### Increasing Blood Glucose Variability Heralds Hypoglycemia in the Critically III Surgical Patient

RM Kauffmann, MD, MPH\*; RM Hayes, BSN, PhD\*\*; BD Buske, BS\*\*; PR Norris, PhD\*; TR Campion Jr, MA\*; M Dortch, PharmD† JM Jenkins, MSN\*; BR Collier, DO, CNSP, FACS\*; AK May, MD, FACS, FCCM\*

\*The Division of Trauma & Surgical Critical Care and \*\*the Informatics Center and † the Department of Pharmaceutical Services

- Vanderbilt University Medical Center, Nashville, TN



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# Introduction

- Hyperglycemia is common in critically ill patients and is associated with increased morbidity and mortality
- Intensive Insulin Therapy (IIT) has been widely adopted
- Concerns persist over rates of hypoglycemia in patients on IIT
- There is emerging evidence that blood glucose variability is a better predictor of adverse outcomes

# **Summary of IIT Literature**

#### Summary Data from Randomized Clinical Trials of Intensive Insulin Therapy in Critically III Patients

Trial Name (Source)†	Leuven 1	Leuven 2	Glucontrol	VISEP	NICE-SUGAR7	Arabi
Author	Van den Berghe	Van den Berghe	Devos	Brunkhorst	Finfer	Arabi
No. of Patients	1548	1200	1101	537	6104	523
Type of ICU	Surgical	Medical	General	General	general	general
Target Glucose: Intensive	80-110	80-110	80-110	80-110	81-108	80-110
Target Glucose: Conventional	180-200	180-200	140-180	180-200	144-180	180-200
Primary Outcome	Death in ICU	Death in hospital	Death in ICU	Death @ 28d	Death @ 90d	Death in ICU
Rate of Outcome; Intensive	4.6	37.3	16.7	24.7	27.5	13.5
Rate of Outcome: Conventional	8.0	40.0	15.2	26.0	24.9	17.1 (0.3)
Morbidity measures	IIT: < ICU LOS, Vent d, RRT, septicemia, neuropathy	IIT < renal failure, vent days, ICU d, Hosp d.	?	No differences LOS, vent days, dialysis	No difference in MSOF, ICU LOS, Hosp LOS, Vent days, renal failure	ITT < % mort in APACHE II < 22 & BMI < 26 < sepsis 20.7 vs 27.2 (0.08)

Meta-analysis of IIT in critical illness

All studies combined:
 – no significant benefit

Surgical ICU studies:
 – significant benefit

	No. deaths / to	ital no. patien	5	Favors IIT	Favors cont
Study	IIT	Control	Risk ratio (95% cay	<	$\rightarrow \longrightarrow$
Mixed ICU					
Yu et al.29	4/28	4/27	0.96 (0.27-3.47)		
Henderson et al. <sup>31</sup>	5/32	7/35	0.78 (0.28-2.22)		
Mitchell et al. <sup>35</sup>	9/35	3/35	3.00 (0.89-10.16)		$\rightarrow$
Wang et al.38	7/58	26/58	0.27 (0.13-0.57)		
Azevedo et al.22	38/168	42/169	0.91 (0.62-1.34)		
McMullin et al. <sup>34</sup>	6/11	4/9	1.23 (0.49-3.04)	-	
Devos et al.13	107/550	89/551	1.20 (0.93-1.55)		-
Brunkhorst et al. <sup>11</sup>	98/247	102/288	1.12 (0.90-1.39)		
lapichino et al.12	15/45	12/45	1.25 (0.66-2.36)		
He et al. <sup>30</sup>	16/58	29/64	0.61 (0.37-1.00)	-	
Zhang et al.40	4/168	6/170	0.67 (0.19-2.35)		•
De La Rosa Gdel et al. <sup>12</sup>	102/254	96/250	1.05 (0.84-1.30)		
Arabi et al. <sup>10</sup>	72/266	83/257	0.84 (0.64-1.09)		-
Mackenzie et al. <sup>21</sup>	39/121	47/119	0.82 (0.58-1.15)		
NICE-SUGAR <sup>18</sup>	829/3010	751/3012	1.10 (1.01-1.20)		
All mixed ICU patients	1351/5051	1301/5089	0.99 (0.87-1.12)		- <b>-</b>
Medical ICU					1
Bland et al.25	1/5	2/5	0.50 (0.06-3.91)		
Van den Berghe et al. <sup>9</sup>	214/595	228/605	0.95 (0.82-1.11)		
Walters et al. <sup>20</sup>	1/13	0/12	2.79 (0.12-62.48)		
Farah et al.27	22/41	22/48	1.17 (0.77-1.78)		
Oksanen et al. <sup>36</sup>	13/39	18/51	0.94 (0.53-1.68)		
Bruno et al.26	2/31	0/15	2.50 (0.13-49.05)		
All Larcal ICU patients	253/724	270/736	1.00 (0.78-1.28)		
Surgical ICU			, , , , ,		
Van den Berghe et al. <sup>8</sup>	55/765	85/783	0.66 (0.48-0.92)	_	
Grey et al.28	4/34	6/27	0.53 (0.17-1.69)		
Bilotta et al.24	6/40	7/38	0.81 (0.30-2.20)		
He et al. <sup>29</sup>	7/150	6/38	0.30 (0.11-0.83)	_	
Bliotta et al. <sup>23</sup>	5/48	6/49	0.85 (0.28-2.60)		
All surgical ICU patients	77/1037	110/935	0.63 (0.28-2.60)		
All ICU patients	1681/6812	1681/6760	0.03 (0.44-0.91)		

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Risk ratio (95% Cl

Griesdale D, CMAJ 2009;180(8):821-827

# Factors Associated with Hypoglycemia

- Time on IIT
- Severity of illness
- Previous diagnosis of diabetes mellitus
- BMI
- Time between BG measurements
- Blood glucose variability

#### Glycemic variability is associated with mortality in the critically ill

- Krinsley JS. Glycemic variability: a strong independent predictor of mortality in critically ill patients.
  - Crit Care Med. 2008;36:3008-3013

 Al Dorzi HM - Glycaemic fluctuation predicts mortality in critically ill patients.

- Anaesth Intensive Care. 2010;38:695-70

# Hypothesis

Individual differences in blood glucose variability over time are associated with hypoglycemia (<50 mg/dL)

Blood glucose variability can be utilized to estimate a patient's risk of hypoglycemia

## **Methods**

Study Design	<ul> <li>Retrospective cohort; 1392 patients</li> </ul>		
Setting	<ul> <li>SICU of Academic Level I Trauma Center</li> </ul>		
Setting	• June 1, 2006- September 1, 2009		
	• Age ≥ 18		
Subjects	<ul> <li>Admitted to SICU, treated with IIT for at least 12 hours with 5 subsequent BG measurements</li> </ul>		
	<ul> <li>Survived &gt;24 hours after SICU admission</li> </ul>		
Data Collection	<ul> <li>Age, gender, weight, APACHE II scores, preexisting diabetes, pressor use</li> </ul>		
	<ul> <li>BG values, insulin dose, test times</li> </ul>		
Outcome of Interest	<ul> <li>Hypoglycemia (&lt;50 mg/dL) at next BG measurement</li> </ul>		
	<ul> <li>SD of BG over the entire SICU stay</li> </ul>		
Measures of BG variability	<ul> <li>Successive change in BG values and temporal</li> </ul>		
	relationship to hypoglycemia		

### **Intensive Insulin Therapy Protocol**

A Computerized Insulin Infusion Titration Protocol Improves Glucose Control With Less Hypoglycemia Compared to a Manual Titration Protocol in a Trauma Intensive Care Unit

Marcus J. Dortch, PharmD\*; Nathan T. Mowery, MD†; Asli Ozdas, PhD‡; Lesly Dossett, MD†; Hanqing Cao, PhD†; Bryan Collier, DO†; Gwen Holder, RN, MSN§; Randolph A. Miller, MD‡; and Addison K. May, MD†

Journal of Parenteral and Enteral Nutrition 2008; 32:18-27

#### Goal range= 80-110 mg/dL

### Insulin Dose= (BG-60) X multiplier {start at 0.03}

Serum BG measured Q2 hours

## Results

- 66, 592 BG measurements on 1392 patients
- 45% of BG measurements were in target range (80-110 mg/dL)
- 84.3% of BG measurements were between 80-150 mg/dL
- Hypoglycemia (<50 mg/dL) occurred in 154/1392 patients (11.1%)

## **Demographics and Clinical Characteristics**

	Ever Hypoglycemic (<50 mg/dL) n= 154	Never Hypoglycemic (<50 mg/dL) n= 1,238	p- value
Age (yrs)	60.7	58.2	0.04
Males (%)	58.4	59.7	0.8
Patient weight (Kg)	81.3	87.4	0.01
History of diabetes (%)	26.6	33.4	0.11
ΑΡΑϹΗΕ ΙΙ	21	19	0.001
ICU LOS	14.8	5	0.001
Average blood glucose	109	108	0.9
Max glucose	197	150	¢0.001
SD blood glucose	35.5	24.3	\$0.001
Mortality (%)	24.7	12.5	0.001

#### **Blood Glucose Variability by Patient over Time**

**Hypoglycemics** 







#### Blood glucose variability increases in 24 hours preceding hypoglycemic event



**Time Prior to Index Blood Glucose Measurement** 

# • Row = 1 patient over time

#### Time These 263 patients were on the protocol for at least 24 hours, never experienced high BG variability, and there were 2 hypoglycemic events from 12 - 24 hours. Proportion of unit encounters These 128 patients were on the protocol for 108 hours, never experienced high BG variability, and there were 2 hypoglycemic events during hours 12 - 24 and 1 each during hours 72-84 and 84 - 96. These 78 patients were on the protocol for 24 hours, experienced high BG variability, and there were 4 hyopglyemic events. 12 - 24 24 - 36 36 - 48 48 - 60 60 - 72 72 - 84 84 - 96 96 - 108 hours hours hours hours hours hours hours hours Hypoglycemic events that occurred during periods of low BG variability are in yellow and events low / normal BG variability during high BG variability are in red. high BG variability 3 hypoglycemic events, 5 hypoglycemic events, off protocol / insufficient data to classify 2 hypoglycemic events, 3 hypoglycemic events, $\circ$ 1 hypoglycemic events, 1 hypoglycemic events,

# 3.3 events/1000 hrs high BGV

• 1 event/1000 hrs low BGV

# Predictors Independently Associated with Hypoglycemia

Variables in multivariable regression model	Exposure	OR	95% CI
Most recent absolute change in BG	IQR (4-34)	1.42*	1.29 – 1.57
Previous hypoglycemic episodes (count) (<60 mg/dL)	0	Reference	
	1	1.69	1.12 – 2.53
	2	1.45	0.94 - 1.90
	3 or more	4.14	2.56 - 6.70
Weight (kg)	IQR (70.1-103)	0.72*	0.56 – 0.93
Time since previous BG measurement (hours)	IQR (1.7-2.3)	1.45*	1.33 – 1.58

\*OR for risk associated with 75<sup>th</sup> percentile compared to 25<sup>th</sup> percentile is shown

# Predictors Not Independently Associated with Hypoglycemia

Variables in multivariable regression model	Exposure	OR	95% CI
Diagnosed diabetes	Y/N	0.88	0.63-1.22
Female sex	Y/N	0.96	0.75 – 1.37
Current vasopressors	Y/N	1.19	0.86 - 1.64
Patient age (years)	IQR (50.6-70)	1.39*	0.92-2.12
Volume of 5% dextrose infused in 2 hours (ml)	IQR (0-73)	0.98*	0.87-1.12
Baseline APACHE II score	IQR (16-26)	0.95*	0.75-1.21
Hours on Protocol	IQR (49-247)	0.91*	0.82-1.02

\*OR for risk associated with 75<sup>th</sup> percentile compared to 25<sup>th</sup> percentile is shown

# Conclusions

- Patients who experience hypoglycemia are characterized by higher BG variability prior to the event
- BG variability increases in the 8 hours preceding a hypoglycemic event
- Patients with high BG variability are at increased risk for hypoglycemia during the period their BG variability remains high
- Prospective measuring of BG variability may provide means for early identification of patients at high risk for hypoglycemia, and provide an opportunity to mitigate this risk



Vanderbilt University Medical Center - Nashville, TN