Update in Inpatient Glycemic Management

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Inpatient Glycemic Management

Outline

• Evidence for/against tight glycemic control in the hospital
• Recommended inpatient glycemic targets
• Rational approach to management of diabetes and inpatient hyperglycemia
Inpatient Glycemic Management
Why do we care?

- Avoid symptomatic hyperglycemia, severe hyper/hypoglycemia
- Hyperglycemia is common in hospitalized patients w/ and w/o known diabetes and associated with adverse pt outcomes
  
  \begin{itemize}
  
  
  \end{itemize}

- Treatment improves outcomes?
  
  \begin{itemize}
  
  \item Early studies suggested improved clinical outcomes with interventions targeting near euglycemia
  
  \item More recent studies have yielded inconsistent results, with the suggestion of harm due to higher rates of hypoglycemia
  
  \end{itemize}
<table>
<thead>
<tr>
<th>Study (population)</th>
<th>Intensive insulin therapy</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>DIGAMI 1 (MI)</td>
<td>Insulin-glucose infusion &gt;24h goal 126-196 f/b multi-dose SQ insulin for ≥3 mo</td>
<td>Significant reduction mortality at 1 and 3.4 years follow up</td>
</tr>
<tr>
<td>Portland Diabetes Project (CABG)</td>
<td>IV insulin infusion POD 0-2 goal 150-200-&gt; 70-110 by 2005</td>
<td>Significant reduction DSWI and mortality</td>
</tr>
<tr>
<td>Leuven 1 (SICU)</td>
<td>IV insulin infusion goal 80-110</td>
<td>Significant reduction morbidity, ICU and hospital mortality at 1 year follow up</td>
</tr>
</tbody>
</table>

# Intensive Insulin Therapy and Potential Harm

<table>
<thead>
<tr>
<th>Study (population)</th>
<th>Intensive insulin therapy</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leuven 2 (MICU)</td>
<td>IV insulin infusion goal 80-110</td>
<td>Reduction morbidity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No overall reduction mortality</td>
</tr>
<tr>
<td></td>
<td></td>
<td>↓ mortality ICU ≥3d</td>
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<tr>
<td></td>
<td></td>
<td>↑ mortality ICU &lt;3d</td>
</tr>
<tr>
<td>VISEP (Sepsis)</td>
<td>IV insulin infusion goal 80-110</td>
<td>No significant reduction mortality at 28 and 90 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Trial stopped early for safety reasons</td>
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<tr>
<td></td>
<td></td>
<td>Higher rate severe hypoglycemia and serious adverse events with intensive therapy</td>
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</tbody>
</table>

**NICE-SUGAR**

Intensive versus Conventional Glucose Control in Critically Ill Patients


- Large international RCT >6000 mixed ICU patients
- Within 24h of admission to ICU, pts with anticipated duration of ICU stay ≥3d were randomly assigned to intensive or conventional glycemic control
  - Intensive 80-108 (achieved 115)
  - Conventional <180 (achieved 144)
- Primary outcome mortality 90 days
NICE-SUGAR
↑ Mortality and Hypoglycemia

Significant ↑ 90d mortality in intensive group
27.5 vs 24.9 %
HR 1.11 (1.01-1.23)

Significant ↑ rate hypoglycemia in intensive group
6.8% vs 0.5%, p<0.001

Trend towards improved outcome with IT in CST treated (p=0.06) and trauma pts (p=0.07)

Meta-Analysis of ICU Studies

13,567 patients

In 14 trials reporting hypoglycemia
RR 6.0 (4.5-8.0)

Conclusion:
IIT -> significant ↑risk hypoglycemia with no overall mortality benefit
May be beneficial to patients admitted to surgical ICU

Why have recent trials failed to reproduce the benefits observed with intensive insulin therapy in earlier trials?

- Single center vs. multicenter
- Variability in devices, techniques, and frequency blood glucose measurements
- Glycemic targets (less glycemic separation)
- Variations in insulin infusion protocols
- Type and amount of nutritional supplementation
Good inpatient glucose management remains important

Hyperglycemia & hypoglycemia are both associated with poor clinical outcomes in a variety of patients

Studies compare “good” with “tight” control

Desire to minimize risk associated with intensive control but avoid adverse outcomes associated with uncontrolled hyperglycemia

May be able to reduce risk/achieve benefit by aiming for higher targets, improving and standardizing protocols, and carefully implementing them
Inpatient Glycemic Control

- Inattention to glycemic control
- Intensive glycemic control
- Moderate glycemic control
American Association of Clinical Endocrinologists and American Diabetes Association Consensus Statement on Inpatient Glycemic Control

Recommended Inpatient Glycemic Targets

**Critically ill patients**
140-180mg/dl

**Noncritically ill patients**
- Premeal <140mg/dl
- Random <180mg/dl

*More or less stringent goals may be appropriate for select patients
*Reassess regimen if glucose <100, Modify regimen if glucose <70

How can recommended glycemic goals be achieved in a reasonable and safe manner that minimizes the risk for hypoglycemic events?
Inpatient Glycemic Management Critically Ill Patients

• **IV insulin infusion preferred**

• Validated infusion protocol with demonstrated safety & efficacy

• Initiate insulin for persistent hyperglycemia starting at threshold no greater than 180mg/dl

• Frequent glycemic monitoring

Inpatient Glycemic Management Non-Critically Ill Patients

- Few prospective randomized clinical trials in general medical/surgical settings

- Challenges
  - Increased risk of hyper and hypoglycemia
  - Glucose monitoring, not always ideal
  - Glucose meters, not always accurate
  - Hyperglycemia rarely focus during hospital stay

- Fear of hypoglycemia and lack of established treatment algorithms lead to
  - Holding medications
  - Reliance on sliding scale insulin
Case

- 60 year old man with T2DM, HTN, HL, admit PNA
- Outpatient regimen: metformin 1gm bid and glyburide 10mg bid
- Reports decreased appetite and mobility due to clinical condition
- 100kg, BMI 35
- Cr 2.2 (baseline 1.2)
- A1c 10.2
How would you manage this patient?

a) Hold metformin, continue glyburide, start correctional insulin
b) Stop oral agents, start correctional insulin alone
c) Stop oral agents, start correctional insulin + basal insulin
d) Stop oral agents, start correctional insulin + basal and nutritional insulin
Non-Insulin Agents Considerations

- Sulfonylureas -> prolonged hypoglycemia
- Metformin -> slow dose titration; several contraindications including severe renal insufficiency, iodinated contrast, hypoperfusion
- TZD -> slow onset action, edema, CHF
- Glinides -> mild glucose lowering effect, hypoglycemia
- DPPIV inhibitors -> generally well tolerated, mild glucose lowering effect, ?CHF
- GLP1 receptor agonists -> slow dose titration, nausea, injectable, potentially costly
- SLGT 2 inhibitors -> mild glucose lowering effect, dehydration, renal insufficiency, UTI, DKA, potentially costly
Physiologic Components of Insulin Therapy

• **Basal insulin**
  Amount of insulin necessary to regulate glucose levels between meals and overnight

• **Nutritional insulin (prandial)**
  Amount of insulin required to cover meals, IV dextrose, enteral nutrition, TPN or other nutritional supplements

• **Correctional insulin**
  Supplemental doses of insulin given to correct hyperglycemia that occurs despite use of basal & nutritional insulin. **Not recommended as monotherapy for >24-48h. NEVER appropriate as monotherapy in type 1 DM**
Types of insulin- Human

**Short Acting**
Regular (HumuLIN & NovoLIN R)

**Intermediate acting**
NPH (HumuLIN & NovoLIN N)

**Premixed** - not generally preferred for hospital use
70% NPH/ 30% Regular (HumuLIN & NovoLIN 70/30)

**Other**
U500
Types of insulin - Analogs

**Rapid acting**
- Lispro (HumaLOG®)- U100 and U200
- Aspart (NovoLOG®)
- Glulisine (Apidra®)

**Long acting**
- Glargine (Lantus® U100, Toujeo® U300)
- Detemir (Levemir®)
- Degludec (Tresiba®)

**Premixed** - not generally preferred for hospital use
- 70% Aspart protamine suspension/ 30% Aspart (NovoLOG Mix 70/30®)
- 50-75% Lispro protamine suspension/ 25-50% Lispro (HumaLOG Mix 75/25®)(HumaLOG Mix 50/50®)
RABBIT-2 Trial: Improved Glucose Levels with Basal-Bolus vs. SSI in non-ICU Patients

66% of pts tx with basal-bolus achieved mean BG <140 versus only 38% of pts tx with SSRI

* $P<.01$; ¶ $P<.05$

RABBIT 2 Surgery: Postoperative Complications During Basal-Bolus and SSI Therapy in General Surgery Patients

* Wound infection, pneumonia, acute renal failure, respiratory failure, and bacteremia.

Glycemic Control in Medical/Surgical Patients Treated with Basal Plus and Basal Bolus Regimens

Basal bolus = ½ glargine qd, ½ glulisine ac + correction ac hs. TDD 0.3-0.5u/kg/d
Basal plus = glargine qd + correction ac hs. TDD 0.15-0.25u/kg/d.

Blood Glucose Levels in Noncritical Care Patients with Type 2 Diabetes Treated with Sitagliptin

Inpatient Glycemic Management
Non-Critically Ill Patients- Summary

- Non-insulin agents inappropriate for most pts
  - DPPIV inhibitors (& glinides) may have some utility in pts with low insulin requirements, variable PO intake, renal insufficiency
- Prolonged “sliding scale” as sole regimen discouraged
- Basal insulin or basal + correction insulin preferred in patients with poor oral intake or NPO
- Scheduled SC insulin with basal bolus + correctional preferred in patients who are eating (but basal plus correctional may also be appropriate- “Basal Plus Trial”)

Approach to Glycemic Management in Non-Critically Ill Patients

1. Assess home BG control
2. Assess factors that may influence BG control
3. Choose frequency of bedside BG monitoring
4. Choose diet
5. Consider treatment options & safety of non-insulin agents
6. Order education if indicated
7. Order insulin
8. Adjust insulin
9. Plan for discharge

- Hx diabetes? type 1 or type 2?
- Outpt regimen? Adherence?
- Outpatient glycemic control? (hyper/hypo, SMBG, a1c, comp)
- Check A1C if Ø doc in last 2-3 mo

- ↑BG: illness, steroids, pressors, TPN, inactivity, withhold DM meds
- ↓BG: poor PO intake, change in diet and/or compliance
- Variable BG: inconsistent carb intake or illness

- QAC, HS if eating meals
- Q4-6h if NPO, receiving TPN or enteral nutrition
- + 3AM if ↑ risk for nocturnal hypo

- CCHO diet preferred if eating
- Consider nutrition consult

- Noninsulin agents
- Insulin (preferred)
## Approach to Ordering Insulin

<table>
<thead>
<tr>
<th>Category</th>
<th>Instructions</th>
</tr>
</thead>
<tbody>
<tr>
<td>For patients on basal and nutritional insulin at home</td>
<td>• Order home regimen but consider reducing doses by 20% (unless home BG high)</td>
</tr>
<tr>
<td>For patients on pre-mixed insulin at home</td>
<td>• Order 50-60% TDD as long-acting insulin</td>
</tr>
<tr>
<td></td>
<td>• Order 40-50% TDD as nutritional insulin, divided into 3 pre-meal doses</td>
</tr>
<tr>
<td></td>
<td>• Consider reducing TDD by 20% unless home BG high</td>
</tr>
<tr>
<td>For patients on basal insulin at home (with or w/o non-insulin therapy)</td>
<td>• Order 50-80% of home basal insulin + correctional insulin</td>
</tr>
<tr>
<td>For patients not previously on insulin</td>
<td>• Order correctional insulin</td>
</tr>
<tr>
<td></td>
<td>• If a1c &gt;8 or BG &gt;/=180 x2 add weight based basal insulin OR basal + nutritional insulin for significant hyperglycemia</td>
</tr>
</tbody>
</table>
Back to our patient

1. Assess home BG control
2. Assess factors that may influence BG control
3. Choose frequency of bedside BG monitoring
4. Choose diet
5. Consider treatment options
6. Order education if indicated
7. Order insulin
8. Adjust insulin
9. Plan for discharge

• T2DM
• Metformin and glyburide
• Adherent
• Polyuria, denies sx hypo
• Retinopathy
• A1c 10.2, uncontrolled

• ↑BG: illness, inactivity
• ↓BG: poor PO intake, AKI

• QAC, HS

• CCHO diet

• Hold metformin, glyburide
• Start Insulin
How to Order Scheduled Insulin

• Calculate Total Daily Dose (TDD) of basal and nutritional insulin based on
  – Weight OR
    • ~0.2-0.3 u/kg/day for lean OR renal insufficiency
    • ~0.4-0.5u/kg/day for overweight/obese
  – Preadmission insulin regimen OR
  – Current insulin needs (correctional insulin use)

• Order ~50% of TDD as basal & ~50% as nutritional
  – Basal: glargine or detemir q12-24h or NPH twice daily
  – Nutritional: rapid-acting insulin with meals ("set dose" or "ICR"= insulin to carb ratio using rule of 500)

• Order correction insulin
  – same insulin as nutritional with meals or meals & HS
  – based on TDD ("sliding scale" or "ISF"= insulin sensitivity factor using rule of 1800)
Case

Order scheduled insulin:

Calculate Total Daily Dose (TDD) of insulin
- 0.5u/kg/day for (obese)
- 0.5 x 100kg = 50 units

Order ~50% basal/ 50% bolus
- 25 units glargine qhs
- 6 units aspart with meals (reduced dose 2/2 poor po intake) OR 500/(TDD=50) = ICR 1:10

Order Correction Insulin
- aspart mod dose ac OR 1800/(TDD=50) = ISF 35
How to Adjust Insulin

- If most BG 140-180, make no change
- If $\geq 2$ BGs $<100$ mg/dl, decrease TDD by 10-20%
- If $\geq 2$ BGs $>180$ mg/dl AND none $<100$ mg/dl, increase TDD by 10-20% OR add 50-100% of previous 24h correction insulin to TDD

- If fasting BG consistently out of range, adjust basal insulin or address bedtime snacking
- If premeal or bedtime BG consistently out of range, adjust or add nutritional insulin to preceding meal
Your patient is now NPO after midnight for procedure tomorrow. What do you do?

a) hold glargine
b) continue glargine at current dose
c) reduce glargine by 10-20%
d) reduce glargine by 50%
Insulin Adjustment for NPO Status

• Hold nutritional insulin
• Continue correction insulin
• Basal insulin: decrease dose by 0-40% for glargine or detemir, 30-50% for NPH
• If full dose basal insulin given and you are concerned about hypoglycemia, initiate D5 or D10 IVF for duration of insulin action

***Holding basal insulin is NEVER appropriate in patient with type 1 diabetes***
Other Nutritional Considerations

• Enteral Nutrition
  – **Continuous tube feedings:** Give insulin glargine q12-24h plus scheduled aspart q4-6h
  – **Cycled tube feedings:** Give premix 70/30 at the start of tube feeds based on correction insulin use
  – **Bolus Tube feedings:** Give fixed dose of nutritional insulin at time of bolus based on correction insulin use

*If enteral nutrition held/stopped abruptly, start D10 at same rate as enteral feeds for duration of insulin action*

• Parenteral Nutrition (TPN)
  – Consider adding regular insulin to TPN bag based on correction insulin use or dextrose content of TPN
Steroid Therapy & Glycemic Control

General Guidelines

For patients not previously on scheduled insulin
• Initiate glucose monitoring and low dose correctional insulin
• Add scheduled insulin if persistent hyperglycemia ≥180
  – prandial +/- basal insulin in ratio ~60% prandial/40% basal

For patients on scheduled insulin already
• ↑ TDD by 20-40% in anticipation of ↑ insulin requirement
• Increase correction scale by 1 step (eg low to mod scale)

Adjust doses as needed to maintain glycemic control

For persistent significant hyperglycemia (>300 mg/dL), more aggressive insulin therapy is indicated
• IV insulin infusion
• Higher dose or more frequent (q4h) correction with RA-insulin
• Endocrine consult
One Suggested Approach for Treatment of Hyperglycemia in Patients Receiving Glucocorticoids

*Administered in AM at time of prednisone administration

<table>
<thead>
<tr>
<th>Prednisone (mg/day)</th>
<th>NPH (units/kg/day)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 40</td>
<td>0.4</td>
</tr>
<tr>
<td>30</td>
<td>0.3</td>
</tr>
<tr>
<td>20</td>
<td>0.2</td>
</tr>
<tr>
<td>10</td>
<td>0.1</td>
</tr>
</tbody>
</table>

*Administered in AM at time of prednisone administration

Glargine preferred if dexamethasone used or Prednisone given 2x/d

Clore JN, Thurber-Hay L. Endocrine Practice 15:469 2009

I generally give ½ this much
Transition IV to SQ

• Calculate 24 hour IV insulin requirement
  Hourly rate IV insulin x 24 = 24h IV insulin requirement
• Convert 75-80% to SQ insulin and give ~ 50% basal, 50% nutritional (or all as basal if patient has been without nutritional support)
• Choose correctional insulin based on TDD

• Remember to overlap SQ and IV by 1-4 hours (depending on insulin given)
• Consider factors that may affect glycemic control, changing insulin requirements
• Can also use weight based method

U500 Insulin in Hospitalized Patients

- Regular Insulin U500
  - 5x as concentrated as U100
  - Available as vial and pen
  - U100 or TB syringes historically used with vials
  - New U500 syringe is now available

- Not appropriate for inpatient use in most patients
- Endocrine consultation is advised/required
- Most inpatients require ~30-50% reduction in dose
- Alternatively, can reduce TDD and convert to traditional basal/bolus

<table>
<thead>
<tr>
<th>If this is your dose of Humulin R U-500</th>
<th>Fill a U-100 insulin syringe up to this marking</th>
<th>Fill a tuberculin syringe up to this marking</th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td>5</td>
<td>0.05</td>
</tr>
<tr>
<td>50</td>
<td>10</td>
<td>0.1</td>
</tr>
<tr>
<td>75</td>
<td>15</td>
<td>0.15</td>
</tr>
</tbody>
</table>
Insulin Pumps (CSII) and Continuous Glucose Monitoring Systems (CGMS)

Medtronic Revel

Medtronic 530G & 630G with Enlite® (pump +CGM)

Animas OneTouch®Ping® & Vibe

OmniPod® (tubeless)

Tandem t:sлим®
Inpatient Insulin Pumps and CGMS

• Criteria for Safe Inpatient Use of CSII
  – Patient willing and able to safely manage pump w/o difficulty
  – Providers agree and are capable of supervising safe and effective pump management

• Inpatient Insulin Pump Protocol- reduces confusion and treatment variability

• If continued insulin pump therapy is not felt to be safe or appropriate for patient
  – Give ~80% of basal insulin as glargine q12-24h
  – Order nutritional + correctional insulin at same dose as pump settings

• Use of CGMS has not been well studied

Hypoglycemia Treatment & Prevention

• Early recognition and treatment
• Hypoglycemia management protocol
• Proper documentation & tracking hypoglycemia
• Prevention is key
  – ID pts at ↑ risk: sepsis, meds (eg long acting SU, quinolones), malnutrition, variable/poor PO intake, advanced age, hx severe hypoglycemia, autonomic/ kidney/ liver/ or cardiac failure
  – Anticipate/recognize changing insulin requirements
  – Consider reducing insulin if BGs <100
  – Proper timing of CBG monitoring and nutritional insulin
  – Administer nutritional insulin pc, based on carb intake
  – Proper management of NPO status

Discharge Planning

• Consider Rx insulin at discharge if A1C >9%, or if pt will be d/c’d on a new regimen of TPN, enteral nutrition or high dose steroids

• Arrange for timely follow up (PCP, Endo)

• Provide dietary/diabetes education, insulin administration teaching, glucose meter + instructions

• Provide necessary (and affordable) prescriptions: test strips, lancets, insulin (vial or pens), syringe/needles or pen needles

• Ensure accurate diabetes discharge medications & instructions

• *unless using correctional insulin prior to admission, most patients do not need correctional insulin at home
• Order pen + pen needle
  Pen needles
  – 5/32 (NANO=4mm) (RECOMMENDED)
  – 3/16 (MINI=5mm)
  – 5/16 (SHORT=8mm)

• Order vial + syringe with needle attached
  Syringes
  – Choose length:
    • 15/64 (MINI=6mm) (RECOMMENDED)
    • 5/16 (SHORT=8mm)
  – Choose size (volume)
    • 0.3cc (30 units)
    • 0.5cc (50 units)
    • 1cc (100 units)
When to call for help

• Consider Endocrinology consultation:
  – Significant glycemic variability
  – Severe hyper/hypoglycemia
  – Multiple admissions for hyper/hypoglycemia
  – Recurrent DKA
  – U500
  – Insulin pump management
  – Enteral/parenteral nutrition
  – Assistance with diabetes diagnosis or regimen
  – Anytime help is desired
Areas for Future Research

• Optimal glycemic targets outside ICU
• Optimal inpatient insulin regimens
• Inpatient use of GLP1-RA and SGLT2 inhibitors
• Impact of hypoglycemia and glycemic variability
• Role of CGMS in hospital
Summary

• Hyperglycemia is common in the hospital and associated with adverse outcomes
• Both hyper and hypoglycemia are bad
• Moderate glycemic targets recommended, using IV insulin in critical illness & SC insulin outside of critical illness
• Noninsulin agents inappropriate for most patients but may be used in select patients
• Good data in critical illness, but optimal glycemic targets, regimens, & impact on outcomes limited outside ICU
• Managing diabetes/hyperglycemia in the hospital is DIFFICULT
• Understanding a rational approach to management is critical to avoid significant hyper/hypoglycemia & adverse outcomes
Thank You

• Acknowledgements
  – Mary Kortykowski MD
  – Amy Donihi, Pharm D