 1.9% to 6.6%, making the number of patients needed to harm between 52 and 15.


Responses to Hypoglycemia in Normal Subjects

80 mg/dl - Decreased insulin secretion
70 mg/dl - Glucagon secretion increased
65 mg/dl - Epinephrine secretion increased
60 mg/dl - Cortisol and GH secretion
60 mg/dl - Initial symptoms of sweating, anxiety, palpitations, hunger and tremor
50 mg/dl - Cognitive dysfunction noted
45 mg/dl - Lethargy and obtundation
30 mg/dl - Coma
20 mg/dl - Convulsions

Prevalence of Symptomatic Hypoglycemia

<table>
<thead>
<tr>
<th>Study</th>
<th>No of events/Total No. patients</th>
<th>Hypoglycemic Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>NICE-SUGAR</td>
<td>206/3016</td>
<td>15/3014 5.99 (8.15-23.12)</td>
</tr>
<tr>
<td>Brunkhorst et al</td>
<td>42/247</td>
<td>12/290 4.11 (2.2-7.63)</td>
</tr>
<tr>
<td>Iapichino et al</td>
<td>8/45</td>
<td>3/45 2.67 (0.76-9.41)</td>
</tr>
<tr>
<td>Arabi et al</td>
<td>76/266</td>
<td>8/257 9.18 (4.52-18.63)</td>
</tr>
<tr>
<td>Mackenzie et al</td>
<td>7/39</td>
<td>1/51 9.15 (1.17-71.35)</td>
</tr>
<tr>
<td>Devos et al</td>
<td>54/550</td>
<td>15/551 3.61 (0.50-5.56)</td>
</tr>
<tr>
<td>Van den Berghe et al</td>
<td>111/595</td>
<td>19/605 5.94 (3.70-9.54)</td>
</tr>
<tr>
<td>Henderson et al</td>
<td>7/32</td>
<td>1/35 7.66 (1.00-58.86)</td>
</tr>
<tr>
<td>Mitchell et al</td>
<td>5/33</td>
<td>0/35 11.00 (0.63-191.69)</td>
</tr>
</tbody>
</table>

Overall 654/6138 98/6209 5.99 (4.47-8.03)

380,000 Emergency Department Visits per Year in the United States From 1993 to 2005 Were Attributed to Hypoglycemia

- 5 million emergency department visits between 1993 and 2005 for hypoglycemia.
  - 25% resulted in hospital admission
  - 72% of patients had hypoglycemia as the primary (first-listed) diagnosis
  - 44% of reported cases occurred in adults ≥65 years of age
- Elderly patients are less likely to recognize symptoms of hypoglycemia.

Asymptomatic Hypoglycemia in Non-ICU Patients with Diabetes

<table>
<thead>
<tr>
<th>Neurological symptoms</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confusion</td>
<td>97 (78%)</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>29 (23%)</td>
</tr>
<tr>
<td>Shurred speech</td>
<td>39 (32%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Adrenergic symptoms</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety</td>
<td>96 (78%)</td>
</tr>
<tr>
<td>Trembling</td>
<td>30 (24%)</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>97 (74%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Odds Ratio</th>
<th>Confidence Interval (95%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1C</td>
<td>0.93 (0.83, 1.03)</td>
</tr>
<tr>
<td>Age &lt; 50 yrs</td>
<td>1.00 (1.00, 1.00)</td>
</tr>
<tr>
<td>51-65 yrs</td>
<td>1.76 (0.77, 4.01)</td>
</tr>
<tr>
<td>&gt; 65 yrs</td>
<td>2.45 (1.10, 5.40)</td>
</tr>
<tr>
<td>BG at event</td>
<td>1.07 (1.00, 1.15)</td>
</tr>
</tbody>
</table>


Gomez et al. ADA 2017
Update on Definition of Hypoglycemia

Before 2017
- Hypoglycemia: < 70 mg/dl
- Severe hypoglycemia: < 40 mg/dl

After 2017
- Hypoglycemia alert: < 70 mg/dl
- Significant hypoglycemia: < 54 mg/dl
- Severe hypoglycemia:
  - No level
  - Severe cognitive impairment requiring external assistance for recovery

Diabetes Care 2017;40:155–157

Questions

- How do we measure glucose variability (GV)?
- How does GV affect clinical outcomes like infection rates, mortality, length of hospital?

MAGE better measure of GV than SD

Two patients with identical mean glucose and SD but different patterns of variability expressed by MAGE

Acute glycemic variations (GV) may be more deleterious than constant exposure to a high glucose concentration


Measures of glucose variability

<table>
<thead>
<tr>
<th>Variability measure</th>
<th>Formula</th>
<th>Explanation of symbols</th>
<th>Discriminating feature</th>
</tr>
</thead>
<tbody>
<tr>
<td>SD</td>
<td>( \sum (x_i - \bar{x})^2 / (n-1) )</td>
<td>( x_i ) = individual observation; ( \bar{x} ) = mean of observations; ( n ) = number of observations</td>
<td>Easy to determine; extensively used</td>
</tr>
<tr>
<td>CV</td>
<td>( s / \bar{x} )</td>
<td>( s ) = standard deviation; ( \bar{x} ) = mean of observations</td>
<td>Easy to determine; SD corrected for mean</td>
</tr>
<tr>
<td>MAGE</td>
<td>( \sum (x_i - B)^2 / (k-1) )</td>
<td>( x_i ) = each blood glucose level; ( B ) = baseline; ( k ) = number of observations</td>
<td>Used most extensively</td>
</tr>
<tr>
<td>CGMSA</td>
<td>( \sum (x_t - B)^2 / k ) where ( k = 0.6 )</td>
<td>( x_t ) = number of observations where there is a change in glucose level ( x ) = 0.6; ( D_t ) = difference between glucose levels; ( GR = GR )</td>
<td>Specifically developed for CDM</td>
</tr>
</tbody>
</table>

SD=standard deviation; CV=coefficient of variation; MAGE=mean amplitude of glycemic excursions; CGM=continuous glucose monitoring; MD=mean of daily differences; SMBG=self-monitored blood glucose; CDM=continuous glucose monitoring; Units are in mmol/l or mg/dl.
Glucose variability and mortality in patients with sepsis

GLI: Squared difference between consecutive glucose measures per unit of actual time between samples


GV as a predictor of mortality within different ranges of mean glucose

Each of the increments of mean glucose level is subdivided into four quartiles of glycemic variability. Q1 represents the lowest quartile; Q4 represents the highest quartile.

GV as a predictor of Hospital mortality in patient treated with TPN

Percentages of hospital mortality across different quartiles of GV of daily BG

1A. GV calculated by SD. 1B. GV calculated by mean daily Q change. P values denote differences in hospital mortality across GV categories. BG = blood glucose; GV = glycemic variability; Q = quartile.


GV Medical vs. Surgical (Mean delta daily, SD and MAGE)

Medical

Surgical

P=NS

P=0.02

P=0.069

BB = Basal Bolus

BP = Basal Plus

Farrokhi et al. ADA 2013

Summary

• Hyperglycemia, hypoglycemia and GV are associated with poor outcomes in hospitalized patients
• In non-diabetic subjects, hyperglycemia and greater glycemic variability are associated with higher hospital mortality and post-operative complications
• In diabetic subjects, glycemic variability does not appear to be associated with increased risk of mortality or post-operative complications, hyperglycemia is.

Improving outcomes

Promote safe and effective glucose control
• Reducing peak hyperglycemia rates
• Reducing hypoglycemia rates
• Reducing glucose variability
• Increasing time in range
Strategies to manage hyperglycemia in the hospital

Case 1
54-year-old man with T2DM for exacerbation of congestive heart failure and cellulitis of left big toe. Home diabetes medications - metformin and glipizide, with good compliance.
ED Labs- A1c 7.6%, BUN 40, creatinine 2.0, BG is 220 mg/dl.

In addition to ordering a carbohydrate consistent diet what should you order for his diabetic management?
- A) Continue home metformin and glipizide doses
- B) Continue home metformin but discontinue glipizide
- C) Continue home glipizide but discontinue metformin
- D) Discontinue both metformin and glipizide

2004 Recommendation
“In summary, each of the major classes of oral agents has significant limitations for inpatient use. Additionally, they provide little flexibility or opportunity for titration in a setting where acute changes demand these characteristics. Therefore, insulin, when used properly, may have many advantages in the hospital setting.

AACE/ADA Target Glucose Level 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
  - Targets <110 mg/dL or >180 mg/dL are not recommended

<table>
<thead>
<tr>
<th>Adjust therapy</th>
<th>Premeal</th>
<th>Postprandial</th>
<th>Adjust therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;100 mg/dL</td>
<td>&lt;100</td>
<td>&lt;100-140</td>
<td>&lt;100-140</td>
</tr>
<tr>
<td>100-140 mg/dL</td>
<td>140-180</td>
<td>140-180</td>
<td>&gt;180</td>
</tr>
</tbody>
</table>


Non- ICU setting:

- Premeal < 140 mg/dL,
- Postprandial < 180 mg/dL
- Adjust therapy if BG < 100 mg/dL

Some patients may be maintained at higher/lower targets.
Renal, liver failure, hypoglycemia unawareness, heart failure

Glycemic Targets

- Once insulin therapy is started, a target glucose range of 140–180 mg/dL (7.8–10.0 mmol/L) is recommended for the majority of critically ill patients A; and noncritically ill patients. C

- Basal insulin or a basal plus bolus correction insulin regimen is the preferred treatment for noncritically ill patients with poor oral intake or those who are taking nothing by mouth. An insulin regimen with basal, nutritional, and correction components is the preferred treatment for noncritically ill hospitalized patients with good nutritional intake. A

Standards of care, 2017

Recommendations for Managing Patients With Diabetes in Non-ICU Setting

Antihyperglycemic Therapy

- Insulin: Recommended
- OADs: Not Generally Recommended

Standards of care, 2017

Metformin and Lactic Acidosis

- Impaired Metformin Clearance
  - Acute and chronic kidney failure

- Lactic Acidosis

- Impaired Tissue Oxygenation
  - Severe sepsis and septic shock
  - Hypovolemia, shock (e.g., surgery)
  - Decompensated heart failure

- Impaired Lactate Metabolism
  - Alcohol abuse
  - Liver failure
  - Nucleoside reverse transcriptase inhibitors


Efficacy of sitagliptin for the hospital management of general medicine and surgery patients with type 2 diabetes (Sita-Hospital): a multicentre, prospective, open-label, non-inferiority randomised trial

Passquel et al. Lancet Diabetes & Endocrinology 2017

- Primary endpoint: no-inferiority in mean BG difference between groups

- Secondary endpoints: hipoglycemia, treatment failure, complications

Lancet Diabetes & Endocrinology 2017

Contraindications to Oral Anti-Diabetic Agents in the Acute Inpatient Setting

<table>
<thead>
<tr>
<th>Class</th>
<th>Examples</th>
<th>Contraindications / Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biguanides</td>
<td>Metformin</td>
<td>Lactic acidosis risk (rare but with ARF); radio-contrast administration; fluctuating renal function; GFR based dosage.</td>
</tr>
<tr>
<td>Sulfonlureas and other insulin secretagogues</td>
<td>Glyburide, Glibenperide, Glipizide, Repaglinide</td>
<td>Long-acting worse, risk of hypoglycemia with low oral intake and fluctuating GFR</td>
</tr>
<tr>
<td>Thiazoladinediones</td>
<td>Pioglitazone</td>
<td>Risk of fluid retention; HF; CI in liver disease; takes 14 days to SS</td>
</tr>
<tr>
<td>Alpha-glucosidase inhibitors</td>
<td>Acarbose</td>
<td>No effect in fasting patient;</td>
</tr>
<tr>
<td>DPP-4 inhibitors</td>
<td>Sitagliptin, saxagliptin, linagliptin</td>
<td>Potential risk of CHF hospitalization (Saxa, aloglptin)</td>
</tr>
<tr>
<td>SGLT2 inhibitors</td>
<td>Empagliflozin, Dapagliflozin, Canagliflozin</td>
<td>Fluid shifts, UTI/yeast infections, euqglycemic DKA</td>
</tr>
</tbody>
</table>

Lancet Diabetes & Endocrinology 2017

Conduct of the study

- 279 completed enrolment and randomisation
- 277 received ≥1 dose of study drug
- 139 completed study and included in the analysis

Lancet Diabetes & Endocrinology 2017
## Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>All (n=277)</th>
<th>Sitagliptin-basal</th>
<th>Basal-bolus</th>
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</thead>
<tbody>
<tr>
<td>Admission-diabetes/therapy (n=275)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diet alone</td>
<td>33 (12%)</td>
<td>15 (12%)</td>
<td>18 (12%)</td>
</tr>
<tr>
<td>Oral agent</td>
<td>105 (41%)</td>
<td>52 (41%)</td>
<td>53 (41%)</td>
</tr>
<tr>
<td>Insulin alone</td>
<td>66 (24%)</td>
<td>34 (25%)</td>
<td>32 (23%)</td>
</tr>
<tr>
<td>Insulin/physical drugs</td>
<td>60 (22%)</td>
<td>31 (22%)</td>
<td>29 (21%)</td>
</tr>
</tbody>
</table>

**Glycemic control at baseline**

- **HbA1c (%)**
  - Basal: 8.7% (2.3)
  - Basal bolus: 8.7% (2.4)

- **HbA1c (%)**
  - Basal: 7.2 (5.3)
  - Basal bolus: 42 (38)

- **HbA1c (%)**
  - Basal: 10 (45)
  - Basal bolus: 52 (28)

- **Randomization blood glucose concentration (mmol/L)**
  - Basal: 3.9 (3.0)
  - Basal bolus: 13.9 (3.3)
  - Basal bolus: 13.9 (3.3)

- **Randomization blood glucose concentration (mM/L)**
  - Basal: 105 (39)
  - Basal bolus: 54 (39)
  - Basal bolus: 54 (39)

- **Randomization blood glucose concentration (mM/L)**
  - Basal: 105 (39)
  - Basal bolus: 54 (39)
  - Basal bolus: 54 (39)

**Total daily dose, U/kg/day**

- Basal: 0.2 ± 0.1
- Basal bolus: 0.3 ± 0.2

- **Total daily dose, U/day**
  - Basal: 24.1 ± 16.2
  - Basal bolus: 34.0 ± 20.1

- **Basal-bolus, U/day**
  - Basal: 17.9 ± 12.5
  - Basal bolus: 16.8 ± 10.4

- **Prandial, aspart/lispro, U/day**
  - Basal: 11.7 ± 7.9
  - Basal bolus: 5.8 ± 5.7

- **Insulin doses and # Injections/day**
  - Basal: 5.5 ± 4.7
  - Basal bolus: 2.8 ± 0.9

**Number of Injections**

- # injections/day (Hospital stay)
  - Basal: 2.2 ± 1.0
  - Basal bolus: 2.9 ± 0.9

---

**Hypoglycemia**

<table>
<thead>
<tr>
<th></th>
<th>Sitagliptin-basal</th>
<th>Basal bolus</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td># patients BG &lt;70 mg/dl, n (%)</td>
<td>13 (9%)</td>
<td>17 (12%)</td>
<td>0.45</td>
</tr>
<tr>
<td># patients BG &lt;40 mg/dl, n (%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>&gt; 0.99</td>
</tr>
</tbody>
</table>

---

**Approach to the Glycaemic Management of General Medical and Surgical Patients in Hospital**

**Saxagliptin in Non-Critically Ill Hospitalized Patients with T2D and Mild Hyperglycemia**

**Mean BG in the Hospital**

**A Case Based Approach to Reduce Glucose Variability in the Hospital**

Roma Gianchandani, MD
Michigan Medicine (Univ of MI)
AADE conference 2017
Conflict of interest

• None

PERSONALIZED BG GOALS IN THE HOSPITAL

SAFETY AND EFFICACY OF PERSONALIZED GLYCEMIC CONTROL IN CRITICALLY ILL PATIENTS: A 2-YEAR BEFORE AND AFTER INTERVENTIONAL TRIAL

James S. Kosiborod, MD, FCCP; Jean-Charles Petron, MD, PhD; Mark B. Hirsch, MD

Case 1

54-year-old man with T2DM for exacerbation of congestive heart failure.
Home diabetes medications - metformin and glipizide, with good compliance.
ED Labs- A1c 7.6%, BUN 40, creatinine 2.0, BG is 220 mg/dl.

In addition to ordering a carbohydrate consistent diet what should you order for his diabetic management?

A) Continue home metformin and glipizide doses
B) Continue home metformin but discontinue glipizide
C) Continue home glipizide but discontinue metformin
D) Discontinue both metformin and glipizide

New FDA Label for Metformin Use (4/2016)

Before 2016:
Warning for creatinine higher than 1.4 mg/dl in women for creatinine is above 1.5 mg/dl in men

Biguanides- FDA changes- 4/2016

• Discontinue at the time of or before an iodinated contrast imaging procedure in patients with
  – eGFR 30-60 mL/minute/1.73 m2
  – History of liver disease
  – Alcoholism
  – Heart failure

• Re-evaluate eGFR at 48 hours after the imaging procedure; restart metformin if renal function is stable.
Sulfonylurea

- Glyburide – should we retire drug?
- Reserve use in Pregnancy Countries which have no other SU

Case 1a

For hospitalized patient with heart failure you have held metformin and glipizide and he has a "carbohydrate consistent" diet. BG range in 220-265 mg/dL range.

What should you order for his diabetes treatment?
A) Sliding scale only
B) Basal insulin only
C) Basal, bolus and correction insulin if eating
D) Basal insulin plus metformin and glipizide

Pharmacologic Therapy of Inpatient Hyperglycemia

Antihyperglycemic Therapy

SC Insulin via “Basal-Bolus” Recommended for most medical-surgical patients

OADs Not generally recommended

Continuous IV Infusion Selected medical-surgical patients

RABBIT-2 TRIAL: Research Question:

In T2DM patients, how does treatment with a basal bolus insulin (BBI) regimen compare with a sliding scale of regular insulin?

BBI: Glargine daily plus glulisine (SA insulin analog) before meals

RABBIT-2 TRIAL:

Umpierrez et al, Diabetes Care 30:2181–2186, 2007

RABBIT-2 TRIAL: Changes in Glucose Levels With Basal-Bolus vs. Sliding Scale Insulin

Hypoglycemia rate:
- Basal Bolus Group:
  - BG < 60 mg/dL: 3%
  - BG < 40 mg/dL: none
- SSRI:
  - BG < 60 mg/dL: 3%
  - BG < 40 mg/dL: none

- 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
0.5 U/kg/d x BG between 201-400 mg/dL

RABBIT 2: Superior glycemic control with basal-bolus vs sliding-scale insulin

**Case 1b**
If this patient with T2DM was admitted for cellulitis with gangrene of left 2nd and 3rd toe for consideration of an amputation, BG ranged between 200-300 mg/dL.

What should your diabetes management be?
A) Sliding scale only
B) Basal insulin only
C) Basal, bolus and correction insulin if eating
D) Basal insulin plus metformin and glipizide

Inpatient Management in non-ICU Setting

RABBIT 2 Surgery TRIAL: - Research Question:
Is there an impact of treatment on T2DM patients with a basal bolus insulin regimen compared with a sliding scale of regular insulin in terms of complication prevention in the hospital?

RABBIT 2 Surgery: GLYCEMIC CONTROL

BG Level After First Day

<table>
<thead>
<tr>
<th>BG Reading &lt;140 mg/dL</th>
<th>BG Reading &lt;140 mg/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.01</td>
<td>0.005</td>
</tr>
<tr>
<td>145</td>
<td>54</td>
</tr>
<tr>
<td>172</td>
<td>31</td>
</tr>
</tbody>
</table>

RABBIT 2 Surgery: Hypoglycemia

- There were no differences in hypoglycemia between patients treated with insulin prior to admission compared to insulin-naive patients.
- There were no differences in hypoglycemia between patients treated with insulin on admission prior to surgery or those enrolled after surgery.

RAndomized Study of Basal Bolus Insulin Therapy in the Inpatient Management of Patients With Type 2 Diabetes Undergoing General Surgery (RABBIT 2 Surgery)
RABBIT 2 Surgery: Postoperative Complications

Case 1a/1b- answer
You have held metformin and glipizide and he has a carbohydrate consistent diet. BG range in 220-265mg/dl range. Heart failure exacerbation or amputation
What should you order for his diabetes treatment?
A) Sliding scale only
B) Basal insulin only
C) Basal, bolus and correction insulin if eating
D) Basal insulin plus metformin and glipizide

Case 2
A 60-year-old man with type 2 diabetes. A1c 8.2% is admitted for hematochezia. An EGD is scheduled for am, and he is made NPO after midnight. Home regimen is glargine 88 units at bedtime and no other insulin.

In addition to starting an aspart sliding scale every 6 hours, what is the most appropriate dose of glargine for the night prior to procedure while he remains NPO?
A) Reduce dose of glargine by 5%
B) Reduce dose of glargine by 50%
C) Reduce dose of glargine by 30%
D) Hold home glargine

"NPO" status in diabetes

- **Basal:** Reduce basal insulin by 30-50% (closer to 30% with good control on an evenly matched “basal-bolus” regimen; closer to 50% for “basal-heavy”)

- **Mealtime:** Mealtime insulin coverage should be temporarily discontinued while NPO

- **Correction:** Continue correctional insulin doses but order for every 6 hours (rather than pre-meal and at bedtime) in order to ensure application of the order

Case 2-answer
A 60-year-old man with type 2 diabetes, A1c 8.2% is admitted for hematochezia. An EGD is scheduled for am, and he is made NPO after midnight. At home he takes glargine 88 units at bedtime and no other insulin.

In addition to starting an aspart sliding scale every 6 hours, what is the most appropriate dose of glargine for the night prior to procedure while he remains NPO?
A) Reduce dose of glargine by 5%
B) Reduce dose of glargine by 50%
C) Reduce dose of glargine by 30%
D) Hold home glargine
Case 3
A 60-yo, T2DM, A1c 8.2% is admitted for hematochezia. EGD and colonoscopy completed. Colonic polyps removed, **started on carb consistent diet.**
At home he takes glargine 88 units qhs. Given 44 units glargine at hs when NPO, with fasting BG of 130s.

In addition to continuing the lantus and aspart sliding scale, what is the most appropriate dose of meal aspart for him?
A) Aspart 14/8 units with full / half meal  
B) Aspart 20 units with each meal/10 with half meal  
C) Aspart 4 units with each meal  
D) Hold aspart

**Insulin Requirements in Health and Illness: Basal Bolus Concept**

<table>
<thead>
<tr>
<th>Healthy</th>
<th>Sick/Eating</th>
<th>Sick/NPO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Units</td>
<td>Correction</td>
<td>Nutritional</td>
</tr>
</tbody>
</table>

**Basal insulin :bolus insulin ratio**

- Most patients need TDD of insulin divided into  
  - 50 percent basal and 50 percent bolus,  
  - 40 percent basal and 60 percent bolus

- Exceptions  
  - Low carbohydrate diets  
  - Cystic fibrosis patients  
  - Glucocorticoids  
  - Enteral or parenteral nutrition

**Case 3 answer**
A 60-yo, T2DM, A1c 8.2% is admitted for hematochezia. EGD and colonoscopy completed. Colonic polyps removed, started on carb consistent diet. He is very hungry now.  
At home he takes glargine 88 units qhs. Given 44 units lantus qhs when NPO, with fasting BG of 130s.

- Basal :Bolus ratio=50:50
  - 44/3= 14 units, half for small meals

In addition to continuing the lantus and aspart sliding scale, what is the most appropriate dose of meal aspart for him?
A) Aspart 14/8 units with full / half meal  
B) Aspart 20 units with each meal/10 with half meal  
C) Aspart 4 units with each meal  
D) Hold aspart

Case 4
What TDD of insulin would you give a 65-year-old woman with T1DM, visiting from out of state, who comes with a hip fracture.
Her pump battery just died. **She weighs 70 kg and her A1c is 7.8%, eGFR 55.** She thinks her TDD is between 30-50 units.

A) 30 units per day  
B) 40 units per day  
C) 55 units per day  
D) 75 units per day

**Taking care of T1DM**
8/4/2017

Average insulin need: 0.5 u/kg/day
Advanced age: -0.1 u/kg/day

Initial TDD: 0.4 u/kg/day

(If she was renal insufficient: -0.1 u/kg/day)

50% basal
15 units glargine hs

I:C = 500/30
1:15

Correction CF 1:50 over 150

70 kg x 0.4 = app 30 u/day

Estimating total daily dose (TDD) of insulin: weight-based dosing

TDD in units of insulin = N x patient’s weight in kg

<table>
<thead>
<tr>
<th>If patient has these features…</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin Sensitive</td>
<td>0.3</td>
</tr>
<tr>
<td>lean or malnourished patients, elderly, chronic kidney disease (stage IV or V CKD), or insulin naïve</td>
<td></td>
</tr>
<tr>
<td>Moderately Insulin Sensitive</td>
<td>0.4-0.5</td>
</tr>
<tr>
<td>Patients without clear features of insulin sensitivity or resistance, including most type 1 diabetics</td>
<td></td>
</tr>
<tr>
<td>Insulin Resistant</td>
<td>0.6 - 1 (may be even higher?)</td>
</tr>
<tr>
<td>Obese, infected/inflamed, post-surgical stress, glucocorticoids, or combination of above, including most type 2 diabetics</td>
<td></td>
</tr>
</tbody>
</table>

Case 4- answer

What TDD of insulin would you give a 60-year-old woman with T1DM, visiting from out of state, who comes with a hip fracture. Her pump battery just died. She weighs 70 kg and her A1c is 7.8%, eGFR 50. She thinks her TDD is between 30-50 units.

A) 30 units per day
B) 40 units per day
C) 55 units per day
D) 75 units per day

Case 5

41-year-old woman with well-controlled T1DM is admitted for a scheduled cholecystectomy. Her home insulin regimen consists of Basal-bedtime glargine 21 units QHS, Bolus-meal aspart 7 units and a LD correction scale
She claims 3 am hypoglycemic episodes/month.
She will be NPO after midnight for her surgery.
You hold scheduled meal insulin after dinner and add a correctional scale.

What would you do in addition:
A) Hold glargine the night prior to surgery
B) Order 15 units glargine HS the night prior to surgery
C) Order 10 units glargine HS the night prior to surgery
D) Hold glargine and start an insulin drip

"NPO" status and type 1 diabetics

Basal: NEVER hold basal insulin in patients with type 1 diabetes due to risk of diabetic ketoacidosis!
Case 5 -answer

41-year-old woman with well-controlled T1DM is admitted for a scheduled cholecystectomy. Her home insulin regimen consists of Basal-bedtime glargine 21 units QHS, Bolus-meal aspart 7 units and a LD correction scale. She claims 3 am hypoglycemic episodes/month. She will be NPO after midnight for her surgery. You hold scheduled meal insulin after dinner and add a correctional scale.

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A) Hold glargine the night prior to surgery
B) Order 15 units glargine HS night prior to surgery
C) Order 10 units glargine HS night prior to surgery
D) Hold glargine and start an insulin drip

Case 6

Calculated TDD of insulin for a 60-year-old man with T2DM weighing 100 kg admitted for cellulitis is 90 units. Takes 3 OADs at home and A1c is 8.2%. Has fever and WBC count of 14,000. BG on admission is 300 mg/dl. What correction scale should you use.

A) Custom dose
B) Moderate dose
C) None
D) High dose

Intensive Management

TDD = 90 units
Basal = 45 units hs (1/2 of total)
Prandial = 45 units (1/2 of total)
46 units/3 = 16/units with BLD

Correction scale

“NPO” status and type 1 diabetics

- NPO with balanced basal bolus regimen
- Basal glargine reduced by 30% if NPO
  \[ \frac{70}{100} \times 21 \text{ units} = 15 \text{ units} \]
- Mealtime: Mealtime insulin should temporarily be discontinued while NPO
- Correction: Continue correctional insulin doses but order for every 6 hours rather than pre-meal and pre-bedtime in order to ensure routine application of the order

Which Correction Scale?

Low Dose Algorithm

<table>
<thead>
<tr>
<th>BG range</th>
<th>0-100</th>
<th>101-199</th>
<th>200-299</th>
<th>300-399</th>
</tr>
</thead>
<tbody>
<tr>
<td>mcg/mL</td>
<td>2 units</td>
<td>4 units</td>
<td>6 units</td>
<td>8 units</td>
</tr>
</tbody>
</table>

Medium Dose

<table>
<thead>
<tr>
<th>BG range</th>
<th>0-100</th>
<th>101-199</th>
<th>200-299</th>
<th>300-399</th>
</tr>
</thead>
<tbody>
<tr>
<td>mcg/mL</td>
<td>1 unit</td>
<td>2 units</td>
<td>3 units</td>
<td>4 units</td>
</tr>
</tbody>
</table>

High Dose

<table>
<thead>
<tr>
<th>BG range</th>
<th>0-100</th>
<th>101-199</th>
<th>200-299</th>
<th>300-399</th>
</tr>
</thead>
<tbody>
<tr>
<td>mcg/mL</td>
<td>2 units</td>
<td>4 units</td>
<td>6 units</td>
<td>8 units</td>
</tr>
</tbody>
</table>

Custom

<table>
<thead>
<tr>
<th>BG range</th>
<th>0-100</th>
<th>101-199</th>
<th>200-299</th>
<th>300-399</th>
</tr>
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<tr>
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<td>6 units</td>
<td>8 units</td>
</tr>
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</table>
Case 6 - answer

Calculated TDD of insulin for a 60-year-old man with T2DM weighing 100kg admitted for cellulitis is 90 units.

Takes 3 OADs at home and A1c is 8.2%. Has fever and WBC count of 14,000. BG on admission is 300mg/dl.

What correction scale should you use.
A) Custom dose
B) Moderate dose
C) None
D) High dose

Case 7

A 48-year-old man with type 2 diabetes is recovering s/p coronary artery bypass graft. A1c is 9.7%

He had poor appetite but is eating now. Glargine has been uptitrated from 28 to 38units qhs. Today his fasting am BG was 76mg/dl but he was persistently hyperglycemic during the day yesterday requiring about 16 units of aspart moderate correction scale.

What do you do next?
A) Keep glargine 38units qhs, decrease aspart to LD scale
B) Decrease glargine to 32 units, decrease aspart scale to LD
C) Decrease glargine back to 32 units and add scheduled doses of aspart with meals
D) Change his glargine to 20units BID

TARGET GLUCOSE LEVELS: NON-ICU

- Premeal < 140 mg/dL,
- Postprandial < 180 mg/dL
- Reassess regimen if BG < 100mg/dL
- Modify therapy when BG < 70mg/dL

Some patients may need higher or lower targets(<200 mg/dL)
- Renal, liver failure, hypoglycemia unawareness, heart failure

LA insulin adjustment

Am BGF
- <100 mg/dl   decrease LA insulin by 10%
- <70 mg/dl   decrease LA by 20% atleast

- 100-140, no hypoglycemia previous day   no change in glargine
- >140   increase glargine by 10%
- >180   increase glargine by 20%

Matching Insulin Doses to Insulin Needs: the “Basal-Bolus” Concept

- Basal Insulin: suppresses glucose production between meal and overnight (~ 50% of TDD)
- Bolus Insulin: consists of mealtime/prandial insulin and correction insulin (combined ~ 50% of TDD)

Case 7

A 48-year-old man with type 2 diabetes is recovering s/p coronary artery bypass graft. A1c of 9.7%

He had poor appetite but is eating now. Glargine has been uptitrated from 28 to 38units qhs. Today his fasting am BG was 76mg/dl but he was persistently hyperglycemic during the day yesterday requiring about 16 units of aspart moderate correction scale.

10/100 x 38= 4 units, Reduce by 4 units atleast

What do you do next?
A) Keep glargine 38units qhs, decrease aspart to LD scale
B) Decrease glargine to 32 units, decrease aspart scale to LD
C) Decrease glargine back to 32 units and add scheduled doses of aspart with meals
D) Change his glargine to 20units BID
**Case 8**

56 year old patient with T2DM for 12 years admitted for elective hernia repair. BMI 39, no other complications or comorbid factors. Meds U-500 insulin- 100 units am, 120 units pm.

A1c-7.6%. **Last dose of U-500 night before surgery and was 50% of dose.** BG checks are between 140-160 mg/dl and appetite is poor.

What would you do with her U-500 insulin?

A) Switch to basal bolus therapy  
B) Use 20% dose of U-500  
C) Use 50% dose of U-500  
D) Use correction scale only.

---

**U-500 INSULIN IN THE HOSPITAL**

- Contact endocrinology/CDE for consultation prior to use in the hospital.
- Dispense U-500 from pharmacy only
- If BG tight and insulin doses are > 0.6 units/kg – more glucose variability on U-500
- U-500 dose needs significant reduction in the hospital – At least 20% dose reduction from home dose.
- Often need to switch to – Basal glargine and bolus lispro with meals.  
  – Twice a day NPH

---

**Case 9**

A 43-year-old woman with systemic lupus erythematosus and diet-controlled type 2 diabetes (A1c 6.6%) was admitted for a lupus flare. She received a 3-day pulse of methylprednisolone 1g IV daily, and now is on prednisone 60mg PO daily with plans for a prolonged taper.

She is currently on a correctional lispro scale before meals and at bedtime. Her BGs on waking up are in the 100-130 mg/dL range, but are rising to 400 mg/dL by bedtime.

What should you do next?

- A) Start metformin  
- B) Start glargine QHS  
- C) Start mealtime lispro  
- D) Increase the lispro correctional scale

---

**STEROIDS AND “BASAL-BOLUS” CONCEPT**

- Corticosteroids raise ALL blood sugars but affect postprandial BG disproportionately.
- Accomplished via adding meal boluses of insulin lispro.
- Need greater increase in BOLUS insulin. -If on basal-bolus- ratio = 40:60 to 30:70
- Alternative, use single dose of NPH with prednisone -Onset/peak/duration all match nicely with the relative effect that a single dose of prednisone in the morning will have on post-prandial glucose.

---

**U-500 INSULIN IN THE HOSPITAL**

- Conversion to basal bolus insulin from U-500  
  - Reduce home dose by 20% at least  
  - Convert this to TDD  
  - Patient eating  
    - Divide 50% into basal LA insulin and 50% into meal insulin  
    - Patient eating  
      - Divide into 50% basal LA insulin and high dose correction

- Conversion to twice daily NPH from U-500  
  - Reduce dose by 20% or more  
  - Divide this reduced TDD into NPH twice a day. Giving 60% am and 40% with dinner.

---

**U-500**

- Needle Shield  
- Needle  
- Plunger  
- Spring Body  
- U-500 Symbol  
- Protective Cap  
- Rubber Stopper  
- Plunger Rod  
- Green 500 units/mL symbol
Case 9

A 43-year-old woman with systemic lupus erythematosus and diet-controlled type 2 diabetes (A1c 6.6%) was admitted for a lupus flare. She received a 3-day pulse of methylprednisolone 1g IV daily, and now is on prednisone 60mg PO daily with plans for a prolonged taper. She is currently on a correctional lispro scale before meals and at bedtime. Her BGs on waking up are in the 100-130mg/dL range, but are rising to 400mg/dL by bedtime.

What should you do next?
– A) Start metformin
– B) Start glargine QHS
– C) Start mealtime lispro
– D) Increase the lispro correctional scale

CONCLUSION

• BG variability and hypo and hyperglycemia in the hospital is related to outcomes
• Using published targets and algorithms it is possible to reduce BG fluctuations

References