Management of Inpatient Hyperglycemia: 2011 Endocrine Society Meeting
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Hyperglycemia in Critically ill patients in ICU Settings.
There is substantial observational evidence linking hyperglycemia in critically ill patients (with and without diabetes) to higher rates of hospital complications, longer hospital stay, higher health care resource utilization, and greater hospital mortality. Although, several cohort studies as well as early randomized clinical trials (RCTs) suggested that tight glucose target (80 to 110 mg/dL [4.4 to 6.1 mmol/L]) reduced hospital complications and mortality, this target has been difficult to achieve without increasing the risk for severe hypoglycemia. In addition, recent RCTs in critically ill patients have failed to show a significant improvement in mortality or have even shown increased mortality risk with intensive glycemic control.

The largest study to date, NICE-SUGAR, a multicenter, multinational RCT, tested the effect of tight glycemic control (target 81-108 mg/dl) on outcomes among 6,104 critically ill participants. Ninety-day mortality was significantly higher in the intensive vs. the conventional group (target 144-180 mg/dl) (78 more deaths; 27.5% versus 24.9%, P = 0.02) in both surgical and medical patients. Mortality from cardiovascular causes was more common in the intensive group (41.6% versus 35.8%; P = 0.02). Severe hypoglycemia was also more common in the intensively treated group (6.8% vs. 0.5%; P<0.001). This study’s findings do not disprove the notion that glycemic control in the ICU is important; however it strongly suggests that it is not necessary to target blood glucose values <140 mg/dl, and that a highly stringent target of <110 mg/dl may actually be dangerous.

In a recent meta-analysis of 26 trials (N=13,567), the pooled relative risk (RR) of death with intensive insulin therapy was 0.93 as compared with conventional therapy (95% CI 0.83–1.04). The pooled hypoglycemia RR with intensive therapy was 6.0 (95% CI 4.5–8.0). The specific ICU setting influenced the findings, with patients in surgical ICUs appearing to benefit from intensive insulin therapy (RR 0.63, 95% CI 0.44–0.91), while those in other critical care settings did not (medical ICU: RR 1.0, 95% CI 0.78–1.28; ‘mixed’ ICU: RR 0.99, 95% CI 0.86–1.12).

Based on recent RCTs, the Endocrine Society, AACE, and ADA recommended raising glycemic targets in the ICU. For the majority of patients in the ICU setting using insulin infusion and targeting blood glucose levels between 140 and 180 mg/dL (7.8 and 10.0 mmol/L) is recommended. Despite the lack of strong scientific evidence, lower glucose targets between 110 and 140 mg/dL (6.1 and 7.8 mmol/L) may be appropriate in selected ICU patients (i.e., ICUs with extensive experience and appropriate support, CABG surgical patients, stable glycemic control without hypoglycemia). Blood glucose targets >180 mg/dl or <110 mg/dl are not recommended.

Hyperglycemia in Non-ICU Settings.
In general medical and surgical non-ICU patient, observational and RCT have also shown a strong association between hyperglycemia and poor clinical outcomes, including prolonged hospital stay, infection, and disability after hospital discharge, and death. In such patients, the presence of hyperglycemia is associated with prolonged hospital stay, infection, disability after hospital discharge, and death. Admission hyperglycemia has also been linked to worse outcomes in patients with community-acquired pneumonia. In a prospective cohort multicenter study of 2,471 patients, those with admission glucose levels of > 11 mmol/L (198 mg/dL) had a greater risk of mortality and complications than those with glucose < 11 mmol/L.
The risk of in-hospital complications increased 3% for each 1 mmol/L increase in admission glucose. In a retrospective study of 348 patients with chronic obstructive pulmonary disease and respiratory tract infection, the relative risk of death was 2.10 in those with a blood glucose of 7-8.9 mmol/L, and 3.42 for those with a blood glucose of >9.0 mmol/L compared to patients with a blood glucose 6.0 mmol/L. For 1 mmol/L (18 mg/dl) increase in blood glucose was associated with a 15% increase in the risk of an adverse clinical outcome, which was defined as death or length of stay of greater than nine days. A recent RCT reported that improving glycemic control with basal bolus vs sliding scale insulin (SSI) in patients with type 2 diabetes undergoing general surgery reduced a composite of postoperative complications including wound infection, pneumonia, bacteremia, respiratory and acute renal failure. In this study a mean daily glucose concentration after the 1st day of basal bolus and SSI was 145±32 mg/dl and 172±47 mg/dl, respectively, p<0.01. There were reductions with basal bolus as compared with SSI in the composite outcome (24.3% and 8.6%, OR: 3.39 (95% CI: 1.50-7.65); p=0.003).

Treatment options for achieving safe and effective glycemic targets.

Insulin therapy is the preferred method of glycemic control in majority of patients in the hospital setting. In the ICU, IV infusion is the preferred route of insulin administration. Numerous examples of successful CII algorithms in achieving glycemic control are reported in the literature. Recently, computer-based algorithms aiming to direct the nursing staff adjusting insulin infusion rate have become commercially available. All published ICU insulin algorithms appear to be equally effective in controlling BG without major clinical outcome differences, including frequency of severe hypoglycemic events, length of ICU and hospital stay or mortality between different treatment algorithms.

Outside of critical care units, subcutaneous insulin administration is used much more frequently. Oral agents have a limited role, and should be avoided in the inpatient setting. Scheduled subcutaneous insulin is the preferred method for achieving and maintaining glucose control in non-ICU patients with diabetes or stress hyperglycemia. The recommended components of inpatient subcutaneous insulin regimens include a basal, nutritional and a supplemental (correction) component. Hospitalized patients often require high insulin doses to achieve target glucose levels due to increased insulin resistance; thus in addition to basal and nutritional insulin requirements, patients often require supplemental or correction insulin for treatment of hyperglycemia. Use of repeated doses of short-acting insulin per sliding scale, as a sole form of therapy in hospitalized patients with diabetes, should be avoided because of persistence of hyperglycemia in type 2 diabetes and risk of ketoacidosis in patients with type 1 diabetes. The use of basal-bolus regimen has been shown to improve glycemic control with a similar rate of severe hypoglycemia than SSI alone and to decrease hospital complications in general surgery undergoing non-cardiac surgery.

This lecture will discussed the evidence in support of improving glycemic control for inpatients with hyperglycemia, recommended glycemic targets in different patient populations, treatment options available for safely achieving glycemic targets avoiding hypoglycemia, available strategies for transitions to outpatient care, and areas of need for future research.

References
#1, Case Presentation:

- 48 y/o male with an 8 yr history of DM admitted 3 day history of fever, cough, and RLL pneumonia on chest x-ray. Previously treated with metformin and sulfonylurea.
- Lab: BG 264 mg/dL, creatinine 1.6 mg/dL, A1C: 8.4%.
- After a brief clinical evaluation and starting antibiotic therapy you have to decide on insulin regimen.

Given this patient’s history and laboratory values, what is the best treatment option for glycemic management?

1. Continue oral antidiabetic agents?
2. Sliding-scale regular insulin?
3. Split-mixed regimen – NPH + Regular insulin?
4. Basal bolus regimen – long + rapid acting analogs?

#2, Case Presentation:

62 y/o male with a 3 cm thyroid nodule, undergoes fine needle aspiration.

FNA results: suspicious for papillary thyroid carcinoma. Surgical intervention is scheduled.

PMH: 10 yr history of T2DM treated with metformin and sulfonylurea.
- Lab: BG 264 mg/dL, creatinine 1.6 mg/dL, A1C: 8.4%, normal TSH and Free T4.

Given this patient’s history and laboratory values, what is the best treatment option for glycemic management?

1. Continuous IV insulin drip?
2. Sliding-scale regular insulin?
3. Split-mixed regimen – NPH + Regular insulin?
4. Basal bolus regimen – long + rapid acting analogs?
Chief complaint:
- Shortness of breath lasting ~48 hours

Patient characteristics
- 58-year-old man; Height: 5'9"; Weight: 244 lb (110 kg)
  - Recent weight gain: ~12 lb in the past 3 months
  - Pedal edema over last 6 months

Physical exam
- BP: 140/90 mm Hg; PR: regular (118 bpm); JVP: elevated; heart sounds: +S3
- Bibasilar crackles; 2+ pedal edema

Chest x-ray
- Mild pulmonary edema

ECG
- Poor R-wave progression in anterior chest leads V1-V5

Pertinent labs
- BNP: 750 pg/mL; cTnI: <0.1 ng/dL
- BG: 428 mg/dL; A1C: 8.5%
- Cr: 2.2 mg/dL; BUN: 40 mg/dL
- GFR (Cockcroft-Gault): 57 mL/min
- Lipids (including LDL): at target

Diagnosis
- CHF
- T2DM, HTN, CHD, and moderate renal dysfunction

Treatment in the ED
- Oxygen therapy, diuresis (IV loop diuretic), ACE inhibitor
- Discontinue TZD, SU, and metformin
- IV insulin initiated

Transfer to cardiology step-down unit

Given this patient's history and laboratory values, what is the best treatment option for glycemic management?

- Continue IV RHI
- Transition to SC insulin (sliding-scale regimen)
- Transition to SC insulin (basal, prandial, and supplemental)
- Resume oral therapy (metformin plus SU plus TZD)