

Glycemic Control in the Hospitalized Patient – Updates in the Field

September 29, 2011

Jeffrey Fish, PharmD, BCPS

University of Wisconsin Hospital and Clinics

email: jfish@uwhealth.org

Disclosures

Nothing to disclose

Objectives

- Review the background information that led to the current treatment recommendations for glycemic control in hospitalized patients
- Evaluate your hospital's compliance with quality measures for glycemic control in the hospitalized patient
- Formulate potential cost saving measures for the use of insulin at your hospital
- Develop strategies for ensuring the safe use of insulin in hospitalized patients

Outline

- Different insulin analogues
- Background / Blood sugar goals / insulin use
 - ICU
 - General care
- Diabetes control in hospitalized patients
 - Hypoglycemia
 - Corticosteroids and glucose control
 - Noninsulin agents
 - Transition from insulin drips
 - Perioperative insulin use
 - Insulin pumps
 - Transition home
 - Glucose monitoring
- Quality measures that pertain to blood glucose control in inpatients
- Potential cost saving measures
- Safety of insulin in hospitalized patients

Insulin Analogues

Type of Insulin	Onset	Peak	Duration	Adjustment When NPO
Novolog [®] (aspart) Humalog [®] (lispro) Apidra [®] (glulisine)	5-15"	1-2 hours	4-6 hours	<ul style="list-style-type: none"> Hold scheduled dose Give as correction/supplemental insulin (formerly "sliding scale") as ordered to cover elevated glucoses (i.e. >150 mg/dL)
Regular	30-60"	2-4 hours	6-10 hours	
NPH	1-2 hours	4-8 hours	10-20 hours	<ul style="list-style-type: none"> (NPH and detemir) Take ½ of AM dose (Give entire PM or HS dose) <p>**If NPH or detemir is being given to cover prednisone, the full dose may be needed. Clarify with the team and get orders for this.</p>
Detemir (Levemir [®])	1-2 hours	8-12 hours	12-24 hours	
Glargine (Lantus [®])	1-2 hours	Flat	~24 hours	<ul style="list-style-type: none"> Give usual dose unless h/o hypoglycemia with full dose
70/30 (NPH/regular) Novolog MIX 70/30 Humalog MIX 75/25 Humalog MIX 50/50	Insulin combinations containing mixtures of long- and short-acting or rapid-acting insulins will have onset, peak and duration of action similar to the individual components			<ul style="list-style-type: none"> Mixtures of long and short-acting or rapid-acting insulins will have onset, peak and duration of action similar to the individual components. Combination insulins should not be used when NPO. Pt should get ½ of the equivalent intermediate-acting insulin as NPH.

from UWHC

Insulin Analogues

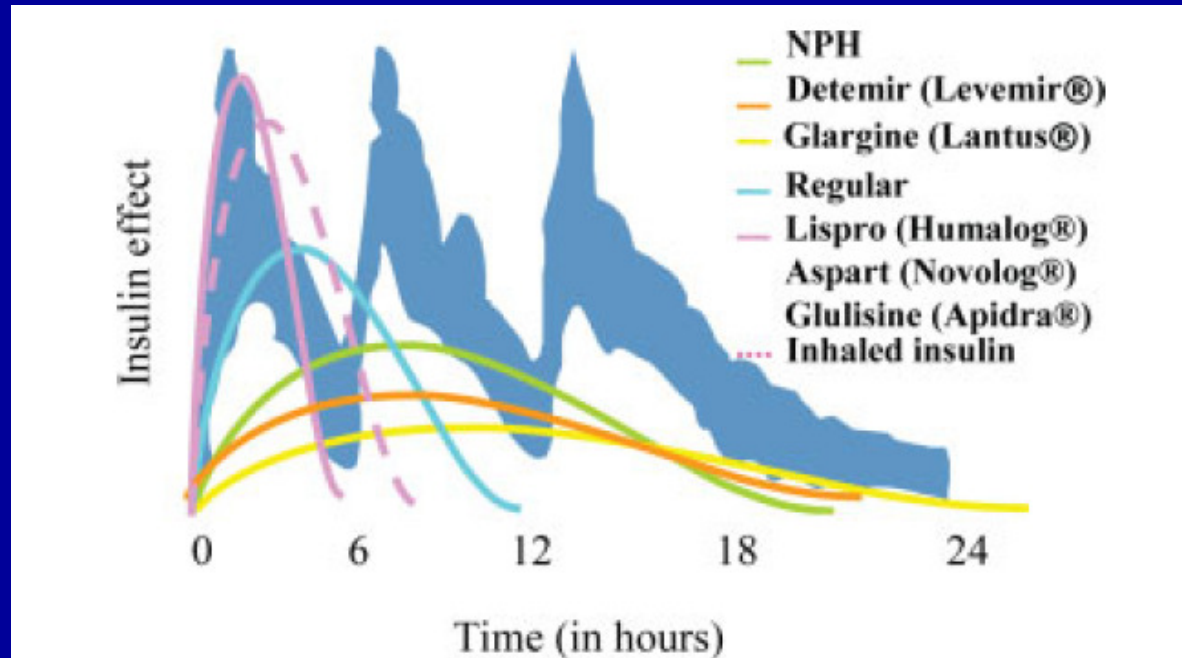


FIGURE 3. Action profiles of the available insulins. **Abbreviation:** NPH, neutral protamine hagedorn. Used with permission from Pendergrass M, Boston, Massachusetts. The dark blue shadows in the background represent normal, endogenous insulin secretion.

Insulin Therapy in Surgical ICU

NEJM 2001;345:1359-67

- Randomized, prospective, controlled trial
- Evaluate the efficacy and safety of intensive insulin therapy (IIT) vs. conventional insulin therapy (CIT) in adult patients with:
 - Admitted to SICU
 - Mechanical ventilation
 - No regard for diabetic status was given
- Randomly assigned to either:
 - IIT: Blood glucose 80-110mg/dl
 - CIT: Infusion only given if blood glucose >215mg/dl
 - Maintained blood glucose 180-200mg/dl
- Data on all 1548 patients enrolled
- On admission, all patients were started on IV glucose 200-300G/24 hours
 - On the next day, patients were begun on parenteral, combined parenteral and enteral or enteral nutrition

Insulin Therapy in Surgical ICU

NEJM 2001;345:1359-67

- Primary Endpoint:
 - All-cause mortality during ICU stay
- Secondary Endpoints:
 - In-hospital mortality
 - Total # of days in ICU & readmission
 - Need for:
 - Prolonged intensive care (>14 days)
 - Ventilator support
 - Renal replacement therapy (CRRT)
 - Inotropic or vasopressor support
 - Antibiotics > 10 days
 - Blood transfusion
 - Bloodstream infections
 - Critical illness polyneuropathy

Insulin Therapy in Surgical ICU

NEJM 2001;345:1359-67

- Statistically significant differences between the IIT group and the CIT group in:
 - Morning blood glucose
 - 153₊₃₃ (CIT) vs 103₊₁₉ (IIT), $p < 0.001$
 - All-cause mortality
 - 8.0% (CIT) vs. 4.6% (IIT), $p < 0.04$; RRR=42%; 95% CI (22% to 62%)
 - All-cause mortality (Cohort = ICU stay > 5 days)
 - 20.2% (CIT) vs. 10.6% (IIT), $p = 0.005$
 - Morbidity:
 - ARF requiring dialysis/CRRT → 8.2% vs. 4.8% $p = 0.007$
 - Septicemia → 7.8% vs. 4.2% $p = 0.003$
 - Antibiotics > 10 days → 17.1% vs. 11.2% $p < 0.001$
- Incidence of hypoglycemia (Blood glucose < 40mg/dl):
 - IIT group: 39 patients (2 had sweating/agitation)
 - CIT group: 6 patients
 - “No instances of hemodynamic deterioration or convulsions”

Insulin Therapy in Medical ICU

NEJM 2006;354:449-61

- Randomized, prospective, controlled trial
- Evaluate the efficacy and safety of intensive insulin therapy (IIT) vs. conventional insulin therapy (CIT) in adult patients:
 - Admitted to MICU
 - Estimated length of stay of at least 3 days
 - No regard for diabetic status was given
- Data on all 1200 patients enrolled
- Patients were fed enterally when hemodynamically stable

Insulin Therapy in Medical ICU

NEJM 2006;354:449-61

- Randomly assigned to either:
 - IIT: Blood glucose 80-110mg/dl
 - CIT: Infusion only given if blood glucose >215mg/dl
 - Maintained blood glucose 180-200mg/dl
- Primary Endpoint:
 - In-hospital mortality
- Secondary Endpoints:
 - ICU mortality / 90-day all cause mortality
 - Total # of days in ICU/hospital & readmission
 - # of days to mechanical ventilator weaning
 - Initiation of dialysis/renal replacement therapy
 - Days of inotropic or vasopressor support
 - Bacteremia/antibiotics > 10 days

Insulin Therapy in Medical ICU

NEJM 2006;354:449-61

- No statistically significant differences between the IIT group and the CIT group in:
 - In-hospital mortality
 - 40.0% (CIT) vs. 37.3% (IIT) $p=0.33$
 - Morbidity
 - Septicemia \rightarrow 7% vs. 8% $p=0.5$
 - Antibiotics $>$ 10 days \rightarrow 24% vs. 21% $p=0.2$
- Subgroup analysis was significant for:
 - In-hospital mortality (Cohort = ICU stay $>$ 3 days, $n=767$)
 - 52.5% (CIT) vs. 43.0% (IIT) $p=0.009$
 - Incidence of hypoglycemia (Blood glucose $<$ 40mg/dl):
 - IIT group: 111 (18.7%) patients (mortality = 46.4%)
 - CIT group: 19 (3.1%) patients (mortality = 66.7%)
 - “No hemodynamic deterioration, convulsions, or other events were noted in association with any hypoglycemic event”

Intensive versus Conventional Glucose Control in Critically Ill Patients (NICE-SUGAR)

NEJM 2009;360:1283-97

- Randomized, prospective, multicenter, controlled
 - Trial was not blinded
- Evaluate the efficacy and safety of intensive control group (ICG) vs. conventional control group (CCG) in adult patients:
 - Admitted to the ICU with an estimated length of stay of at least 3 days
- Randomly assigned to either:
 - IIT: Blood glucose 81-108mg/dl
 - CIT: Blood glucose 144-180mg/dl
- 6104 patients enrolled
- Nutritional management was left to the discretion of the treating clinicians

Intensive versus Conventional Glucose Control in Critically Ill Patients (NICE-SUGAR)

NEJM 2009;360:1283-97

- Primary Endpoint:
 - All-cause mortality within 90 days after randomization
- Secondary Endpoints:
 - Duration of mechanical ventilation
 - Renal replacement therapy (CRRT)
 - Hospital length of stay
 - ICU length of stay
 - Transfusions
 - Positive blood cultures
- Serious adverse events:
 - Blood glucose level <40mg/dl

Intensive versus Conventional Glucose Control in Critically Ill Patients (NICE-SUGAR)

NEJM 2009;360:1283-97

- Mean blood glucose level
 - 144 ± 23 (CCG) vs 115 ± 15 (ICG), $p < 0.001$
- 90 day mortality
 - 24.9% (CCG) vs 27.5% (ICG), $p = 0.02$; OR=1.14; 95% CI (1.02 to 1.28)
- No difference in ICU or hospital length of stay
- No difference in number of days of mechanical ventilation, renal replacement therapy, transfusions or positive blood cultures
- Incidence of hypoglycemia (blood glucose < 40 mg/dl)
 - 0.5% (CCG) vs 6.8% (ICG); $p < 0.001$
 - “No long-term sequelae of severe hypoglycemia were recorded”

Treatment Recommendations

- American College of Physicians (ACP)
 - Qaseem A, et al. Use of Intensive Insulin Therapy for the Management of Glycemic Control in Hospitalized Patients: A Clinical Practice Guideline from the American College of Physicians. *Ann Intern Med* 2011;154:260-7.
 - Conducted a meta-analysis of 21 trials
 - *Ann Intern Med* 2011;154:268-282
 - Found no benefit associated with intensive insulin therapy on short-term mortality (28-day, hospital, or ICU)
 - Found no benefit associated with intensive insulin therapy for 90- or 180-day mortality
 - 13 trials

ACP Recommendations

- Recommendation 1: *Recommends not using intensive insulin therapy to strictly control blood glucose in non-SICU/MICU patients with or without diabetes mellitus*
 - Strong recommendation, moderate-quality evidence
 - Includes patients with myocardial infarction, stroke or acute brain injury or those under perioperative care
 - A nonsignificant reduction in the incidence of infection was observed
 - Avoid targets less than 140 mg/dl
 - Optimal targets in patients not receiving care in the SICU or MICU cannot be precisely defined

ACP Recommendations

- Recommendation 2: *Recommends not using intensive insulin therapy to normalize blood glucose in SICU/MICU patients with or without diabetes mellitus*
 - Strong recommendation, high-quality evidence
 - Some studies show an increase in mortality associated with intensive insulin therapy and hypoglycemia

ACP Recommendations

- Recommendation 3: *Recommends a target blood glucose level of 140-200 mg/dl if insulin therapy is used in SICU/MICU patients*
 - Weak recommendation, moderate-quality evidence
 - Associated with a lower risk for hypoglycemia
 - Minimizing the risk for hypoglycemia is critical in critically ill patients
 - Current studies do not provide enough information to determine whether blood glucose levels of 180-200 mg/dl are associated with similar outcomes as lower blood glucose levels

Treatment Recommendations

- American Association of Clinical Endocrinologists and American Diabetes Association (AAACE/ADA)
 - Moghissi ES, et al. Consensus Statement on Inpatient Glycemic Control. Diabetes Care 2009;32:1119-31
 - “Central goals were to identify reasonable, achievable and safe glycemic targets and to describe the protocols, procedures, and system improvements needed to facilitate their implementation”

AACE/ADA Recommendations

- Critically ill patients
 - Insulin therapy should be initiated for treatment of persistent hyperglycemia, starting at a threshold of no greater than 180 mg/dl
 - Once insulin has been started, a goal of 140-180 mg/dl is recommended for the majority of critically ill patients
 - Intravenous insulin infusions are the preferred method for achieving and maintaining glycemic control
 - Recommend using validated infusion protocols with demonstrated safety and efficacy, and with low rates of hypoglycemia
 - Frequent glucose monitoring is essential to minimize the occurrence of hypoglycemia and to optimize control

AACE/ADA Recommendations

- Noncritically ill patients
 - For the majority of noncritically ill patients, the premeal target should generally be <140 mg/dl in conjunction with random blood glucose values <180 mg/dl
 - Provided these targets can be safely achieved
 - Reassess regimen if blood glucoses decline to <100 mg/dl
 - More stringent targets may be appropriate in stable patients with previous tight control
 - Less stringent targets may be appropriate in terminally ill patients or patients with severe comorbidities
 - Scheduled subcutaneous administration, with basal, nutritional and correction components, is preferred
 - Prolonged therapy with sliding scale insulin as the sole regimen is discouraged
 - Noninsulin antihyperglycemic agents are not appropriate in most hospitalized patients who require therapy for hypoglycemia

AACE/ADA Recommendations

- Safety Issues

- Overtreatment and undertreatment of hyperglycemia represent major safety concerns
- Education of hospital personnel is essential in engaging the support of those involved in the care of inpatients with hyperglycemia
- Caution is required in interpreting results of point of care glucose meters in patients with anemia, polycythemia, hypoperfusion, or use of some medications
- Buy-in and financial support from hospital administrators are required for promoting a rational system approach to inpatient glycemic management

AACE/ADA Recommendations

- Cost
 - Appropriate inpatient management of hyperglycemia is cost-effective
- Discharge Planning
 - Preparation for discharge to the outpatient setting should begin at the time of hospital admission
 - Discharge planning, patient education, and clear communication with outpatient providers are critical for ensuring a safe and successful transition to outpatient glycemic management

AACE/ADA Recommendations

- Areas of Needed Research
 - Stress hyperglycemia
 - Mechanisms, insulin resistance, optimal and safe targets
 - Severe hypoglycemia
 - Patients at risk and outcomes / costs
 - Glycemic targets on general medical and surgical units
 - Glycemic variability on outcomes
 - Hospital systems and safety measures needed to improve glycemic control and patient outcomes
 - Strategies for insulin treatment and monitoring
 - Pediatric inpatient populations

Proposed New ADA Guidelines

- Noncritically ill patients: new guidelines will suggest keeping the blood glucose between 100 and 140 mg/dl
 - Umpierrez GE. Cleveland Clinic J Med 2011

Sliding-Scale Insulin

- Diabetes Care 2009;32:S13-S61
- Problems
 - Regimens prescribed on admission are likely to be used throughout the hospital stay
 - Treats hyperglycemia after it has already occurred
 - Can lead to rapid changes in blood glucose levels, which may exacerbate both hyper- and hypoglycemia

Randomized Study of Basal-Bolus Insulin Therapy in the Inpatient Management of Patients With Type 2 Diabetes (RABBIT 2 Trial)

- Prospective, two center, open-label, randomized trial
 - 130 nonsurgical, insulin-naïve patients with known diabetes for >3 months admitted to medical general services
 - Excluded patients on steroids, SCr \geq 3 mg/dl
 - Oral antidiabetic drugs were discontinued on admission
- Goal: maintain fasting and premeal blood glucose levels <140 mg/dl
 - Primary endpoint: Determine differences in mean daily blood glucose concentrations between treatment groups
 - Secondary endpoints: Differences in number of hypoglycemic events, severe hyperglycemic episodes, hospital length of stay and mortality
- Randomly assigned to sliding scale insulin (SSI-65 patients) or basal bolus regimen (65 patients)--next slide
- Umpierrez GE, et al. Diabetes Care 2007;30:2181-6

RABBIT 2 Trial

A. Basal-bolus regimen with insulin glargine and glulisine

- Discontinue oral antidiabetic drugs on admission.
- Start total daily insulin dose:
 - 0.4 units · kg body wt⁻¹ · day⁻¹ when the admission blood glucose concentration is 140-200 mg/dl
 - 0.5 units · kg body wt⁻¹ · day⁻¹ when the admission blood glucose concentration is between 201-400 mg/dl
- Give one-half of total daily dose as insulin glargine and one-half as insulin glulisine.
- Give insulin glargine once daily at the same time of the day.
- Give insulin glulisine in three equally divided doses before each meal. Hold insulin glulisine if patient is not able to eat.

Supplemental insulin

Give supplemental insulin glulisine following the "sliding-scale" protocol for blood glucose >140 mg/dl.

- If a patient is able and expected to eat all or most of his/her meals, give supplemental glulisine insulin before each meal and at bedtime following the "usual" column.
- If a patient is not able to eat, give supplemental glulisine insulin every 6 h (6-12-6-12), following the "insulin-sensitive" column.

Insulin adjustment

- If the fasting or mean blood glucose during the day is >140 mg/dl in the absence of hypoglycemia, increase insulin glargine dose by 20% every day.
- If patient develops hypoglycemia (<70 mg/dl), decrease glargine daily dose by 20%.

Blood glucose monitoring

Measure blood glucose before each meal and at bedtime (or every 6 h if n.p.o.).

B. Sliding scale regimen with regular insulin

- Discontinue oral antidiabetic drugs on admission.
- If patient is able and expected to eat all or most of his/her meals, give regular insulin before each meal and at bedtime, following the "usual" column.
- If patient is not able to eat, give regular insulin every 6 h (6-12-6-12), following the "insulin sensitive" column.

Insulin adjustment

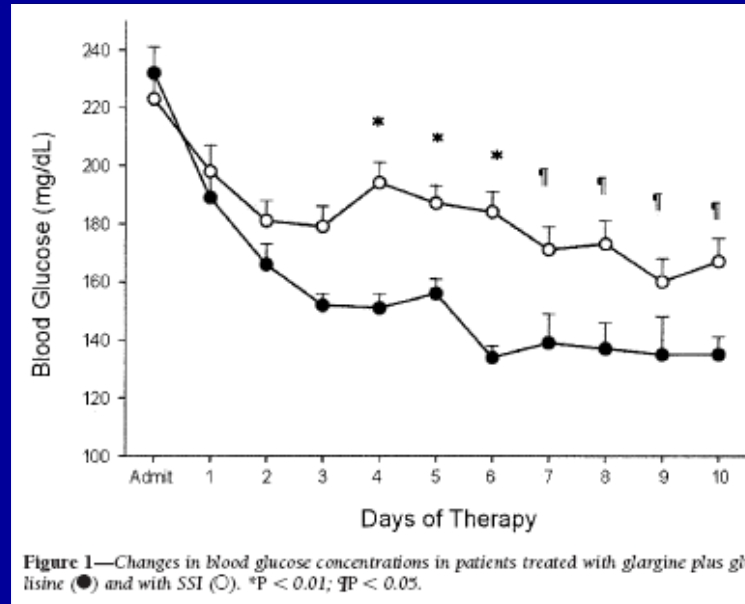
- If fasting and premeal plasma glucose are persistently >140 mg/dl in the absence of hypoglycemia, increase insulin scale from the "insulin sensitive" to the "usual" column or from the "usual" to the "insulin-resistant" column.
- If a patient develops hypoglycemia (blood glucose <70 mg/dl), decrease regular insulin from "insulin-resistant" to "usual" column or from the "usual" to "insulin-sensitive" column.

Blood glucose monitoring

Measure blood glucose before each meal and at bedtime (or every 6 h if n.p.o.).

RABBIT 2 Trial

- Primary results:



- Percent of patients with mean glucose <140 mg/dl: 66% of basal-bolus, 38% of SSI
 - 14% of patients in SSI group remained with blood glucose >240 mg/dl at day #4
- Daily insulin dose: basal-bolus: glargine 22 ± 2 units, glulisine 20 ± 1 unit; SSI: regular 12.5 ± 2 units
- 2 patients in each group had a blood glucose <60 mg/dl
- No difference in hospital length of stay or mortality

Randomized Study of Basal-Bolus Insulin Therapy in the Inpatient Management of Patients With Type 2 Diabetes Undergoing General Surgery (RABBIT 2 Surgery)

- Prospective, randomized, 3 center, open-label trial
 - 211 noncritically ill patients admitted for general or emergency surgery with a > 3 month history of diabetes treated with diet, oral antidiabetic agents or ≤ 0.4 units/kg/day of insulin
 - Excluded cardiac surgery patients, hepatic disease or $\text{SCr} \geq 3$ mg/dl
 - Oral antidiabetic drugs were discontinued on admission
- Goal: maintain fasting and premeal blood glucose levels between 100-140 mg/dl
 - Primary endpoints: differences in mean daily blood glucose concentrations between treatment groups and a composite endpoint of wound infection, pneumonia, bacteremia, respiratory failure and acute renal failure
 - Secondary endpoint: differences in hypoglycemic events, length of hospital stay, surgical complications, admission to the ICU and death
- Randomly assigned to sliding scale insulin (SSI- 107patients) or basal-bolus regimen (104 patients)--next slide
- Umpierrez GE, et al. Diabetes Care 2011;34:256-61

RABBIT 2 Surgery

1. Basal Bolus Regimen with Insulin Glargine and Glulisine
1.A. Insulin Orders
<ul style="list-style-type: none"> Discontinue oral antidiabetic drugs (sulfonylureas, repaglinide, nateglinide, metformin, pioglitazone, rosiglitazone, sitagliptin) and non-insulin injected antidiabetic medication (pramlinitide, exenatide) on admission. Starting insulin total daily dose (TDD): 0.5 units per kg of body weight. <ul style="list-style-type: none"> Reduce insulin TDD to 0.3 units per kg of body weight in patients ≥ 70 years of age and/or with a serum creatinine ≥ 2.0 mg/dL. Give half of total daily dose as insulin glargine and half as insulin glulisine. Give insulin glargine once daily, at the same time of the day. Give insulin glulisine in three equally divided doses before each meal. Hold insulin glulisine if patient not able to eat.
1.B. Supplemental insulin
<ul style="list-style-type: none"> Give supplemental insulin glulisine following the “sliding scale” protocol (1E) for blood glucose > 140 mg/dl. If a patient is able and expected to eat all, give supplemental glulisine insulin before each meal and at bedtime following the “usual” column. If a patient is not able to eat, give supplemental glulisine insulin every 6 hours (6-12-6-12) following the “sensitive” column.
1.C. Insulin adjustment
<ul style="list-style-type: none"> If the fasting and predinner BG is between 100 - 140 mg/dl in the absence of hypoglycemia the previous day: no change If the fasting and predinner BG is between 140 - 180 mg/dl in the absence of hypoglycemia the previous day: increase insulin TDD by 10% every day If the fasting and predinner BG is >180 mg/dl in the absence of hypoglycemia the previous day: increase insulin TDD dose by 20% every day If the fasting and predinner BG is between 70 - 99 mg/dl in the absence of hypoglycemia: decrease insulin TDD dose by 10% every day If a patient develops hypoglycemia (BG <70 mg/dL), the insulin TDD should be decreased by 20%.
1.D. Blood glucose monitoring. Blood glucose will be measured before each meal and at bedtime (or every 6 hours if a patient is not eating) using a glucose meter

2. Regular Insulin By Sliding Scale
2.A. Insulin Orders
<ul style="list-style-type: none"> Discontinue oral antidiabetic drugs (sulfonylureas, repaglinide, nateglinide, metformin, pioglitazone, rosiglitazone, sitagliptin) and non-insulin injected antidiabetic medication (pramlinitide, exenatide) on admission. Patients who are not eating or with intermittent nutritional intake <ul style="list-style-type: none"> If a patient is not able to eat or if the nutritional intake is uncertain/intermittent, regular insulin will be administered every 6 hours following the “insulin sensitive” recommended dose of the sliding scale protocol (2D). Patients who are eating <ul style="list-style-type: none"> If a patient is able and expected to eat most of his/her meals, regular insulin will be administered before each meal and at bedtime following the “usual” recommended dose of the sliding scale protocol.
2.B. Insulin adjustment
<ul style="list-style-type: none"> If the fasting and pre-meal plasma glucose are persistently >140 mg/dL in the absence of hypoglycemia, the insulin scale of regular insulin could be increased from sensitive to usual, or from the usual to resistant scale. If a patient develops hypoglycemia (blood glucose <60mg/dL), the sliding scale of regular insulin should be decreased from insulin resistant to usual scale or from the usual to sensitive scale.
2.C. Blood glucose monitoring. Blood glucose will be measured before each meal and at bedtime (or every 6 hours if a patient is not eating) using a glucose meter.

RABBIT 2 Surgery

- Primary results
 - See figure
 - Frequency of composite endpoint:
 - SSI 24.3% vs basal-bolus 8.6% (p=0.003)
- Percent of glucose readings <140 mg/dl: 53% of basal-bolus, 31% of SSI
 - 12% of patients in SSI group remained with blood glucose >240 mg/dl at day #4
- Daily insulin dose after 24 hours: basal-bolus: glargine 21.8 ± 8.6 units, glulisine 14.8 ± 7.6 units; SSI: regular 12.3 ± 6.5 units
- Blood glucose <70 mg/dl
 - 23.1% basal-bolus vs. 4.7% SSI (p<0.001)
- Blood glucose <40 mg/dl
 - 3.8% basal-bolus vs. 0% SSI (p=0.057)
- No difference in hospital length of stay or mortality

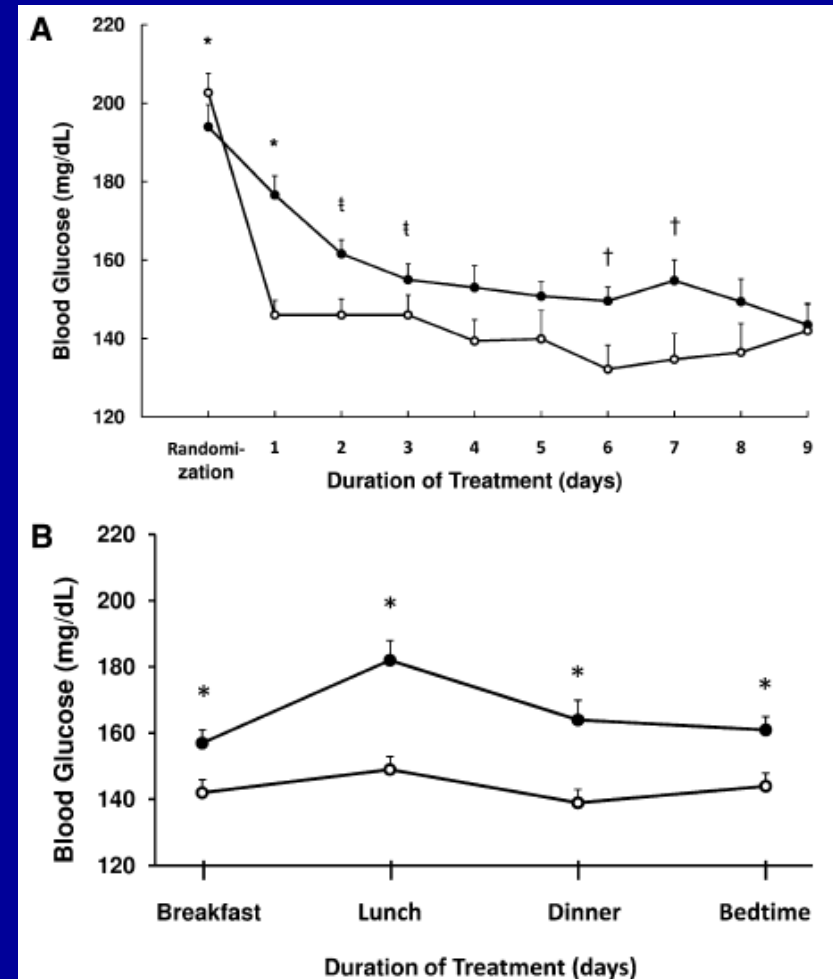


Figure 1—A: Glucose levels during basal-bolus and SSI treatment. Changes in blood glucose concentration after the 1st day of treatment with basal-bolus with glargine once daily plus glulisine before meals (○) and with SSI 4-times daily (●). *P < 0.001, †P = 0.02, ‡P = 0.01. B: Glucose levels before meals and bedtime. Pre-meal and bedtime glucose levels were higher throughout the day in the SSI group (●) compared with basal-bolus regimen (○).

**Comparison of Inpatient Insulin Regimens with
Detemir plus Aspart Versus Neutral Protamine
Hagedorn plus Regular in Medical Patients with Type
2 Diabetes**

- Prospective, randomized, 2 center trial, open-label trial
 - 130 noncritically ill, nonsurgical patients with a known history of diabetes > 3 months treated with diet, oral antidiabetic agents or insulin
 - Excluded patients expected to go to surgery, hepatic disease or $\text{SCr} \geq 3 \text{ mg/dl}$
 - Oral antidiabetic drugs were discontinued on admission
- Goal: maintain fasting and premeal blood glucose levels between < 140 mg/dl
 - Primary endpoint: differences in mean daily blood glucose concentrations between treatment groups
 - Secondary endpoints: differences in hypoglycemic events, length of hospital stay and death
- Randomly assigned to detemir / aspart (67 patients) vs NPH / regular (63 patients)
- Umpierrez GE, et al. J Clin Endocrinol Metab 2009;94:564-9

DEAN Trial

1. Detemir plus aspart insulin treatment orders

A. Insulin-treated patients

Give total outpatient insulin daily dose, one half as detemir and one half as aspart insulin.

Detemir is given once daily, at the same time of the day.

Aspart is given in three equally divided doses before each meal.

To prevent hypoglycemia, if a subject is not able to eat, hold dose of aspart insulin.

B. No insulin-treated patients (diet or oral agents)

Hold oral antidiabetic drugs on admission.

Starting total daily insulin dose:

BG between 140 and 200 mg/dl: 0.4 U/kg · d

BG between 201 and 400 mg/dl: 0.5 U/kg · d

Give half of total insulin dose as detemir and half as aspart insulin.

Detemir is given once daily, at the same time of the day.

Aspart is given in three equally divided doses before each meal.

To prevent hypoglycemia, if a subject is not able to eat, hold dose of aspart insulin.

C. Insulin adjustment

If premeal BG <140 mg/dl in the absence of hypoglycemia: no change.

If premeal BG between 140 and 180 mg/dl: increase detemir insulin dose by 10%.

If premeal BG >180 mg/dl: increase detemir insulin dose by 20%.

If BG <60 mg/dl, decrease insulin detemir daily dose by 20%.

D. Supplemental insulin

Give aspart insulin after the supplemental insulin scale before each meal and at bedtime if able to eat, or every 6 h if not able to eat.

2. NPH plus regular insulin treatment orders

A. Insulin-treated patients

Total outpatient insulin daily dose to be given two thirds in the morning and one third in the evening.

Give morning and evening dose as two thirds NPH and one third regular insulin.

To prevent hypoglycemia, if a subject is not able to eat, hold dose of regular insulin.

B. No insulin-treated patients (diet or oral agents)

Hold oral antidiabetic drugs on admission.

Starting total daily insulin dose:

BG between 140 and 200 mg/dl: 0.4 U/kg · d

BG between 201 and 400 mg/dl: 0.5 U/kg · d

Give two thirds of total insulin dose in the morning and one third in the evening.

Give morning and evening dose as two thirds NPH and one third regular insulin.

To prevent hypoglycemia, if a subject is not able to eat, hold dose of regular insulin.

C. Insulin adjustment

If premeal BG <140 mg/dl in the absence of hypoglycemia: no change.

If premeal BG between 140 and 180 mg/dl: increase NPH insulin dose by 10%.

If premeal BG >180 mg/dl: increase daily NPH insulin dose by 20%.

If BG <60 mg/dl: decrease NPH insulin dose by 20%.

D. Supplemental insulin

Give short-acting insulin after the supplemental insulin scale before each meal and at bedtime if able to eat, or every 6 h if not able to eat.

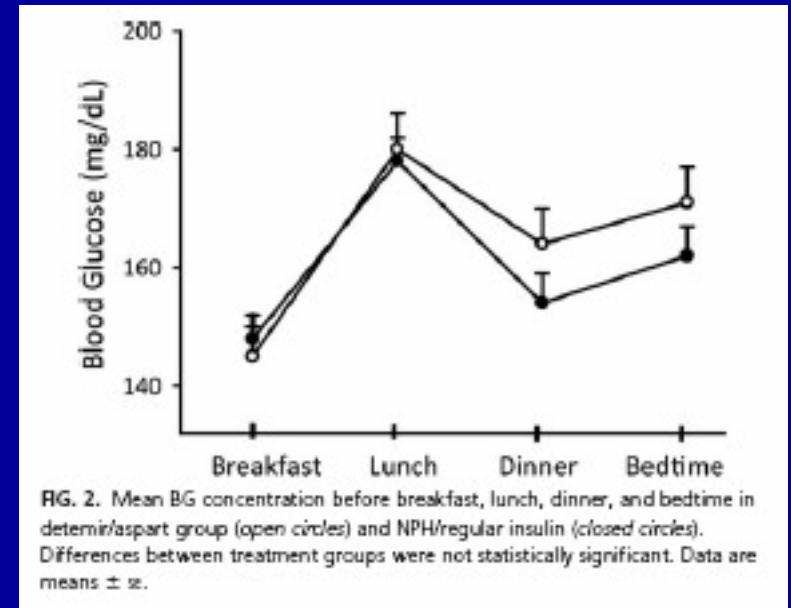
3. Supplemental insulin protocol

Before meal: supplemental scale insulin (no. of units)—add to scheduled insulin dose.

Bedtime: give half of supplemental insulin dose.

DEAN Trial

- Primary results
 - See figure
- Percent of patients with premeal glucose readings <140 mg/dl: 45% of detemir / aspart vs 48% of NPH / regular (p=NS)
 - 12% of patients in SSI group remained with blood glucose >240 mg/dl at day #4
- Daily insulin dose: detemir / aspart 57 ± 45 units; NPH / regular: 45 ± 32 units
- Blood glucose <40-59 mg/dl
 - 28.4% detemir / aspart vs. 23.8% NPH / regular
- Blood glucose <40 mg/dl
 - 4.5% detemir / aspart vs. 1.6% NPH / regular
- No difference in hospital length of stay or mortality (no deaths)



Take Home Points From 3 Trials

- Don't use a sliding-scale regimen as a single agent in diabetic patients
- Regular and NPH insulin are still good
- One insulin regimen does not fit all patients
- Patients on insulin at home should continue insulin in the hospital
 - Recommend lowering home regimen by 25% to allow for lower food intake
- Current basal-bolus regimens are associated with an unacceptable high rate of hypoglycemia
 - Current study comparing basal-correction doses vs. a basal bolus regimen

Estimating Insulin Doses in Hospitalized Patients

1. Estimate the total amount of insulin the patient would need over one day, if getting adequate nutrition = Total Daily Dose (TDD), as outlined in Figure 5.
2. Define the patient's nutritional situation (e.g., NPO, eating, continuous tube feeds, etc.).
3. Decide how the TDD will be divided into component insulins, and which type of insulin will be used for each.
 - Provide 50% of the TDD as a long-acting, "peakless" basal insulin. In certain situations a more conservative estimate of basal insulin may be appropriate (e.g., tube feeding).
 - Administer the remainder of the TDD in equally divided doses of nutritional insulin, matched to the type and timing of nutrition provided, as outlined in Table 2.
 - Select a correctional insulin dose scale.
4. Monitor blood glucoses on a schedule appropriate for the insulin regimen, and adjust insulin doses as needed. The clinician should critically assess the insulin regimen on at least a daily basis.

FIGURE 4. A stepwise approach to physiologic insulin dosing in the hospital.

The **total daily dose (TDD)** of insulin is the total number of units of insulin that a patient requires over the course of a day to meet basal and nutritional needs. It can be estimated in one or more of 3 different ways:

1. Consider the total daily dose of insulin that the patient required before hospitalization, and glycemic control on that regimen. Adjust dose(s) upward if uncontrolled hyperglycemia prior to admission or downward if hypoglycemia present.
2. Weight-based estimation: $TDD \text{ (in units)} = \text{the patient's weight (in kg)} \times N \text{ (units/kg/day)}$. Select multiplier based on the features listed in the table.

Dose-guiding features...	N (units/kg/day)
Likely insulin sensitivity (lean or malnourished patients, especially if type 1 diabetes), elderly, acute or chronic kidney disease (especially dialysis-requiring)	0.3
Patients with neither features of insulin sensitivity nor insulin resistance	0.4
Likely insulin resistance (obese), or receiving high doses of corticosteroids	0.5-0.6 or higher

3. Transitioning from an insulin drip to subcutaneous insulin: Calculate the average hourly drip rate once the drip delivery rate has stabilized. Then, multiply by 20 to get a conservative estimate of the daily insulin need. Then, determine whether that dose represents basal insulin (patient was not receiving nutrition) or TDD (patient was receiving nutrition).

FIGURE 5. Three approaches for estimating an appropriate initiation total daily dose (TDD) of insulin.

Preferred Insulin Regimens for Different Nutritional Situations

Nutritional Situation	Necessary Insulin Components	Preferred Regimen*
NPO (or clear liquids)	Basal insulin: 50% of TDD. Nutritional insulin: None.	Basal insulin: glargine given once daily or detemir given twice daily. Nutritional insulin: None. Correctional insulin: Regular insulin q 6 hours or RAA insulin q 4 hours. Other comments: Dextrose infusion (eg, D5 containing solution at 75-150 cc/hour) recommended when nutrition is held. An IV insulin infusion is preferred for management of prolonged fasts or fasting type 1 diabetes patients.
Eating meals	Basal insulin: 50% of TDD. Nutritional insulin: 50% of TDD, divided equally before each meal.	Basal insulin: glargine given once daily or detemir given twice daily. Nutritional insulin: RAA insulin with meals. Correctional insulin: RAA insulin q AC and HS (reduced dose at HS).
Bolus tube feeds	Basal insulin: 40% of TDD. Nutritional insulin: 60% of the TDD, divided equally before each bolus feed.	Basal insulin: glargine given once daily or detemir given twice daily. Nutritional insulin: RAA insulin with each bolus. Correctional insulin: RAA insulin with each bolus.
Continuous tube feeds	Basal insulin: 40% (conservative) of TDD. Nutritional insulin: 60% of the TDD in divided doses.	Basal insulin: glargine given once daily or detemir given twice daily. Nutritional insulin: RAA insulin q 4 hours or regular insulin q 6 hours. Correctional insulin: Should match nutritional insulin choice.
Parenteral nutrition	Insulin is usually given parenterally, with the nutrition	Initially, a separate insulin drip allows for accurate dose-finding. Then, 80% of amount determined as TDD using drip is added to subsequent TPN bags as regular insulin. Use correctional subcutaneous insulin doses cautiously, in addition

Abbreviations: HS, at bedtime; IV, intravenous; NPO, nothing by mouth; q 4 hours, every 4 hours; q 6 hours, every 6 hours; q AC, before every meal; RAA, rapid-acting analog; TDD, total daily dose; TPN, total parenteral nutrition.

*These are the preferred regimens for most patients in these situations by consensus of the SHM Glycemic Control Task Force. Alternate regimens may appropriately be preferred by institutions or physicians to meet the needs of their own patient population. RAA insulins include lispro, aspart, and glulisine.

Hypoglycemia

- Diabetes Care 2009;32:S13-S61
- A plan for treating hypoglycemia should be established for each patient
- Additional risk factors for hypoglycemia in hospitalized patients:
 - Altered nutritional state, heart failure, renal or liver disease, malignancy, infection / sepsis
- Additional triggering events
 - Sudden reduction of corticosteroid dose
 - Altered ability of patient to report symptoms
 - Reduction of oral intake / emesis / new NPO status
 - Inappropriate timing of short- or rapid-acting insulin in relation to meals
 - Reduction of rate of administration on IV dextrose
 - Unexpected interruption of enteral / parenteral nutrition

Corticosteroid-Induced Hyperglycemia

- AACE/ADA 2009 guidelines
 - Institute glucose monitoring for at least 48 hours in patients receiving high-dose corticosteroids
 - Initiate insulin therapy when appropriate
 - Patients already being treated for hyperglycemia, early adjustment of insulin doses is recommended
 - During steroid tapers, insulin doses should be proactively adjusted to avoid hypoglycemia
- Clore JN, et al. Endocr Pract 2009;15:469-74
 - Predominant mechanism for glucose intolerance during corticosteroid administration is reduced insulin sensitivity
 - Additive issues if combined with calcineurin inhibitors (cyclosporine and tacrolimus)
 - Pharmacodynamic profiles for glucose tolerance with prednisone and prednisolone is a peak in 4-8 hours and a duration of 12-16 hours
 - Mirrors the kinetics of NPH insulin
 - More prolonged effect with dexamethasone-> ~ 20 hours
 - May need long-acting agents

Corticosteroid-Induced Hyperglycemia

- Clore JN, et al. Endocr Pract 2009;15:469-74
- Debatable whether you need to treat if short term (<1 month) of steroid therapy
- Treatment
 - Usually need insulin instead of oral agents
 - Method 1: give prandial therapy if steroids are given once daily
 - Glucose levels elevate with breakfast and lunch and decline gradually towards normal overnight
 - Method 2: give once daily NPH

Prednisolone dosage (mg/day)

≥ 40mg

30mg

20mg

10mg

NPH insulin dosage (units / kg)

0.4

0.3

0.2

0.1

- If patient is already receiving insulin, the doses listed are added to usual basal insulin
- When dexamethasone is used, insulin glargine or detemir could be substituted for NPH

Noninsulin Glucose-Lowering Agents

- Diabetes Care 2009;32:S13-S61 / J Hosp Med 2008;3:S17-S28
- Sulfonylureas
 - Risk of hypoglycemia
 - Some are long acting
- Meglitinides (repaglinide [Prandin])
 - Lack of clinical trial data
 - Primarily prandial in effect
- Metformin
 - Risk of lactic acidosis
 - Cardiac disease, hypoperfusion, renal insufficiency, old age and chronic pulmonary disease
- Thiazolidinediones (pioglitazone, rosiglitazone)
 - Risk of increased intravascular volume->CHF
 - Long delay to onset of action (2-3 weeks)
 - Contraindicated in liver disease
- Alpha-glucosidase inhibitors (acarbose)
 - Primarily prandial in effect
 - Abdominal bloating and flatus
- GLP-1 mimetics (exenatide [Byetta], liraglutide [Victoza])
 - Mainly effective on postprandial glucose
 - Limited inpatient experience
 - Abdominal bloating and nausea secondary to delayed gastric emptying
- DPP IV inhibitors (sitagliptin)
 - Limited inpatient experience

Transition from Intravenous to Subcutaneous Insulin Therapy

- Diabetes Care 2009;32:S13-S61
- Administer the first dose of SC insulin before discontinuation of IV infusion
 - Rapid or short acting: 1-2 hours prior
 - At UWHC:
 - Rapid acting: give 15 minutes prior along with basal insulin
 - Short acting: give 30 minutes prior
 - Intermediate- or long-acting: 2-3 hours prior
 - At UWHC:
 - Intermediate-acting: give 2 hours prior (if only insulin given)
 - Long-acting: give 4 hours prior (if only insulin given)
- Use a combination of short/rapid- and intermediate/long-acting insulins
 - Basal insulin can be initiated at any time of the day
- 80% of the IV insulin requirement over the preceding 24 hours
- Sliding scale insulin alone is not appropriate in diabetic patients

Perioperative Insulin

- Blood glucose levels should be checked every 1-2 hours before, during, and after the procedure until stable
- Insulin-requiring patients:
 - Consider initiating an insulin drip, especially in type 1 patients and/or insulin-requiring type 2 patients undergoing major surgery
 - Always provide basal insulin to type 1 patients to suppress ketosis. Never place type 1 patients on supplemental scale only -- even if the patient is NPO
- For surgeries and procedures not requiring an insulin drip:
 - NPH: Give $\frac{1}{2}$ of usual dose on the AM of surgery or procedure
 - Glargine / Detemir: Give usual dose (it does not need to be decreased unless the patient is having recurrent episodes of hypoglycemia)
 - Regular / Aspart: hold usual dose until the patient is eating again but provide supplemental insulin as needed
- Consider using insulin aspart for rapid correction of hyperglycemia and reduced chance of hypoglycemia
- Patients on pre-mixed insulin, such as 70/30 will need to be given NPH only on the day of the procedure. The dose should be calculated as $\frac{1}{2}$ of the NPH portion of the pre-mixed insulin
 - Example: Patient usually gets 34 units of 70/30. The NPH portion is 70 percent of 34 = 24 units. Give $\frac{1}{2}$ of 24 = 12 units on the day of the procedure

from UWHC

Insulin Pumps

- Patients can usually self-manage insulin pumps in the hospital
 - Need the mental and physical capacity to do this
- Nursing personnel must document basal and bolus doses at least daily
- Need hospital personnel with expertise in subcutaneous insulin infusions
- Hospitals should have a policy / procedure on how to handle these patients

Regimen after hospital D/C

- Admission A1C <7: continue home regimen of oral antidiabetic agents or insulin or both
- Admission A1C 7-9: restart the home oral agents and continue long-acting agent at 50-80% of hospital dose
- Admission A1C >9: discharge on a basal-bolus regimen at the same dosage as in the hospital
 - Could also restart the oral agents and add long-acting agent at 80% of the hospital dose

Point of Care Meters

- Rice MJ, et al. Anest Analg 2010;110:1056-65
- 2 methods available for glucose testing
 - Central laboratory device (CLD) or point-of-care device (POC)
 - Continuous glucose monitoring technology may be used in the future
- Advantages of POC devices
 - Less expensive
 - Immediate results
 - Minimal sample volume
- Disadvantages of POC devices
 - Lack of accuracy as compared to CLD
- FDA standards for POC monitors (ISO 15197:2003)
 - 95% of individual glucose results need to be within ± 15 mg/dl for reference values <75 mg/dl and within $\pm 20\%$ for reference values >75 mg/dl
- Studies have shown that POC meters have a disturbing lack of accuracy with low blood glucose values
- FDA advises manufacturers that they must “...clarify that critically ill patients (e.g., those with severe hypotension or shock, hyperglycemic-hyperosmolar state, hypoxia, severe dehydration, diabetic ketoacidosis) should not be tested with blood glucose meters because inaccurate results may occur”

Drug Interference with POC Meters

- Some POC meters are not able to distinguish glucose from other sugars such as maltose, galactose and xylose
 - Utilize test strips with glucose dehydrogenase pyrroloquinolinequinone (GDH-PQQ) or glucose-dye-oxidoreductase (GDO)
 - Accu-Chek (Roche), FreeStyle (Abbott), and Ascensia (Bayer)
- Could result in falsely elevated blood glucose levels and inappropriate insulin administration
- Included products
 - Extraneal (icodextran)-peritoneal dialysis solution
 - Gamimune N 5% and Octagam (IVIG)
 - Orencia (abatacept) for rheumatoid arthritis
 - WinRHo SDF liquid (Rho(D) immune globulin IV)
 - D-Xylose (d-xylose absorption test)-test for malabsorption
 - HepaGam B (hepatitis B immune globulin)
 - Adept adhesion reduction solution (icodextran)-reduce post surgical laparoscopic adhesions in gynecologic surgery
 - Bexxar (tositumonab radioimmunotherapy agent)
- Need to use clinical laboratory testing until maltose containing agent is no longer used
- ISMP issued alert in November 2008

Quality Measures

- Pay for Performance Measures
 - Hospital-Acquired Conditions
 - Hospitals will not receive additional payment for cases in which one of the selected conditions was not present on admission
 - Manifestations of poor glycemic control
 - Diabetic ketoacidosis
 - Nonketotic hyperosmolar coma
 - Hypoglycemic coma
 - Secondary diabetes with ketoacidosis
 - Secondary diabetes with hyperosmolarity
- Surgical Care Improvement Project (SCIP)
 - The percent of cardiac surgery patients with glucose levels <200 mg/dl by 6AM of the first and second postoperative day
 - Anesthesia end date being postoperative day zero

Potential Cost Savings

- Draw up individual doses of long-acting agents instead of dispensing entire vial
 - Issues we have faced at UWHC
 - Losing partial doses in the pneumatic tube system
 - Syringe needle bending in pneumatic tube system
- Change formulary long-acting agent to least expensive
 - Glargine vs. Detemir
 - Data that detemir can be given once daily
 - Limited data on glucose control with changing from glargine to once daily detemir

Safe Use of Insulin

- Use of insulin pens (ISMP Medication Safety Alert, May 8, 2008)
 - Advantages
 - Pens are labeled by manufacturer with name and strength
 - Each pen is individually labeled with patient name
 - Insulin is in a form ready for administration
 - Lessens nursing time needed to prepare and administer
 - Reduce medication waste
 - Disadvantages
 - Needstick injuries
 - Technique errors
 - “Wet Spot” on the skin after administration
 - Not tip and roll insulin suspensions
 - Using pens like multidose vials
 - Using pens for multiple patients
 - Different pens may look the same
 - May read digital display wrong if upset down (used left-handed)
 - UWHC: add barcodes for scanning / pediatric use / labeling for take home use / cost
 - Safe practice recommendations
 - Conduct failure mode and effects analysis (FMEA) analysis prior to implementing
 - Formulary control: limit the variety of pens
 - Health care professionals and patient education
 - Written guidelines for each type of pen used
- Segregating different agents
- Nursing double checks

Conclusions

- Treatment of hyperglycemia in the hospitalized patient is a very difficult issue and education of practitioners is essential
- Appropriate blood glucose goals should be recognized for all patients
 - These goals may change when new AACE / ADA guidelines come out
- Non-insulin agents should not be used in hospitalized patients
- Prolonged sliding scale insulin should not be the sole method used for blood sugar control for inpatients

Questions?