Relationship between glucose meter error and glycemic control efficacy

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Learning objectives

• List regulatory and clinical issues related to use of glucose meters for critically ill hospitalized patients

• Weigh the benefits of glycemic control vs. the risks of hospital-acquired hypoglycemia

• Discuss the impact of glucose meter accuracy on glycemic control effectiveness

• Review various recommendations for glucose meter accuracy
Glucose meters in the hospital

• Multiple uses for glucose meters in hospital
  o Dose subcutaneous insulin for diabetic mildly ill patients
    - Same accuracy requirements as home use
  o Screen for neonatal hypoglycemia
  o Screen for hypoglycemia or hyperglycemia in hospitalized patients
  o Manage intravenous insulin for critically ill patients on glycemic control
    - Hourly glucose measurement, hourly IV insulin adjustment
    - Narrower insulin dosing ranges, more opportunity for dosing errors
Glycemic control vs. hypoglycemia

- Van den Berghe 2001

- 1500 ICU patients randomized into two groups:
  - Conventional treatment: maintain glucose 180-200 mg/dl, insulin infusion if glucose > 215 mg/dl
  - Intensive insulin therapy: Intravenous insulin if glucose > 110 mg/dl, maintain glucose 80-110 mg/dl

- Primary findings:
  - Among patients in ICU > 5 days, mortality reduced ~ 30% in intensive insulin group
  - Bloodstream infections, acute renal failure, RBC transfusions, polyneuropathy all reduced 40-50% in intensive insulin group
  - Increased rate of hypoglycemia in intensive group (6x, 5% of intensive group)
Glycemic control vs. hypoglycemia

- Leuven II (NEJM 2006)
  - Repeat of study in medical ICU
  - TGC only effective in patients with > 3 d ICU stay
  - Hypoglycemia significant limitation, increased mortality for patients < 3 d in ICU
  - 6-fold increased rate of hypoglycemia (18.7%)
  - Glucose meters instead of ABG

- Subsequent studies
  - Mixed outcome results (more negative than positive)
  - Glucose targets varied
  - Average 5-fold increase in rate of hypoglycemia
  - Leuven I used arterial blood gas glucose
  - Most other studies used glucose meters or methods/sample types differed by location
Glycemic control vs. hypoglycemia

- Single episode of severe hypoglycemia (< 40 mg/dL) associated with increased mortality
  - OR 2.3 X for death (Krinsley, 2007)
- In same population patients glycemic control reduced mortality
- Sensitivity analysis performed to determine how much SH would offset TGC
  - 4X increase in SH (from 2.3% to 9.2%) predicted to completely offset survival benefit of glycemic control
  - Could glucose meter inaccuracy be leading to hypoglycemia?
Technologic limitations of glucose meters

- Number of factors influence relationship of glucose meter to true (usually lab plasma) glucose
  - Whole blood vs. plasma (conversion factor)
  - Sample type (capillary vs. venous catheter vs. arterial catheter)
    - Physiologic and technologic limitations
  - Interferences (medications, pO2, others)
Technologic limitations of glucose meters

- Whole blood vs. plasma glucose
  - Whole blood glucose ~ 15% lower than plasma glucose
  - US Vendors now calibrate reagents to express “plasma-equivalent” units
Technologic limitations of glucose meters

- Conversion of WB to plasma equiv glucose
  - Function of water content of plasma (PW), water content of red cells (RW), and percent red cells in WB (Hematocrit)
  - Vendors used agreed upon standards for one conversion factor
  - Does patient acuity impact validity of PW, RW and Hct assumptions?

Lyon ME and Lyon AW Clin Biochem 2011;44:412-7
Technologic limitations of glucose meters

- Conversion of WB to plasma equiv glucose
  - Compared PW, RW, Hct values among outpatients, inpatients, and adult ICU patients
  - Adult ICU patient mean and distribution PW, RW, and Hct values differed markedly from assumptions
  - Lower Hct and higher PW in adult ICU patients predicted to result in 8.3% of results with > 10% error at value of 10 mM (180 mg/dL)

*Lyon ME and Lyon AW Clin Biochem 2011;44:412-7*
Technologic limitations of glucose meters

• Hematocrit “interference”

-50.0 -40.0 -30.0 -20.0 -10.0 0.0 10.0 20.0
Hematocrit (%)

• > 10% overestimation at low Hct
• > 10% underestimation at high Hct

Technologic limitations of glucose meters

- Capillary vs. arterial/venous glucose
- Impact of BP, edema and shock, tissue perfusion
  - Blood pressure: Shock (systolic BP less than 80 mm Hg) associated with falsely decreased or increased capillary glucose measurement
- Accuracy of capillary WB at low and high glucose
  - Khan et al Arch Pathol Lab Med 2006;130:1527-32
- Technologic vs. physiologic limitations of capillary sampling largely unknown
Technologic limitations of glucose meters

• Venous catheter WB glucose in critically ill

• Overestimates venous plasma glucose
  o Cook et al, Am J Crit Care 2009;18:65-75

• Bias with venous catheter samples differs by meter technology
  o Karon et al, Diabetes Technol Ther 2009;11:819-25

• Arterial catheter whole blood best available sample for glucose meter monitoring

• Assess meter technology with venous catheter whole blood if that will be primary sample type
Technologic limitations of glucose meters

- Interference studies, ascorbic acid

Ascorbic acid effect, glucose = 70 mg/dL

Glucose meters in hospital

- Error and outliers with WB glucose

<table>
<thead>
<tr>
<th>Condition</th>
<th>Sample type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shock, hypotension, dehydration, edema</td>
<td>Capillary</td>
</tr>
<tr>
<td>Hematocrit effect</td>
<td>All</td>
</tr>
<tr>
<td>Failure to let alcohol dry</td>
<td>Capillary</td>
</tr>
<tr>
<td>Underdosing strips</td>
<td>Capillary, All</td>
</tr>
<tr>
<td>PW or RW effect</td>
<td>All, CVC &gt; art line?</td>
</tr>
<tr>
<td>Medication interference</td>
<td>All</td>
</tr>
<tr>
<td>pH, O2 or CO2 tension</td>
<td>All</td>
</tr>
<tr>
<td>Use of expired or incorrectly stored strips</td>
<td>All</td>
</tr>
<tr>
<td>Temperature extremes</td>
<td>All</td>
</tr>
<tr>
<td>Incorrect calibration info</td>
<td>All</td>
</tr>
<tr>
<td>Improper/incorrect disinfection</td>
<td>All</td>
</tr>
<tr>
<td>Operator error/untrained operators</td>
<td>All</td>
</tr>
</tbody>
</table>
Glucose meter regulatory issues timeline

- March 2010
  - FDA public forum on glucose meter accuracy
  - Consensus that 2003 ISO 15197 not appropriate for ICU glucose meter use (95% results within ± 15 mg/dL for glucose < 75 mg/dL, ± 20% for glucose ≥ 75 mg/dL)
  - Debate about whether separate home and hospital, or home/hospital/ICU criteria needed
  - FDA announced new criteria forthcoming
Glucose meter regulatory issues timeline

• 2011 NACB guidelines on glucose meter accuracy
  o 95% of glucose meter results within…
    - ± 15 mg/dL at glucose < 100 mg/dL
    - ± 15% at glucose ≥ 100 mg/dL

• November 2012, AccuChek Inform II FDA approval
  o No draft guidance on required accuracy
  o Limitation statement: “the performance of this meter has not been evaluated on critically ill patients”
  o FDA notes limitation statement to be added to all approved hospital use glucose meters
  o FDA opinion is that critical care use constitutes “off label” use of device
Glucose meter regulatory issues timeline

- January 2013 CLSI POCT12-A3 guidelines on glucose meter accuracy
  - 95% of glucose meter results within...
    - $\pm 12$ mg/dL at glucose < 100 mg/dL
    - $\pm 12.5\%$ at glucose $\geq 100$ mg/dL
    - 98% within 2003 ISO 15197 guidelines

- 2013 ISO 15197 revision
  - 95% of glucose meter results within...
    - $\pm 15$ mg/dL at glucose < 100 mg/dL
    - $\pm 15\%$ at glucose $\geq 100$ mg/dL
    - use of Parkes Error grid (99% zones A and B)
Glucose meter regulatory issues timeline

- **Sept 2014**
  - StatStrip receives FDA approval for all hospitalized patients
    - Venous and arterial whole blood only (neonates)

- **Nov 2014**
  - CMS memo to state surveyors, use meters according to intended use and limitation statement, other use “off-label”
    - Makes critical care use for most meters high complexity
    - Validation requirements in specific patient population
    - Personnel requirements (4 yr degree, transcripts)

- **Oct 2016**
  - FDA final guidance for glucose meter manufacturers
    - Home use: slightly more stringent but similar to ISO 15197
    - Hospital use: similar to CLSI POCT12A-3
Glucose meters in the hospital

• Will improving glucose meter accuracy and reducing interferences and outliers lead to better patient outcomes during glycemic control in the ICU?
Variables impacting glycemic control outcome

• Elements of glycemic control protocol that may impact patient outcome
  o Glucose target range
  o Sophistication of dosing algorithm (point to point vs. trending)
  o System to prompt glucose measurement (manual vs. IT system)
  o System to relate gluc conc to insulin dose (paper vs. electronic)
  o **Accuracy of glucose monitoring device**
    - Hematocrit, bias and precision, medication interference
  o Competency of staff performing measurement
Variables impacting glycemic control outcome

- TGC protocols associated with 5 X increase incidence of hypoglycemia

- Absolute rates of hypoglycemia vary widely between TGC studies depending on target and protocol
  - 0.34% (Stamford Hospital)
  - 18.7% (Leuven II)

- Does the glucose meter accuracy have anything to do with glycemic control outcomes or rate hypoglycemia?
Mayo glucose meter accuracy study

• Can “newer” glucose meter technologies achieve 12-15% total error when fresh whole blood samples are tested on critically ill patients after cardiovascular surgery?
  – If so, because bias or imprecision is reduced?
  – Where are we at today, how did we get there (reducing bias or reducing imprecision)

• Does reducing glucose meter error improve efficacy of glycemic control in the cardiovascular ICU?
  – Does it matter?
Mayo glucose meter accuracy study

- At Mayo Rochester StatStrip replaced AccuChek Inform 10/2012

- Assess impact on accuracy and precision of glucose measurements in ICU
  - Accuracy when routine clinical samples tested at bedside
    - Retrospective study with Inform and StatStrip
  - Precision with fresh arterial whole blood from critically ill patients
Mayo glucose meter accuracy study

- **Precision (prospective study)**

- **AccuChek Inform I (20 ICU patients with 5x measurement at the bedside)**
  - CV of 2.0% at an average glucose value of 142 mg/dL (7.89 mM)

- **StatStrip (20 ICU patients with 5x measurement at the bedside)**
  - CV of 2.7% at an average glucose value of 140 mg/dL (7.78 mM)

- Both meters precise when fresh whole blood tested at bedside
Mayo glucose meter accuracy study

- Accuracy (retrospective study)
  - Over 3 month period, 1602 Inform whole blood glucose measurements performed within 5 minutes of drawing serum glucose (Roche Hexokinase)
  - Over separate 3 month period, 1093 StatStrip whole blood glucose performed within 5 minutes of serum glucose
Mayo glucose meter accuracy study

- Median bias 11 mg/dL (0.61 mM)
- Median (IQR) % bias 9 (4 to 14) %
Mayo glucose meter accuracy study

- Median bias 1 mg/dL (0.06 mM)
- Median (IQR) % bias 1 (-3 to 5) %
# Mayo glucose meter accuracy study

<table>
<thead>
<tr>
<th></th>
<th>Inform (n=1602)</th>
<th>StatStrip (n=1093)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent within 10%</td>
<td>55%</td>
<td>89%</td>
</tr>
<tr>
<td>lab</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percent with 20%</td>
<td>92%</td>
<td>98%</td>
</tr>
<tr>
<td>lab</td>
<td></td>
<td></td>
</tr>
<tr>
<td>% within 12.5%/12.5</td>
<td>69%</td>
<td>95%</td>
</tr>
<tr>
<td>mg/dL (CLSI POCT12-A3) serum</td>
<td></td>
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</tr>
</tbody>
</table>

- By reducing bias, reduced TEa from ~20% → 12.5%
Is StatStrip accurate in different ICU settings?

- Prospective accuracy study across 5 ICUs
  - 2 Netherlands, 1 Belgium, 2 US sites
  - Surgical, medical, burn patients
  - 1815 paired measurements from 1698 patients
  - 96.1% met CLSI POCT12-A3 criteria
  - 99% zone A Parkes Error Grid, 100% zones A/B
  - 99.1% (223/225) concordance in characterizing hypoglycemia (glucose < 70 mg/dL)

Impact of insulin dosing errors on glycemic control in ICU

• Impact on patient outcome
  o ICU/hospital mortality
  o Hospital morbidity (infections, transfusions, renal failure)
  o Requires randomized trial > 1000 patients

• Impact on glycemic control efficacy
  o Glycemic variability
  o Time within target range
  o Incidence hypo and hyperglycemia
  o Requires 50-150 patients per study arm
Impact of insulin dosing errors on glycemic control in ICU

• Why measure glycemic control efficacy?
  o Hypoglycemia important outcome
  o Hyperglycemia is what is being avoided
  o Glycemic variability
    − More variability = more hypo and hyperglycemia
    − Increased variability (extreme high and low) may alone decrease survival in ICU
  o ↑ time in target range, ↓ hypo and hyperglycemia, ↓ variability = better protocol
  o Can reducing meter error alone lead to a better protocol?
Study design

- Given improved accuracy of meter in ICU
  - ~20% → 12.5% TEa

- Can we measure impact on glycemic control efficacy?

- Retrospective review patients post cardiovascular surgery placed on glycemic control in CVS ICU
  - 12-24 consecutive (30-120 min) glucose values on insulin drip
  - Period 1 (70 patients monitored with AccuChek Inform)
  - Period 2 (70 patients monitored with StatStrip)
  - No change infusion protocol, testing personnel, etc
**Study design**

- **Measures glycemic variability**
  - Standard deviation (SD)
  - Continuous overall net glycemic action (CONGA)
  - Percent values in target range (110-150 mg/dL)
  - Incidences of hypoglycemia and hyperglycemia

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ± SD age (range)</td>
<td>68 ± 12 (28-92)</td>
<td>65 ± 12 (29-86)</td>
<td>0.22</td>
</tr>
<tr>
<td>Gender</td>
<td>39 M/ 31 F</td>
<td>42 M/ 28 F</td>
<td>0.61</td>
</tr>
<tr>
<td>Diabetes</td>
<td>35 ND/ 35 T2DM</td>
<td>35 ND/ 35 T2DM</td>
<td></td>
</tr>
<tr>
<td>Median (range) number glucose values</td>
<td>22 (12-24)</td>
<td>21 (12-24)</td>
<td>0.16</td>
</tr>
</tbody>
</table>
# Results—Glycemic variability and time within target range

## Overall results (non-diabetic and T2DM)

<table>
<thead>
<tr>
<th></th>
<th>Period 1 (n=70)</th>
<th>Period 2 (n=70)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (IQR) glucose (mg/dL)</td>
<td>141 (126, 156) mg/dL</td>
<td>136 (125, 148) mg/dL</td>
<td>0.005</td>
</tr>
<tr>
<td>Median (IQR) standard deviation (SD)</td>
<td>21.6 (16.9, 26.3) mg/dL</td>
<td>13.7 (12.4, 19.1) mg/dL</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Median (IQR) CONGA</td>
<td>19.4 (16.0, 24.2) mg/dL</td>
<td>13.5 (10.9, 17.3) mg/dL</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Median (IQR) percent values in target range (%)</td>
<td>66.7 (50, 74.2) %</td>
<td>74.5 (58.5, 86.7) %</td>
<td>0.002</td>
</tr>
</tbody>
</table>

*Glycemic variability decreased and time in target range increased with improved meter accuracy*
Results—Glycemic variability and time within target range

- Non-diabetic patients only

<table>
<thead>
<tr>
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<th>Period 1 (n=35)</th>
<th>Period 2 (n=35)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (IQR) standard deviation (SD)</td>
<td>18.7 (16.3, 25.6) mg/dL</td>
<td>15.4 (12.4, 19.9) mg/dL</td>
<td>0.004</td>
</tr>
<tr>
<td>Median (IQR) CONGA</td>
<td>18.3 (13.3, 21.6) mg/dL</td>
<td>13.5 (10.2, 19.0) mg/dL</td>
<td>0.04</td>
</tr>
<tr>
<td>Median (IQR) time in target range (%)</td>
<td>68.8 (61.9, 79.2) %</td>
<td>73.7 (62.5, 87.5) %</td>
<td>0.10</td>
</tr>
</tbody>
</table>

- Glycemic variability (SD and CONGA) decreased ~ 20%
- No significant change in time in target range
## Results—Glycemic variability and time within target range

- **Type 2 diabetes only**

<table>
<thead>
<tr>
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<th>Period 1 (n=35)</th>
<th>Period 2 (n=35)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (IQR) standard deviation (SD) mg/dL</td>
<td><strong>22.4</strong> (17.7, 28.0)</td>
<td><strong>13.6</strong> (12.3, 18.3)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Median (IQR) CONGA mg/dL</td>
<td><strong>21.4</strong> (18.3, 27.5)</td>
<td><strong>13.5</strong> (11.7, 15.2)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Median (IQR) time in target range (%)</td>
<td><strong>61.9</strong> (46.7, 72.7)</td>
<td><strong>78.3</strong> (54.2, 85.7)</td>
<td>0.006</td>
</tr>
</tbody>
</table>

- ~40% decrease in glycemic variability (SD and CONGA)
- ~25% increase in time in target range
Bigger impact on patients with Type 2 diabetes
Results—Incidence of hypo and hyperglycemia

- **Hypoglycemia** (< 70 mg/dL, 3.89 mM)
  - 1 patient, 1 value Period 1
  - 0 patients, 0 values Period 2

- **Hyperglycemia** (> 200 mg/dL, 11.11 mM)
  - 26 patients (7 non-diabetic and 19 T2DM), Period 1
  - 6 patients (1 non-diabetic and 5 T2DM), Period 2
Pediatric burn patients

- Similar before and after retrospective study design
  - 63 patients monitored with Inform 1
  - 59 patients monitored with StatStrip
  - Glycemic target 80-130 mg/dL (lower)

- Mean bias 7.4 ± 13.5 (Inform 1) vs. -1.7 ± 6.9 mg/dL (StatStrip)

- Glycemic control improved with StatStrip (CONGA, CV, MAGE, MODD)

- Time to therapeutic range 13.1 → 5.7 hours

- Time in range 57.9 → 85.2%

- Tran et al, Pediatr Crit Care Med 2016;17:e406-12
Conclusions

• Glucose meter use in the hospital
  o Capillary sampling and hematocrit effects major issues
  o Technology can address hematocrit effects
  o Capillary sampling limitations remain largely undefined
Conclusions

• Glucose meter use in the hospital
  o Often done on non-diabetic patients
  o Tighter glucose ranges, more opportunities to “translate” glucose measure error into insulin dosing error
  o Sources of error (hematocrit, medication interferences, sample type differences) more pronounced effects

• Newer glucose meter technologies reduce error of glucose measurement when used at the bedside on critically ill patients

• Evidence emerging that improving glucose meter performance (reducing error) will improve efficacy of glycemic control
Questions?