Journal of Diabetes Science and Technology
Volume 7, Issue 5, September 2013

ORIGINAL ARTICLE

Retrospective Outcomes of Glucose Control in Critically Ill Children

Sarah B. Kandil, M.D.,[1] Debra Spear, R.N., C.C.R.N.,[2] Neal J. Thomas, M.D., M.Sc.,[2] Stuart A. Weinzimer, M.D.,[3] and Edward Vincent S. Faustino, M.D.[1]

Abstract

Background:

Hyperglycemia is a significant problem for critically ill children. Treatment for hyperglycemia remains controversial. This study explores the effect of controlling blood glucose (BG) in hyperglycemic critically ill children.

Methods:

A retrospective cohort of nondiabetic critically ill children (defined as requiring mechanical ventilation and/or vasopressors) with BG persistently ≥150 mg/dl and treated with insulin (treatment group) were compared with a historical cohort of similar children who did not receive interventions to control hyperglycemia (baseline group).

Results:

There were 130 children in the treatment group and 137 children in the baseline group. Mean BG in the treatment group was 140 ± 24 mg/dl compared with 179 ± 47 mg/dl in the baseline group ($p < .001$). After adjusting for patient characteristics, cointerventions, and glucose metrics, patients in the treatment group had 2.5 fewer intensive care unit (ICU)-free days (i.e., number of days alive and discharged from ICU within 28 days after inclusion) than the baseline group ($p = .023$). Glucose control was not independently associated with duration of ICU stay, ventilator-free days, vasopressor-free days, or mortality.

Conclusions:

Blood glucose control appears associated with worse outcomes in critically ill children. Our data combined with conflicting results in adults leads us to strongly advocate for the conduct of randomized trials on glucose control in critically ill children.

J Diabetes Sci Technol 2013;7(5):1220–1228

Author Affiliations: [1]Department of Pediatrics, Section of Pediatric Critical Care Medicine, Yale University School of Medicine, New Haven, Connecticut; [2]Department of Pediatrics, Division of Pediatric Critical Care Medicine, Pennsylvania State University College of Medicine, Hershey, Pennsylvania; and [3]Department of Pediatrics, Section of Endocrinology, Yale University School of Medicine, New Haven, Connecticut

Abbreviations: (BG) blood glucose, (CI) confidence interval, (GVI) glucose variability index, (ICU) intensive care unit, (ICUFD), intensive care unit-free days, (PIM2) Pediatric Index of Mortality, (PSHCH) Penn State Hershey Children's Hospital, (VFD) ventilator-free days, (VPFD) vasopressor-free days, (YNHCH) Yale New Haven Children's Hospital

Keywords: hyperglycemia, hypoglycemia, intensive care, mechanical ventilation, pediatrics

Corresponding Author: Sarah Kandil, M.D., 333 Cedar St., P.O. Box 208064, New Haven, CT 06520-8064; email address sarah.kandil@yale.edu

Introduction

Hyperglycemia is common in critically ill adults and is associated with increased mortality and duration of stay in the intensive care unit (ICU).[1–3] The effect of intensive glucose control—in which blood glucose (BG) is controlled within a narrow range with intravenous insulin—on the mortality and duration of ICU stay of critically ill adults is unclear. Single-center trials by Van den Berghe and coauthors[1,2] demonstrated that, with BG controlled at 80–110 mg/dl during critical illness, mortality and morbidity outcomes of surgical and medical patients improved significantly. Subsequent multicenter trials failed to replicate the results of Van den Berghe and coauthors' studies. In particular, the NICE-SUGAR (Normoglycaemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation) study, which enrolled more than 6000 critically ill patients, demonstrated a 1.14-fold increased risk of mortality with glucose control.[3] There is less data to determine the effect of glucose control in critically ill children. Although it appears that hyperglycemia is associated with worse outcomes in critically ill children compared with normoglycemic children in the ICU,[4–6] the causative nature of the association is unclear. There are two published randomized trials on intensive glucose control in children that also have conflicting results. The first study by Vlasselaers and coauthors[7] suggested that mortality rate, duration of ICU stay, and vasopressor requirement is lower with intensive glucose control whereas the later trial, SPECS (Safe Pediatric Euglycemia after Cardiac Surgery), conducted by Agus and coauthors,[8] demonstrated no difference between treatment with glucose control and standard care, specifically with respect to infection rates or mortality.

In 2005, Yale New Haven Children's Hospital (YNHCH) and Penn State Hershey Children's Hospital (PSHCH) ICUs participated in a validation study of a bedside computerized algorithm to control BG in critically ill children. Even after the study was terminated, both centers continued to control BG. Prior to 2005, BG was not controlled in critically ill children admitted to either center. This sequence of events provided a natural experiment that provided us the opportunity to assess the association of BG control with clinical outcomes. In this study, we aimed to explore the association of BG control with clinical outcomes, particularly mortality-adjusted length of stay, in critically ill children.

Methods

Study Design

We performed a retrospective cohort study with historical controls at two academic centers; YNHCH has a 19-bed ICU while PSHCH has a 12-bed ICU. Both are mixed medical–surgical and cardiac ICUs in tertiary referral centers. Pediatric intensivists manage all patients admitted to the ICU in both centers. The investigational review board of both centers approved the study and waived the need for informed consent.

Children <18 years old admitted to the ICU with persistent BG ≥150 mg/dl for at least two checks 1 h apart were eligible. Those who required invasive mechanical ventilation and/or vasopressors were included in the study. Children were excluded if they had diabetes mellitus or received subcutaneous insulin or insulin for reasons other than control of hyperglycemia (e.g., hyperkalemia).

Eligible patients were selected from two time periods. The treatment group included all patients admitted in both ICUs from January 2006 to December 2007, after glucose control protocols were implemented. Eligible patients in this group who did not receive intravenous insulin were excluded. The baseline group included all patients admitted from January 2003 to December 2004, prior to implementation of any glucose control protocols. Eligible patients in this group who received any form of insulin were excluded. In both centers, potential study patients were identified using electronic databases and then confirmed with medical record review. The study periods were chosen to be as close to each other without including the transitional year (i.e., 2005) to minimize secular trends in practice outside of the use of glucose control.

All data were collected from review of medical records. Data included age, gender, diagnosis, severity of illness score [Pediatric Index of Mortality (PIM2)],[9] use and duration of invasive mechanical ventilation and vasopressors, use of

corticosteroids, caloric intake from carbohydrate sources, BG values, insulin dose, duration of ICU stay, and mortality. We included the following vasopressors: dopamine (≥5 mcg/kg/min), dobutamine (≥5 mcg/kg/min), epinephrine, norepinephrine, milrinone, phenylephrine, or vasopressin (if used for hypotension). Caloric intake included parenteral and enteral carbohydrate sources. Noncarbohydrate caloric intake was not collected.

Once eligibility criteria had been met, BG values were recorded until the patient was discharged from the ICU. In the treatment group, BG values were recorded only up to 48 h after insulin was discontinued if this occurred prior to ICU discharge. The blood compartment from which BG was measured (i.e., arterial, venous, or capillary) was not available in the medical records and, therefore, not included in the analysis. For every patient, we determined the initial BG, mean BG, glucose variability index (GVI),[10] and presence of hypoglycemia. Hypoglycemia was defined as BG ≤40 mg/dl. This threshold is typically used to define severe hypoglycemia in critically ill adult and pediatric patients.[1–3,11–13]

The primary outcome measure was 28-day intensive care unit-free days (ICUFD), a composite measure of length of ICU stay and mortality defined as number of days within 28 days from study entry that a patient was alive and discharged from the ICU.[14] Secondary outcome measures included ICU length of stay, ventilator-free days (VFD), vasopressor-free days (VPFD), and all-cause ICU mortality. Both VFD and VPFD were calculated similar to ICUFD (i.e., the number of days within 28 days from study entry that the patient was alive and free from invasive mechanical ventilation or vasoactive agents, respectively).

Blood Glucose Control Protocols

Blood glucose in the treatment group was controlled using three different methods. Both YNHCH and PSHCH participated in the validation of the eProtocol insulin, a computerized bedside decision support tool for titrating intravenous insulin with the intent of controlling BG at 80–110 mg/dl.[15] The BG of patients admitted in both centers from January to December 2006 was controlled with eProtocol insulin. After the study, YNHCH implemented a paper-based glucose control protocol with a target BG range of 90–119 mg/dl.[11] No protocols were implemented in PSHCH after the eProtocol insulin validation study; however, BG was controlled to a target range of 80–140 mg/dl with insulin infusions titrated as per attending physician's discretion. Overall, for patients in the treatment group, BG was controlled within 80–140 mg/dl.

Statistical Analysis

Data are presented as mean ± standard deviation or as counts (percentage), depending on the type of data. Continuous data were compared between the treatment and baseline groups using Mann–Whitney *U* tests, while categorical data were compared using chi-squared tests. We also determined the association of glucose control, patient characteristics, cointerventions, and glucose metrics with ICUFD, duration of ICU stay, VFD, and VPFD using linear regression. To control for potential differences in patient characteristics, glucose metrics, and cointerventions between the two groups, we performed stepwise backward linear regression with entry $p < .10$ and exit $p > .25$. The magnitude of the associations in the unadjusted and adjusted models is presented as B estimates with 95% confidence interval (CI). The association between mortality and glucose control, patient characteristics, cointerventions, and glucose metrics was assessed using logistic regression. We adjusted the association between mortality and glucose control in the presence of the other factors using stepwise backward logistic regression model with similar entry and exit criteria as the linear regression. Odds ratios with 95% CI were calculated in the unadjusted and adjusted models. For each of the regression models, we assessed multicollinearity using the variance inflation factor. We used a threshold of >4.0 as indicative of significant multicollinearity between variables. A $p < .05$ was considered statistically significant, unless otherwise specified. SPSS v.19 for Windows (IBM Corp., Chicago, IL) was used for all analyses.

Results

Patient Characteristics

A total of 130 patients in the treatment group (63 patients from YNHCH and 67 patients from PSHCH) and 137 patients in the baseline group (68 patients from YNHCH and 69 patients from PSHCH) were included in the study (**Table 1**).

Patient characteristics were similar between the two groups, except for admitting diagnosis and PIM2. There were fewer surgical patients in the treatment group compared with the baseline group (25.4% versus 46.0%; $p < .001$). Patients in the treatment group also had higher severity of illness scores compared with the baseline group ($p < .001$). Though not specifically collected for this study, a prior study reported stress hyperglycemia rates between 16% and 75% in nondiabetic children in one of the centers, depending on the cutoff values used.[4]

Table 1.
Characteristics of Hyperglycemic Critically Ill Children in the Treatment and Baseline Groups[a]

Characteristic	Treatment *N* = 130	Baseline *N* = 137	*P* value
Patient characteristics			
Center of origin (YNHCH), *N*	63 (48.5%)	68 (49.6%)	0.903
Age (months), mean ± SD	78.8 ± 94.7	70.5 ± 75.4	0.407
PIM2, mean ± SD	15.7 ± 25.7	10.9 ± 22.3	0.001
Male gender, *N*	65 (50.0%)	76 (55.5%)	0.370
Diagnosis			0.006
Respiratory	42 (32.3%)	33 (24.1%)	
Cardiac surgery	20 (15.4%)	30 (21.9%)	
Noncardiac surgery and trauma	13 (10.0%)	33 (24.1%)	
Sepsis	25 (19.2%)	15 (11.0%)	
Other medical conditions	30 (23.1%)	26 (19.0%)	
Surgical diagnosis, *N*	33 (25.4%)	63 (46.0%)	<0.001
Cointerventions			
Mechanical ventilation, *N*	123 (94.6%)	136 (99.3%)	0.026
Vasopressors, *N*	93 (71.5%)	87 (63.5%)	0.161
Corticosteroids, *N*	91 (70.0%)	53 (38.7%)	<0.001
Carbohydrate calories (cal/kg/day), mean ± SD	18.0 ± 15.0	13.8 ± 13.8	0.003
Glucose metrics			
Daily BG (mg/dl), mean ± SD	140 ± 24	179 ± 47	<0.001
GVI (mg/dl/h), mean ± SD	15.9 ± 10.1	11.2 ± 29.5	<0.001
Insulin dose (U/kg/h), mean ± SD	0.05 ± 0.04	0.00 ± 0.00	<0.001
Hypoglycemia, *N*	16 (12.3%)	2 (1.5%)	<0.001
First BG (mg/dl), mean ± SD	221 ± 72	211 ± 72	0.136
Outcomes			
ICUFD, mean ± SD	11.8 ± 9.5	16.8 ± 9.9	<0.001
Duration of ICU stay (days), mean ± SD	16.3 ± 19.6	7.6 ± 7.6	<0.001
VFD, mean ± SD	14.5 ± 10.5	19.0 ± 10.2	<0.001
VPFD, mean ± SD	18.7 ± 11.0	21.4 ± 10.3	0.006
Mortality, *N*	27 (20.8%)	23 (16.8%)	0.405

[a] SD, standard deviation.

Nearly all the patients were on invasive mechanical ventilation, and more than half of the patients were on vasopressors. Caloric intake from carbohydrate sources was significantly higher in the treatment group compared with the baseline group (18.0 ± 15.0 versus 13.8 ± 13.8 cal/kg/day; $p = .003$). More patients in the treatment group received corticosteroids compared with the baseline group (70.0% versus 38.7%; $p < .001$).

Glucose Metrics

Mean BG was significantly lower in the treatment group compared with the baseline group (140 ± 24 versus 179 ± 47 mg/dl; $p < .001$) despite having statistically similar initial BG (221 ± 72 mg/dl in the treatment group versus 211 ± 72 mg/dl in the baseline group; $p = .136$; **Table 1**). Patients in the treatment group, on average, received 0.05 ± 0.04 U/kg/h of insulin and had a higher GVI ($p < .001$). Significantly more patients developed hypoglycemia in the treatment group compared with the baseline group (12.3% versus 1.5%; $p < .001$).

Clinical Outcomes

Patients in the treatment group had significantly fewer ICUFD at 11.8 ± 9.5 versus 16.8 ± 9.9 days in patients in the baseline group ($p < .001$; **Table 1**). When adjusted for other variables, glucose control was independently associated with ICUFD (**Table 2**). Patients in the treatment group had 2.5 ICUFD (95% CI: -4.7, -0.4; $p = .023$) less than those in the baseline group. The PIM2 score, mechanical ventilation use, vasopressor use, GVI, and caloric intake were also independently associated with ICUFD, while center of origin, diagnosis, use of corticosteroids, and hypoglycemia were not. None of the other outcomes, including mortality, were associated with glucose control in the adjusted analysis (data not shown). There was no significant multicollinearity among the variables in any of the regression models.

Table 2.
Factors Associated with Intensive Care Unit-Free Days

Variable	Unadjusted analysis			Adjusted analysis		
	B estimate	95% CI	*P* value	B estimate	95% CI	*P* value
Glucose control	-0.25	-7.33, -2.66	<0.001	-2.52	-4.68, -0.36	0.023
Center of origin (PSHCH versus YNHCH)	0.02	-2.12, 2.71	0.811	1.50	-0.64, 3.63	0.169
Age (per 1 month increase)	0.16	0.01, 0.03	0.006			
PIM2 (per 0.10 increase)	-0.05	-0.023, -0.014	<0.001	-0.01	-0.02, -0.01	<0.001
Male gender	-0.08	-3.97, 0.85	0.203			
Surgical diagnosis	3.80	1.33, 6.27	0.003	1.75	-0.58, 4.07	0.141
Mechanical ventilation	-0.16	-16.30, -2.32	0.009	-9.80	-15.70, -3.90	0.001
Vasopressor	-6.15	-8.62, -3.68	<0.001	-5.04	-7.27, -2.81	<0.001
Corticosteroids	-0.11	-4.59, 0.22	0.075	-1.46	-3.75, 0.83	0.210
Carbohydrate calories (cal/kg/day)	-0.21	-0.22, -0.06	0.001	-0.12	-0.19, -0.05	0.001
Daily BG (per 10 mg/dl increase)	0.88	-0.08, 0.49	0.152			
GVI (mg/dl/h)	-0.19	-0.14, -0.03	0.001	-0.06	-0.10, -0.02	0.008
Hypoglycemia	-0.22	-13.30, -3.90	<0.001	-2.80	-6.89, 1.29	0.179
First BG (per 10 mg/dl increase)	-1.69	-0.40, -0.07	0.006			

Discussion

In this retrospective cohort study, we explored the association between BG control and clinical outcomes in critically ill children. We report that glucose control appears to be independently associated with worse outcomes, particularly fewer ICUFD. The fewer ICUFD in those with glucose control is most likely due to longer duration of ICU stay, as mortality was not associated with glucose control in both unadjusted and adjusted analyses. This study is the first to evaluate the outcomes of glucose control in a multicenter usual practice setting. Other studies report outcomes for very specific populations and protocols.[1,2,7,8]

Studies on glucose control in critically ill adults were designed to detect differences in mortality.[1–3] Due to the low mortality rates in critically ill children,[14] the large number of children needed to determine the mortality benefit of glucose control in this population will likely be insurmountable. Since studies in adults demonstrated differences in mortality and ICU length of stay,[1–3] it seemed logical to use ICUFD, a mortality-adjusted measure of duration of ICU stay, as the primary outcome measure.[14]

In the present study, glucose control was independently associated with fewer ICUFD, suggesting a worse outcome in the treated group. This is consistent with the findings of the NICE-SUGAR study.[3] While ICUFD was not reported, patients randomized to the treatment group in the NICE-SUGAR study had a higher mortality rate with similar ICU length of stay compared with the control group. This would translate to fewer ICUFD in the treatment group. In contrast, in the two studies by Van den Berghe and coauthors[1,2] in critically ill adults and the Vlasselaers and coauthors[7] study in critically ill children, patients randomized to glucose control would have more ICUFD since mortality rates were lower and ICU lengths of stay were shorter in the glucose control group compared with the no control group. It is difficult to comment for the SPECS trial, given that the two groups had similar ICU lengths of stay and mortality rates. However, given that the SPECS trial involved a homogenous population of postoperative cardiac surgery patients with a short ICU stay, effects may not yet be apparent.

Possible factors that explain these contrasting outcomes, particularly with the pediatric trials, are differences in patient populations, variations in methodologies for BG control (including clinician compliance), glucose variability, nutritional support, and corticosteroid use.[16–18] Since this study was retrospectively performed, we cannot control for the type of BG control used in the two centers. It is possible that the methods of BG control, with three different BG targets, may have led to worse outcomes in the treatment group. Although BG target and protocol associated with the most favorable clinical outcome is unknown,[19–21] a consistent target range for all patients in the treatment group would have been preferred. While it is unknown what the clinician compliance rate was for this study, previous reports from eProtocol investigators document over 90% compliance, and one of our centers has reported a 70% compliance rate with the paper protocol.[11,15] Our sample size does not allow us to control for BG control method.

The lack of association of BG control with the other outcomes investigated may reflect the non-organ-specific effect of glucose control. It is also likely that we do not have adequate sample size to detect differences in organ dysfunction.

Hypoglycemia is a significant concern in the practice of glucose control.[12,13,22] Similar to other studies,[12,16] rates of hypoglycemia in the present study were significantly higher in the treatment group compared with the baseline group. However, hypoglycemia was not independently associated with ICUFD. We previously hypothesized that hypoglycemia is merely a reflection of the patient's underlying illness, such that the presence of hypoglycemia does not affect the patient's outcome.[12,13] In addition, in the ICU setting, where patients are closely monitored, hypoglycemia is likely detected before the typical neurologic and cardiac effects ensue.[12,13]

We used historical controls in our study because of the absence of concurrent controls in our centers. Both centers decided to control BG after 2005. The use of controls from other centers would have introduced additional biases in our study. The use of historical controls in a quasi-experimental study may provide important information regarding the effect of interventions. Observation studies (including those with historical cohorts) have been shown to neither overestimate nor underestimate summary results when compared with randomized controlled trials of several major medical interventions.[23] Studies on the prevention of catheter-associated blood stream infection in critically ill children, for example, has utilized historical controls to demonstrate the effectiveness of the bundled interventions.[24–27] Similarly, Krinsley[28] demonstrated the effect of glucose control in critically ill adults using historical controls.

The nonrandomized and nonconcurrent nature of this type of study design, however, may result in imbalances in patient characteristics and secular trends other than the treatment being evaluated. To control for imbalances in patient characteristics, we adjusted our estimate of the outcome measures using regression analysis. The persistence of association of glucose control with ICUFD with regression suggests that the treatment effect is not likely due to any of the covariates tested for. We recognize that not all covariates can be adjusted for given the retrospective nature of the

study; however, to minimize secular bias, we chose time periods close to each other. Despite the choice of treatment periods, the use of steroids and care of central lines to decrease infections occurred during the study periods. We controlled for steroid use in our regression analysis, and this was not significantly associated with ICUFD. As our results show, a decrease in catheter-associated blood stream infections with improved care of central lines would potentially increase ICUFD during the treatment group and not decrease it. Thus, it is unlikely that the changes in steroid use or care of central lines in critically ill children explain our results. It is still possible that residual confounding effect remains to explain our study results.

The present study has strengths. Surveys have shown that there is wide variation in physicians' beliefs and practices with respect to BG control in critically ill children.[22,29,30] This probably represents the current usual practice of glucose control in critically ill children with variations of protocols used and BG measurements from different blood compartments using BG meters.[12,13] The present study included patients from two ICUs with a broad mix of diagnoses. Center of origin was not related to our outcome measures. To our knowledge, this is the first study to investigate the association of glucose control and ICUFD, VFD, and VPFD. Pediatric critical care practitioners consider these outcome measures clinically significant.[14] The present study evaluated the relationship of glucose variability and caloric intake on outcomes of critically ill children treated with glucose control, which have not been studied before.

Other limitations should also be considered. The frequency of BG measurements might have affected the glucose metrics presented in this study.[4] In particular, there was no standard frequency of BG measurements for either group. The decisions to discharge patients from the ICU, wean patients from the ventilator, or discontinue vasopressors were not protocolized and were subject to the discretion of the attending physician and the rest of the clinical care team. Finally, this study is retrospective in nature, and as such, causation cannot be established.

The conflicting conclusions from prior studies emphasize the importance of conducting multicenter randomized controlled trials to determine the efficacy and safety of intensive glucose control in critically ill children. Based on our data, such a trial will need to randomize nearly 3000 critically ill children to detect a 1-day difference in ICUFD with a two-sided alpha of 0.05 and 80% power. Currently, several randomized controlled trials have either completed enrollment or are in active enrollment.

Conclusion

It appears possible that glucose control can be independently associated with worse outcomes in critically ill children, particularly less ICUFD. The conflicting conclusions from different studies emphasize the need for randomized trials in critically ill children.

Funding:

This research is partially supported by a National Institutes of Health (NIH) training grant, NIH T32 HL07272 (the development of cardiovascular and pulmonary function; Sarah B. Kandil). This review is also supported in part by a grant from the Clinical and Translational Science Award grant number UL1 RR024139 and from KL2 RR024138 from the National Center for Research Resources and the National Center for Advancing Translational Science, components of the NIH and NIH Roadmap for Medical Research (Edward Vincent S. Faustino). Funding for eProtocol insulin was provided by contract number HHSN268200425210C, "Re-Engineering Clinical Research in Critical Care," in response to Broad Agency Announcement, NIH Roadmap "Re-Engineering the Clinical Research Enterprise: Feasibility of Integrating and Expanding Clinical Research Networks."

Disclosures:

Stuart Weinzimer is on the editorial board for *Journal of Diabetes and Science Technology.*

References:

1. Van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, Vlasselaers D, Ferdinande P, Lauwers P, Bouillon R. Intensive insulin therapy in critically ill patients. N Engl J Med. 2001;345(19):1359–67.
2. Van den Berghe G, Wilmer A, Hermans G, Meersseman W, Wouters PJ, Milants I, Van Wijngaerden E, Bobbaers H, Bouillon R. Intensive insulin therapy in the medical ICU. N Engl J Med. 2006;354(5):449–61.
3. NICE-SUGAR Study Investigators, Finfer S, Chittock DR, Su SY, Blair D, Foster D, Dhingra V, Bellomo R, Cook D, Dodek P, Henderson WR, Hébert PC, Heritier S, Heyland DK, McArthur C, McDonald E, Mitchell I, Myburgh JA, Norton R, Potter J, Robinson BG, Ronco JJ. Intensive versus conventional glucose control in critically ill patients. N Engl J Med. 2009;360(13):1283–97.
4. Faustino EV, Apkon M. Persistent hyperglycemia in critically ill children. J Pediatr. 2005;146(1):30–4.
5. Srinivasan V, Spinella PC, Drott HR, Roth CL, Helfaer MA, Nadkarni V. Association of timing, duration, and intensity of hyperglycemia with intensive care unit mortality in critically ill children. Pediatr Crit Care Med. 2004;5(4):329–36.
6. Hirshberg E, Larsen G, Van Duker H. Alterations in glucose homeostasis in the pediatric intensive care unit: Hyperglycemia and glucose variability are associated with increased mortality and morbidity. Pediatr Crit Care Med. 2008;9(4):361–6.
7. Vlasselaers D, Milants I, Desmet L, Wouters PJ, Vanhorebeek I, van den Heuvel I, Mesotten D, Casaer MP, Meyfroidt G, Ingels C, Muller J, Van Cromphaut S, Schetz M, Van den Berghe G. Intensive insulin therapy for patients in paediatric intensive care: a prospective, randomised controlled study. Lancet. 2009;373(9663):547–56.
8. Agus MS, Steil GM, Wypij D, Costello JM, Laussen PC, Langer M, Alexander JL, Scoppettuolo LA, Pigula FA, Charpie JR, Ohye RG, Gaies MG; SPECS Study Investigators. Tight glycemic control versus standard care after pediatric cardiac surgery. N Engl J Med. 2012;367(13):1208–19.
9. Slater A, Shann F, Pearson G; Paediatric Index of Mortality (PIM) Study Group. PIM2: a revised version of the Paediatric Index of Mortality. Intensive Care Med. 2003;29(2):278–85.
10. Wintergerst KA, Buckingham B, Gandrud L, Wong BJ, Kache S, Wilson DM. Association of hypoglycemia, hyperglycemia, and glucose variability with morbidity and death in the pediatric intensive care unit. Pediatrics. 2006;118(1):173–9.
11. Faraon-Pogaceanu C, Banasiak KJ, Hirshberg EL, Faustino EV. Comparison of the effectiveness and safety of two insulin infusion protocols in the management of hyperglycemia in critically ill children. Pediatr Crit Care Med. 2010;11(6):741–9.
12. Faustino EV, Bogue CW. Relationship between hypoglycemia and mortality in critically ill children. Pediatr Crit Care Med. 2010;11(6):690–8.
13. Faustino EV, Hirshberg EL, Bogue CW. Hypoglycemia in critically ill children. J Diabetes Sci Technol. 2012;6(1):48–57.
14. Curley MA, Zimmerman JJ. Alternative outcome measures for pediatric clinical sepsis trials. Pediatr Crit Care Med. 2005;6(3 Suppl):S150–6.
15. Thompson BT, Orme JF, Zheng H, Luckett PM, Truwit JD, Willson DF, Duncan Hite R, Brower RG, Bernard GR, Curley MA, Steingrub JS, Sorenson DK, Sward K, Hirshberg E, Morris AH; Reengineering Critical Care Clinical Research Investigators. Multicenter validation of a computer-based clinical decision support tool for glucose control in adult and pediatric intensive care units. J Diabetes Sci Technol. 2008;2(3):357–68.
16. Griesdale DE, de Souza RJ, van Dam RM, Heyland DK, Cook DJ, Malhotra A, Dhaliwal R, Henderson WR, Chittock DR, Finfer S, Talmor D. Intensive insulin therapy and mortality among critically ill patients: a meta-analysis including NICE-SUGAR study data. CMAJ. 2009;180(8):821–7.
17. Van den Berghe G, Schetz M, Vlasselaers D, Hermans G, Wilmer A, Bouillon R, Mesotten D. Clinical review: Intensive insulin therapy in critically ill patients: NICE-SUGAR or Leuven blood glucose target? J Clin Endocrinol Metab. 2009;94(9):3163–70.
18. Rake AJ, Srinivasan V, Nadkarni V, Kaptan R, Newth CJ. Glucose variability and survival in critically ill children: Allostasis or harm? Pediatr Crit Care Med. 2010;11(6):707–12.
19. Moghissi ES, Korytkowski MT, DiNardo M, Einhorn D, Hellman R, Hirsch IB, Inzucchi SE, Ismail-Beigi F, Kirkman MS, Umpierrez GE; American Association of Clinical Endocrinologists; American Diabetes Association. American Association of Clinical Endocrinologists and American Diabetes Association consensus statement on inpatient glycemic control. Endocr Pract. 2009;15(4):353–69.
20. Dellinger RP, Levy MM, Carlet JM, Bion J, Parker MM, Jaeschke R, Reinhart K, Angus DC, Brun-Buisson C, Beale R, Calandra T, Dhainaut JF, Gerlach H, Harvey M, Marini JJ, Marshall J, Ranieri M, Ramsay G, Sevransky J, Thompson BT, Townsend S, Vender JS, Zimmerman JL, Vincent JL; International Surviving Sepsis Campaign Guidelines Committee; American Association of Critical-Care Nurses; American College of Chest Physicians; American College of Emergency Physicians; Canadian Critical Care Society; European Society of Clinical Microbiology and Infectious Diseases; European Society of Intensive Care Medicine; European Respiratory Society; International Sepsis Forum; Japanese Association for Acute Medicine; Japanese Society of Intensive Care Medicine; Society of Critical Care Medicine; Society of Hospital Medicine; Surgical Infection Society; World Federation of Societies of Intensive and Critical Care Medicine. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. Crit Care Med. 2008;36(1):296–327.
21. Institute for Healthcare Improvement. Implement effective glucose control. http://www.ihi.org/knowledge/Pages/Changes/ImplementEffectiveGlucoseControl.aspx. Accessed April 30, 2012.
22. Hirshberg E, Lacroix J, Sward K, Willson D, Morris AH. Blood glucose control in critically ill adults and children: a survey on stated practice. Chest. 2008;133(6):1328–35.
23. Concato J, Shah N, Horwitz RI. Randomized, controlled trials, observational studies, and the hierarchy of research designs. N Engl J Med. 2000;342(25):1887–92.
24. Jain M, Miller L, Belt D, King D, Berwick DM. Decline in ICU adverse events, nosocomial infections and cost through a quality improvement initiative focusing on teamwork and culture change. Qual Saf Health Care. 2006;15(4):235–9.
25. Kim JS, Holtom P, Vigen C. Reduction of catheter-related bloodstream infections through the use of a central venous line bundle: epidemiologic and economic consequences. Am J Infect Control. 2011;39(8):640–6.

26. Miller MR, Griswold M, Harris JM 2nd, Yenokyan G, Huskins WC, Moss M, Rice TB, Ridling D, Campbell D, Margolis P, Muething S, Brilli RJ. Decreasing PICU catheter-associated bloodstream infections: NACHRI's quality transformation efforts. Pediatrics. 2010;125(2):206–13.

27. Miller MR, Niedner MF, Huskins WC, Colantuoni E, Yenokyan G, Moss M, Rice TB, Ridling D, Campbell D, Brilli RJ; National Association of Children's Hospitals and Related Institutions Pediatric Intensive Care Unit Central Line-Associated Bloodstream Infection Quality Transformation Teams. Reducing PICU central line-associated bloodstream infections: 3-year results. Pediatrics. 2011;128(5):e1077–83.

28. Krinsley JS. Effect of an intensive glucose management protocol on the mortality of critically ill adult patients. Mayo Clin Proc. 2004;79(8):992–1000.

29. Preissig CM, Rigby MR. A disparity between physician attitudes and practice regarding hyperglycemia in pediatric intensive care units in the United States: a survey on actual practice habits. Crit Care. 2010;14(1):R11.

30. Hirshberg EL, Sward KA, Faustino EV, Nadkarni VM, Agus MS, Morris AH, Lacroix J. Clinical equipoise regarding glycemic control: a survey of pediatric intensivist perceptions. Pediatr Crit Care Med. 2013;14(2):123–9.