Glucose Meter Use in Various Settings

North Texas Point of Care Network
August 15, 2013

Brad S. Karon, M.D., Ph.D.
Associate Professor of Laboratory Medicine and Pathology
Department of Laboratory Medicine and Pathology
Mayo Clinic
Rochester, MN
Objectives

• Define uses of glucose meters in home, outpatient, inpatient ICU and NICU settings

• List various proposed and established guidelines for glucose meter accuracy

• Weigh benefits of glycemic control vs. adverse effects of hypoglycemia

• Define an approach for establishing accuracy criteria for glucose monitors used in the critical care environment
Why measure glucose?

• **Traditional glucose meter use**
  - **Monitor glucose level for subq dosing**
    - In home
    - In hospital
    - Wide therapeutic ranges
    - Wide distribution of glucose values
  
  - **Critically ill patients:**
    - Keep glucose levels < 200 mg/dL (IV or subq)

• **Error grid analysis used to determine accuracy requirements for meters**
Why measure glucose?
Why measure glucose?

- **Error Grid zones**
  - **A** = Clinical accurate
  - **B** = Clinically irrelevant deviation (> 20%)
  - **C** = Unnecessary overcorrection possible
  - **D** = Dangerous failure to detect and treat
  - **E** = Erroneous treatment

- % A and B most common form of evaluation
- Most meters look good
“New” reasons for glucose measurement

INTENSIVE INSULIN THERAPY IN CRITICALLY ILL PATIENTS

GREET VAN DEN BERGHE, M.D., PH.D., PIETER WOUTERS, M.SC., FRANK WEEKERS, M.D., CHARLES VERWAEST, M.D., FRANS BRUYNINCKX, M.D., MIET SCHETZ, M.D., PH.D., DIRK VLASSELAERS, M.D., PATRICK FERDINANDE, M.D., PH.D., PETER LAUWERS, M.D., AND ROGER BOUILLON, M.D., PH.D.
“New” reasons for glucose measurement

- Management of hyperglycemia in noncritically ill hospitalized patients
  - **Consensus guideline** (Endocrine society, ADA, AHA)
    - All patients lab blood glucose testing admission
    - No Hx diabetes with glucose $>7.8$ mM (140 mg/dL) be monitored by bedside POC glucose 24-48 hr
    - Enteral/parenteral nutrition, corticosteroids monitor by bedside POC glucose 24-48 hr
    - Premeal target $<7.8$ mM and random $<10$ mM (180 mg/dL) majority of non-critically ill patients
    - Bedside capillary POC glucose

Umpierrez et al., J Clin Endocrinol Metab 2012:97:16-38
Neonatal hypoglycemia

- Postnatal glucose homeostasis in late-preterm and term infants
  - Pediatrics 2011;127:575-9
- Common during first 1-12 hrs life
- Infants of diabetic mothers, SGA, LGA, septic or sick at risk
- No definition of NH
- Treatment guidelines
  - Symptomatic: glucose < 40 mg/dL (IV glucose)
  - Asymptomatic at-risk infants
    - Birth-4 hrs: < 25 and 25-40 mg/dL
    - 4 - 24 hrs: < 35 and 35-45 mg/dL
Neonatal hypoglycemia

- **Laboratory information**
  - Plasma or blood glucose using enzymatic method (hexokinase, glucose oxidase, dehydrogenase)

- “There is no point of care method that is sufficiently reliable to be used as the sole method for screening for NH”

- Point of care glucose results must be confirmed by laboratory glucose ordered stat
“New” uses for glucose monitors in hospital

- Error grid analysis makes every meter look good
- Error grids designed to assess accuracy needs/risk associated with subq insulin dosing
- What about intravenous insulin therapy?
- What about hospital-based screening adults?
- What about screening for neonatal hypoglycemia?
- No consensus accuracy guidelines exist
Glucose meter accuracy guidelines

  - 95% of glucose meter results within...
    - ± 15 mg/dL at glucose < 75 mg/dL
    - ± 20% at glucose ≥ 75 mg/dL
  - CLSI C30-A2 under revision
    - to come out as POCT12-A3

- **American Diabetes Association**
  - ± 10% of true value for all devices for all purposes (home use, hospital use)
  - ± 5% of true value is idea

- **NACB (2011)**
  - 95% of glucose meter results within...
    - ± 15 mg/dL at glucose < 100 mg/dL
    - ± 15% at glucose ≥ 100 mg/dL
A Question for you...
Issues with hospital use of glucose meters

- **Whole blood vs. plasma glucose**
  - Whole blood glucose ~ 15% lower than plasma glucose
  - Caused confusion to clinicians, labs didn’t like it
  - US Vendors now calibrate reagents to express “plasma-equivalent” units
  - If calibration works, essentially no difference between glucose meter (whole blood) and lab (plasma) glucose
Issues with hospital use of glucose meters

- Hematocrit “interference”

- 10% overestimation at low Hct, low glucose
- 20-40% underestimation at high Hct, high glucose

Issues with hospital use of glucose meters

- **Capillary vs. arterial/venous glucose**
- **Impact of BP, edema and shock**
  - 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
Issues with hospital use of glucose meters

- Venous catheter WB glucose in critically ill

- Overestimates venous plasma glucose
Issues with hospital use of glucose meters

- Consensus that arterial WB best sample in ICU
  - Capillary sampling leads to errors in patients with hypotension, edema
  - Technical limitations venous catheter glucose meter measurement
    - Method dependent, end user should assess if venous catheter will be common source
## Issues with hospital use of glucose meters

- **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? CVC?</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>
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

- **NICE SUGAR (NEJM 3/2009)**
  - Multi-center trial of TGC (42 hospitals, Australia, New Zealand, Canada, US)
  - TGC increased mortality in mixed medical and surgical ICU patients
  - 14-fold increase in hypoglycemia (6.8% intensive group)
  - Multiple meters and lab methods used
Glycemic control vs. hypoglycemia

- **TGC protocols** associated with 5-14 X increase in 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)
Glycemic control vs. hypoglycemia

- TGC protocols associated with 5-14 X increase in 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)
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 TGC
Glycemic control vs. hypoglycemia

- Theoretically increased SH may offset benefits of glycemic control

- Realize not all SH caused by insulin in ICU
  - Liver failure, sepsis, etc.

- Rates and percent increase in SH differ dramatically by site and TGC protocol

- System of administering intravenous insulin must lower glucose without causing hypoglycemia
A Question for you...
Glycemic control vs. hypoglycemia

Perspectives

Tight Glucose Control in the Intensive Care Unit: Are Glucose Meters up to the Task?

Mitchell G. Scott,1* David E. Bruns,2 James C. Boyd,2 and David B. Sacks3
Variables impacting glycemic control outcome

- **Elements of glucose monitoring systems that may impact patient outcome**
  - Glucose target range
  - Sophistication of dosing algorithm (point to point vs trending)
  - System to prompt glucose measurement (manual vs IT system)
  - System to relate gluc conc to insulin dose (paper vs electronic)

- **Accuracy of glucose monitoring device**
  - Hematocrit, bias and precision, medication interference

- **Competency of staff performing measurement**
Variables impacting glycemic control outcome

- **Glucose meter use OK in ICU?**
  - **Petersen et al.** *Clin Chim Acta* 2008;396:10-13
    - Arterial whole blood on meter OK for managing TGC, capillary not (Parkes error grid analysis)
  - **Hoedemaekers et al.** *Crit Care Med* 2008;36:3062-66
    - Arterial whole blood on meters not accurate enough for management of critically ill patients (ISO)
  - **Slater-Maclean et al.** *Diabetes Tech Ther* 2008;10:169-77
    - Arterial (but not capillary) whole blood on some meters OK for management of critically ill (consensus error grid analysis, bias)
Variables impacting glycemic control outcome

- No consensus on level of accuracy required for glycemic control, whether meters OK
- Ideal study would relate meter accuracy to patient outcome
- With changing glycemic protocols, does glycemic target impact required glucose meter accuracy?
Quality Specifications for Glucose Meters: Assessment by Simulation Modeling of Errors in Insulin Dose

James C. Boyd* and David E. Bruns
Error simulation models

- Boyd and Bruns, Clin Chem 2001;47:209-14
- Randomly generated glucose values between 150-450 mg/dL
- Assume target ranges of 30 or 50 mg/dL (subq dosing algorithms)
- Result simulation to model effect of various levels of bias and imprecision on dosing category
- Acceptable performance if ≥ 2 dose category errors occurred ≤ 0.2% of time
- Meter performance acceptable for subq dosing
Error simulation models

• **Accuracy requirements for TGC?**
  - Karon, Boyd and Klee, Clin Chem 2010;56:1091-7

Histogram of 29,920 glucose values for patients on intravenous insulin
Median value = 116 mg/dL (IQR 102-135)

86% values ≤ 150 mg/dL, dose cat change ≤ 20 mg/dL
Error simulation models--TGC

- Start with distribution of glucose values in patients on TGC
- Sample this distribution, for each initial value sampled simulate 10,000 values with distribution of bias and imprecision:
  - Glucose (simulated) = Glucose initial +
  - \([n(0,1) \times CV \times \text{glucose (initial)}] + [\text{Bias} \times \text{glucose (initial)}]\)
  - \(n(0,1)\) random number drawn from gaussian distribution centered on zero with SD=1
  - CV varies from -20 to +20%
  - Bias varies from 0 to 20%
Error simulation models--TGC

- Calculate % simulated values that fall in same insulin dosing category as initial
- Calculate % 1, ≥ 2, or ≥ 3 category dosing errors based on Mayo TGC protocol
- Express results as contour plots, showing % dosing errors as a function of bias and imprecision
- Superimpose boundaries for 10%, 15% and 20% total error (TEa) on contour plots
Error simulation models -- TGC

Mayo Intensive Insulin 2 Step Dosing Errors (%)
Error simulation models -- TGC

Mayo Intensive Insulin 3 Step Dosing Errors (%)
For each of 29,920 initial values:

Generate 1000 simulated values with distribution of X% error using SAS (Carey, NC)

Determine how many simulated values would change insulin dosing category relative to original value
Error simulation models--TGC

- 3 sets of 29,290,000 simulated values assuming 10%, 15% or 20% total error

- For each set calculated % 0, 1, 2, ≥ 3 category dosing error based on Mayo TGC protocol

- Gaussian model allows estimation of positive (too much insulin given) and negative (too little insulin given)

- Class I (critical) discrepancy defined as initial value < 80 mg/dL with simulated value > 110 mg/dL (Kost et al., Clin Chim Acta 2008;389:31-9)
  - Corresponds to 3 category positive (too much insulin) dosing error
  - Acceptable performance defined <0.2% 3 category dosing errors
## Error simulation models--TGC

<table>
<thead>
<tr>
<th>Error condition</th>
<th>10% TEa % Bias/ CV</th>
<th>10% TEa Gaussian</th>
<th>15% TEa % Bias/ CV</th>
<th>15% TEa Gaussian</th>
<th>20% TEa % Bias/ CV</th>
<th>20% TEa Gaussian</th>
</tr>
</thead>
<tbody>
<tr>
<td>1cat</td>
<td>Up to 60%</td>
<td>28%</td>
<td>Up to 80%</td>
<td>39%</td>
<td>Up to 90%</td>
<td>45%</td>
</tr>
<tr>
<td>2 cat</td>
<td>0.2%</td>
<td>0.2%</td>
<td>Up to 5%</td>
<td>2%</td>
<td>Up to 20%</td>
<td>6%</td>
</tr>
<tr>
<td>2 cat positive</td>
<td>0.1%</td>
<td></td>
<td>1.3%</td>
<td></td>
<td></td>
<td>3.8%</td>
</tr>
<tr>
<td>≥ 3 cat</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0.02%</td>
<td>0.2%</td>
<td>0.3%</td>
</tr>
<tr>
<td>≥ 3 cat positive</td>
<td>0%</td>
<td>0%</td>
<td>0.02%</td>
<td>0.24%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Error simulation models -- TGC

- Only 20% T Ea condition allowed 3 category or critical errors in either model
  - Imprecision drives 3 category dosing errors
- Models predict that 15% T Ea may avoid large positive insulin dosing errors (hypoglycemia)
- Decreasing acceptable error tolerance from 20% to 10% will decrease 2 category errors
  - 2 cat positive (too much insulin) common at 20% T Ea
  - Additional studies necessary to understand impact of 2 category dosing errors
- Assumes single value leads to hypoglycemia via single dosing error
Error simulation models

• What can simulation models tell us about need for accuracy when moderate glycemic targets used?

• New ICU protocol adopted 4/2010
  - Glycemic target 110-150 mg/dL
  - Little or no insulin if glucose below 110 mg/dL

• 25,948 glucose values gathered from 1513 patients over 3 months (10-12/2010) in 3 ICU
  - Cardiovascular surgery, vascular surgery, medical ICU

• Rate of severe hypoglycemia (<40 mg/dL) and moderate hypoglycemia (40-60 mg/dL)
  - SH in 4/1513 pts (0.25%)
  - MH in 33/1513 pts (2.2%)
Error simulation models--MGC

Histogram of 25,948 glucose values for ICU patients
Median value = 134 mg/dL (IQR 118-154 mg/dL)

70% glucose values dose cat change ≤ 20 mg/dL
Error simulation models--MGC

- Repeat simulation—2 or more category errors
## Error simulation models--MGC

<table>
<thead>
<tr>
<th>Error condition</th>
<th>10% TEa % Bias/CV</th>
<th>10% TEa Gaussian</th>
<th>15% TEa % Bias/CV</th>
<th>15% TEa Gaussian</th>
<th>20% TEa % Bias/CV</th>
<th>20% TEa Gaussian</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 cat</td>
<td>Up to 60%</td>
<td>29%</td>
<td>Up to 80%</td>
<td>39%</td>
<td>Up to 90%</td>
<td>83%</td>
</tr>
<tr>
<td>2 cat</td>
<td>0.2%</td>
<td>0.2%</td>
<td>Up to 5%</td>
<td>2%</td>
<td>Up to 20%</td>
<td>6%</td>
</tr>
<tr>
<td>2 cat positive</td>
<td></td>
<td>0.08%</td>
<td></td>
<td>0.9%</td>
<td></td>
<td>3.0%</td>
</tr>
<tr>
<td>≥ 3 cat</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0.02%</td>
<td>0.2%</td>
<td>0.3%</td>
</tr>
<tr>
<td>≥ 3 cat positive</td>
<td></td>
<td>0%</td>
<td></td>
<td>0.002%</td>
<td></td>
<td>0.06%</td>
</tr>
</tbody>
</table>
Error simulation models--MGC

- Only 20% TEa condition allowed 3 category or critical errors in either model
  - Unlike simulation models for TGC, very few 3 cat positive (too much insulin) errors predicted under any error condition
  - May help explain low rate observed SH and MH?

- Observation that 20% TEa allows large insulin dosing errors may be generalized to glycemic protocols where majority of glucose values in 20 mg/dL “window”
Recent FDA precaution added to Roche Inform II

- Under “limitations of use” in package insert
  - “the performance of this meter has not been evaluated on critically ill patients”
- FDA backed off original labeling suggesting not approved for ICU use
- Limitation will be added to all FDA-approved meters
- What does this mean for end users?
  - Short term: Doesn’t add to what we discussed today
  - Long term: FDA will define accuracy criteria for ICU use of glucose meters
Conclusions

• Glycemic control in the ICU a hot topic
  o Many variables impact effectiveness of glycemic control

• Arterial whole blood optimal sample for bedside glucose monitoring

• Issues to consider in selecting hospital-use glucose monitor
  o Hematocrit effect
  o Medication interferences
  o Data on accuracy with different sample types
  o Built-in error proofing
  o Overall accuracy
Conclusions

- 95% of glucose meter results should be within...
  - 10%, 15%, 20% of reference result
  - may depend upon glycemic target/protocol
  - number of outliers probably more important
    - outliers lead to excess insulin, hypoglycemia
    - vendor technology can prevent outliers
      - Hct, underdosing, med effect, strip calibration, etc
  - Selecting a hospital use glucose monitor
    - Device should meet ± 15% for accuracy
    - Focus on hematocrit effect, outlier prevention
    - Focus on whole system for glycemic control, not just the meter
References


References

- Petersen et al. Comparison of POCT and central laboratory glucose results using arterial, capillary and venous samples from MICU patients on tight glycemic control. Clin Chem Acta 2008;396:10-3


• Karon et al. Accuracy of whole blood glucose measurement when venous catheter whole blood samples are used on glucose meters. Diabetes Technol Ther 2009;11:819-25.
