Inpatient Glycemic Control: Finding Balance

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The Scope of the Problem:
- Diabetes is increasing rapidly throughout the world
  - Nearly 26 million with diabetes in the U.S.
  - 70% of those presenting with ACS will have diabetes or prediabetes
- People with diabetes and prediabetes have an increased rate of hospitalization
- 25-40% of adults in the hospital have hyperglycemia.

Hyperglycemia In the Hospital

Diabetes:
- Previously diagnosed
- Previously undiagnosed
  - HbA1c > 6.5% during admission
Hyperglycemia without diabetes diagnosis
- Diabetes diagnosed on follow-up
- Prediabetes with overt hyperglycemia during acute physiologic stress
- Hyperglycemia due to physiologic stress without underlying metabolic abnormality
  - normal follow-up testing

Inpatient Glucose Control: A survey of 126 hospitals, ICU and Non-ICU
Cook CB et al. J Hosp Med 2009:E7-E17
- Mean glucose was about the same for ICU and Non-ICU but spread was greater in the ICU
- Higher BGs in smaller hospitals
- Above 180 mg/dl
  - 46% in ICU
  - 31.7% in non-ICU
- Hypoglycemia (under 70 mg/dl)
  - 10.1% ICU
  - 3.5% non-ICU

There has long been evidence of increased complications in the hospital associated with diabetes and hyperglycemia.
- Strong associations with increased infections known for decades
- Well demonstrated potential mechanisms of injury
- Increased morbidity
- Increased mortality
- Some uncertainty as to the magnitude of hyperglycemia as the cause of all bad outcomes and could be partly a marker of severe illness (stress hyperglycemia)
Detrimental Physiologic Impact of Hyperglycemia

Metabolic stress response

- ↑ Stress hormones and peptides
  - ↑ Glucose
  - ↓ Insulin
  - ↑ FFA
  - ↑ Ketones
  - ↑ Lactate
  - ↑ Reactive O₂ species
  - ↑ Transcription factors
  - ↑ Secondary mediators
  - ↑ Platelet aggregation
  - ↓ IPA activity
  - ↑ PAI levels

- Immune dysfunction
- Infection dissemination
- Cellular injury/apoptosis
  - Inflammation
  - Tissue damage
  - Altered tissue/wound repair
  - Acidosis
  - Infarction/ischemia

- Prolonged hospital stay
- Disability
- Death


Improved Outcomes with Basal-Bolus Insulin in Non-ICU Surgical Patients

Complications include:
- Wound infection
- Pneumonia
- Acute respiratory failure
- Acute renal failure
- Bacteremia

n = 107 p = 0.003
n = 104

The evolution of practice over the last decade

- Before 2001
  - Some concern but no consistency of glucose control and no guidelines
  - Lacked prospective evidence for the benefit of intensive glucose management
  - Accumulating evidence in cardiac surgery and MIs

- Van den Berghe 2001
Reports of clear and relatively dramatic improvement in outcomes among surgical patients (primarily cardiac surgery patients)
These patients received early TPN and this could have contributed to results
Relatively low acuity index
Comparator group started therapy >215 mg/dl
This led to institutional changes to improve glucose control.

December 2003
American College of Endocrinology convened a consensus conference to set guidelines. Many groups participated in the process (e.g. ADA, AHA, ACP, SHM and others)
The recommendations were to target a glucose < 110 mg/dl in those in ICUs

Developing Inpatient Protocols
• Assemble an inclusive multidisciplinary team
  o Nursing -- Diabetes Specialist
  o Hospitalists -- Intensivists
  o Anesthesia -- ER Personnel
  o Surgeons -- Pharmacists
  o Quality Assurance -- Others
• Start with an available protocol to customize
• Administrative support
• P&T Committee approval
• Education/training for all involved individuals
• Forms (orders, flowsheets, kardex)
• Collect data, evaluate, & adjust protocols

Glucometrics Guide Progress
• Data collection:
  o Automatic or manual
  o Must be validated (reviewed)
• Primary parameters
  o Efficacy (according to goals)
  o Safety (frequency of hypoglycemia at various levels)
• Multiple options for meaningful expression
• The process is greatly aided by advancing technology, particularly relating to EMRs

Strategies to Improve Glucose Control
• Hospital protocols for all to use
• Staff education - physician, nurses, others
• Development of a “glycemic consult team”
  o Diabetes educator driven
  o NP or Pharm D model
  o Endocrinologist model
  o Hospitalists
    • Alone
    • In concert with an endocrinologist and nurse.
• 2004-2009
  o Multiple studies attempted but many problems encountered.
Many studies were stopped early due to excess hypoglycemia
- Studies seemed to be showing no benefit though they were underpowered
- Almost all of these studies had quite good control of glucose in the control arm
- Some evidence that hypoglycemia could be contributing to off-setting complications in the intensively treated groups.
- Evidence emerged that MICU studies with high acuity index patients had worse outcomes

- **2009 - NICE SUGAR Study**
  - Large study of mixed ICU population
  - Results showed no benefit to goal of < 110 and some evidence of worse outcomes
  - Control group targeted glucose control of 140-180 mg/dl with a mean of 143 mg/dl

**DON’T MISINTERPRET THE MESSAGE:**
- Glucose control still matters in the hospital
- The initially proposed goals were probably two aggressive
  - Could relate to inability of insulin infusion protocols to avoid hypoglycemia
  - Could be that some ill individuals are particularly at risk even with relative hypoglycemia.
- Hypoglycemia and hyperglycemia are both problems.

**Hyperglycemia-related mortality in the ICU is related to disease state.**
- Disease states with an association
  - Unstable angina
  - Acute MI
  - CHF
  - Arrhythmia
  - Respiratory failure
  - GI bleed
  - Pneumonia
  - Sepsis
  - Acute renal failure
  - CVA
  - PE
  - Colectomy
  - Valve surgery
  - Genitourinary surgery

**Low Glucose means are associated in increase mortality. Hypoglycemia is causing a problem**
Glucose Monitoring Considerations: Methods May Create Problems.

- Glucose values vary by assay method
  - Central lab
    - Generally best but glucose will drop if in a red top
  - Blood gas machine
  - POC meters
    - Likely not as accurate in the ICU
    - No specific evidence they cause a dosing problem
    - Most accurate from 80 – 150 mg/dl
- Glucose values vary by type of sample
  - Whole blood vs Plasma
  - Arterial vs venous

2009 - - New guidelines form the AACE and ADA

- Intensive care goals are 140-180 mg/dl
  - 110-140 still reasonable for some patients
- Non-ICU patients
  - Premeal < 140 mg/dl
  - Random glucose < 180 mg/dl
  - Adjust when glucose levels < 100 mg/dl

General Points to remember in the hospital

- Oral agents are seldom indicated
- An individual, interested and experienced physician can adjust therapy optimally but protocols are necessary to improve glucose control in all patients.
  - Protocols must be generated with involvement of multiple stakeholders
  - Results must be monitored (glucometrics) to determine effectiveness of the protocol
- Select an effective insulin infusion protocol for ICU (used in non-ICU setting in some institutions)
• Use a physiologic basal-bolus regimen
  o Plus supplemental insulin for correction
  o Avoid sliding scale insulin alone

• Avoid clinical inertia
  o Use prior day results to adjust insulin daily

• Make careful transitions in insulin regimen
  o Insulin drip to SC treatment

• Have clear protocol for hypoglycemia

Starting Insulin In The Hospital In Patients With Type 2 Diabetes
• Consider a 24 hour insulin dose of 0.5-0.6 units/kg/day
  o Lower dose in elderly and thin

• Give 50% of this as basal
  o Glargine or detemir once daily
  o NPH 2-4 times daily

• Give 50% for meals if eating
  o Apportion according to relative meal size
  o Can give after the meal if intake uncertain

• Use supplemental scale and adjust

Avoid Sliding Scale Insulin
• Supplemental insulin is OK -- sliding scale is not!
• May use a protocol with various levels of expected insulin sensitivity or use outpatient rules of sensitivity with allowance for stress
• If supplemental doses do not reduce the next glucose to < 150 mg/dl, increase the scale appropriately
• Supplemental requirements should be reviewed each 24 hours and often added to the next day’s baseline dose at the appropriate times

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

Mean overall BG difference between the groups during hospital stay was 27 mg/dL ($P<.01$)

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Transition from IV to subcutaneous insulin is a critical time
  o Frequent loss of control.
o Transitioning guidelines
  - Place patients needing significant IV insulin doses on physiologic insulin regimens (meal plus basal).
  - Don’t use basal insulin alone in patients with very poor control on two or more oral agents.
  - Use correction doses for temporary hyperglycemia.
  - Overlap SC and IV to minimize “hyperglycemia escape” related to short ½ life of IV insulin.
  - **Or give 10% bolus of rapid-acting analog at transition**
  - Use post meal rapid analogs for uncertain ability to consume food.

o Transitioning **without evidence** of rapidly improving blood glucose
  - Calculate the IV basal insulin requirement
  - Insulin delivered overnight for 4 hours (stability)
  - Multiply by 6 = 24 hour basal requirement
  - Multiply by **80%** to get a safe SC dose /24 hours
  - Glargine or detemir in single doses or NPH in 2+ doses
  - Example:
    - Overnight the patient averaged 1.2 u/hr = 4.8 u/4 hours
    - 4.8 x 6 = 30 units
    - 30 x .8 = 24 units
    - 24 units glargine or detemir before breakfast or bedtime or 24 u N in 2-4 doses
    - Adjust according to overnight glucose control

o Transitioning **with evidence** of rapid glucose improvement
  - Multiply by **60%** rather than 80%

**There is a movement to determine fasting glucose and A1c when admitted**
  - A1c helps determine the risks of the hospitalization but also helps decide therapy at discharge
    - More likely to need additional therapy over previous therapy if A1c was high at admission.
    - Can help define those with previous diabetes

**Special situations:**
  - Steroids
    - Often are given in the morning resulting in high insulin requirements during the day but much less basal needed at night.

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<td><strong>Regular/ Analog</strong></td>
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<td><strong>NPH</strong></td>
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<td><strong>Or Glargine/Detemirr</strong></td>
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o Alimentation
  ▪ Must tailor the insulin regimen to the type of feeding

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<th>Nutrition Method</th>
<th>Insulin Component</th>
<th>Possible Approach</th>
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| Bolus tube feedings    | • Basal insulin 40% of TDD  
  • Nutritional insulin 60% of TDD as RAA | RAA insulin scheduled with each bolus feeding  
  + RAA insulin correction (later increase scheduled)  
  + Basal insulin (glargine qd or le vemir q 12) |
| Continuous tube feedings | • Basal insulin 40% of TDD  
  • Nutritional insulin as 60% of TDD as divided doses | RAA q 4 hours  
  Regular q 6 hours or NPH q 8 hours  
  + Basal insulin |
| Parenteral nutrition   | • Give insulin IV with nutrition | Dose find with IV insulin infusion followed by 80% placed in TPN  
  Plus correction insulin. |

Hypoglycemia is also dangerous

• Features increasing the risk of hypoglycemia
  • Advanced age
  • Renal failure
  • Liver disease
  • Concurrent illness (cerebral vascular accident, congestive heart failure, shock, sepsis)
  • Ventilator use
  • Concurrent medications (β-blockers, quinolones, steroids, epinephrine)

Events Triggering In-Hospital Hypoglycemia:

• Transportation off ward, causing meal delay
• Failure to measure blood glucose before insulin doses
• New NPO status
• Interruption of
  o IV dextrose therapy
  o Total parenteral nutrition
  o Enteral feedings
  o Continuous venovenous hemodialysis

References:


