Glucose control, organ failure, and mortality in pediatric intensive care*

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Objective: **In ventilated children, to determine the prevalence of hyperglycemia, establish whether it is associated with organ failure, and document glycemic control practices in Australasian pediatric intensive care units (PICUs).**

Design: **Prospective inception cohort study.**

Setting: **All nine specialist PICUs in Australia and New Zealand.**

Patients: **Children ventilated >12 hrs excluding those with diabetic ketoacidosis, on home ventilation, undergoing active cardiopulmonary resuscitation on admission, or with do-not-resuscitate orders.**

Interventions: **None.**

Measurements and Main Results: **All blood glucose measurements for up to 14 days, clinical and laboratory values needed to calculate Paediatric Logistic Organ Dysfunction (PELOD) scores, and insulin use were recorded in 409 patients. Fifty percent of glucose measurements were >6.1 mmol/L, with 89% of patients having peak values >6.1 mmol/L. The median time to peak blood glucose was 7 hrs. Hyperglycemia was defined by area under the glucose-time curve >6.1 mmol/L above the sample median. Thirteen percent of hyperglycemic subjects died vs. 3% of nonhyperglycemic subjects. There was an independent association between hyperglycemia and a PELOD score ≥10 (odds ratio 3.41, 95% confidence interval 1.91–6.10) and death (odds ratio 3.31, 95% confidence interval 1.26–7.7). Early hyperglycemia, defined using only glucose data in the first 48 hrs, was also associated with these outcomes but not with PELOD ≥10 after day 2 or with worsening PELOD after day 1. Five percent of patients received insulin.**

Conclusions: **Hyperglycemia is common in PICUs, occurs early, and is independently associated with organ failure and death. However, early hyperglycemia is not associated with later or worsening organ failure. Australasian PICUs seldom use insulin. (Pediatr Crit Care Med 2008; 9:147–152)**

KEY WORDS: blood glucose; hyperglycemia; insulin; child; intensive care; multiple organ failure; severity of illness index; logistic models; mechanical ventilation; mortality

Hyperglycemia is common in critically ill adults and possibly harmful (1, 2). Randomized controlled trials in adults outside intensive care units (ICUs) showed a benefit from strict glucose control (3, 4). Van den Berghe and colleagues (5) reduced mortality by maintaining blood glucose between 4.4 and 6.1 mmol/L, using insulin, in adults in the surgical ICU. The benefit might have been from insulin, normoglycemia, or both. However, the authors cautioned against applying their findings to patients not represented in their trial. Subsequently, they showed a reduction in morbidity, but not mortality, by preventing new kidney injury, and they showed earlier weaning and earlier ICU and hospital discharge as well in adult medical ICU patients treated similarly (6). All the benefit was in patients staying in ICU >3 days.

Australasian (Australian and New Zealand) adult intensivists have not widely adopted this approach, because of differences in populations and nutritional practices and because of concern about hypoglycemia (7). Hence, the Clinical Trials Group of the Australian and New Zealand Intensive Care Society is conducting a randomized controlled trial of intensive glucose control in adults (8).

Hyperglycemia also occurs in children in pediatric intensive care units (PICUs) and is associated with harm. The Pediatric Risk of Mortality (PRISM) score (9) includes abnormal blood glucose as an independent mortality predictor. Hyperglycemia independently predicted poor outcome from head injury in children in two studies (10, 11). An earlier study showed no harm from hyperglycemia in head-injured children, but hyperglycemia was defined using a high threshold (15 mmol/L) (12). Hyperglycemic children

***See also p. 231.**

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with burns had poorer skin graft take and higher rates of bacteremia and mortality (13). In cardiac surgery, hyperglycemia was associated with neurologic deficit (14) and death (15, 16). Although PICU mortality was independently associated with both peak blood glucose and the duration of blood glucose >7.0 mmol/L (17), aggressive glycemic control is not standard practice in PICUs, because of the lack of evidence for benefit and because of concern about hypoglycemia. Additionally, an Australasian PICU trial with a mortality end point is not feasible because of the small available sample size (6,000–7,000 annual admissions, compared with >100,000 adults) and low mortality rate (3.2% in 2004) (18). Morbidity, such as organ dysfunction scoring, is a potential end point for clinical trials in PICUs (19). Multiple organ failure is associated with mortality in children in PICU (20–22).

We chose the Paediatric Logistic Organ Dysfunction (PELOD) score to measure organ failure because, when the study began, it was the only validated pediatric multiple organ failure score (23). Despite poor calibration, it has good discrimination for mortality: the area under the curve (AUC) for the receiver operating characteristic is 0.91 (24). Moreover, the PELOD is used in ongoing studies by the Pediatric Acute Lung Injury and Sepsis Investigators network and the Canadian Critical Care Trials Group (25). It was a recommended organ dysfunction score for sepsis at the 2001 International Sepsis Definitions Conference (26). The PELOD assigns up to 20 points per system (neurologic, cardiovascular, renal, respiratory, hematologic, and hepatic), with a maximum total of 71 (23). In 2004, 96% of patients in the Australian and New Zealand Pediatric Intensive Care Registry (ANZPIC Registry) stayed <14 days, (median 1.1 days) (18). Children who develop multiple organ failure usually do so early (85% on admission) and recover quickly: median 3 days (20). Therefore, following patients for >1 wk using the PELOD will detect most cases of multiple organ failure and follow its resolution.

Australasian PICUs routinely transfer data from the medical record to the ANZPIC Registry for calculation of the Pediatric Index of Mortality 2 (27) but not for the PELOD score.

There are few data on the prevalence, timing, and duration of hyperglycemia in PICUs (28, 29, 17). Data are insufficient for a sample size estimation for a randomized controlled trial of intensive glucose control in children. Therefore, we performed a cohort observational study to determine the prevalence of hyperglycemia in children ventilated >12 hrs in the PICU, to establish whether hyperglycemia was associated with multiple organ failure, and to describe the current glycemic control practices in Australasian PICUs.

We hypothesized that in children ventilated >12 hrs in the PICU, there is an association between hyperglycemia and organ system failure.

Table 1. Study sample variables compared with the Australian and New Zealand Pediatric Intensive Care (ANZPIC) Registry population

	Glucose Study	ANZPIC Registry
No.	409	2,071
Male, n (%)	230 (56.2)	1210 (58.4)
Age, months, median (IQR)	10.1 (2.0–48.7)	23.2 (4.0–91.1)
LOS, days, median (IQR)	3.6 (1.8–6.9)	1.2 (0.4–3.2)
Cardiopulmonary bypass, n (%)	106 (25.9)	339 (16.4)
Recovery from a procedure, n (%)	180 (44.0)	872 (42.1)
Elective, n (%)	172 (42.1)	855 (41.3)
Ventilation, n (%)	409 (100)	1094 (53.4)
Duration of ventilation, days, median (IQR)	2.4 (0.9–4.8)	1.04 (0.5–3.5)
PIM2 risk of death, median (IQR)	3.1 (1.7–5.4)	1.2 (0.4–3.2)
Deaths, n (%)	33 (8.0)	67 (3.3)

IQR, interquartile range; LOS, length of stay; PIM2, Pediatric Index of Mortality 2.

Table 2. Diagnostic categories

Diagnostic Category	No. of Subjects (%)
Injury[a]	33 (8.1)
Cardiovascular	26 (6.4)
Post-cardiac surgery	131 (32.0)
Respiratory	88 (21.5)
Neurological	46 (11.3)
Other postoperative	49 (12.0)
Other	36 (8.8)
Total	409 (100.0)

[a] Includes head injury.

MATERIALS AND METHODS

All nine specialist PICUs in Australia and New Zealand participated. Local research ethics committees waived the requirement for informed consent at all hospitals except the Women's and Children's Hospital, Adelaide, where consent was obtained for all subjects.

Subjects. We included all patients ventilated >12 hrs, excluding those admitted for diabetic ketoacidosis, those on home ventilation, those undergoing cardiopulmonary resuscitation at the time of admission to the PICU who died, and those with do-not-resuscitate orders made before PICU admission. Data from patients who were ventilated after admission were collected from the time they were ventilated. No interventions or investigations were done for study purposes only. We studied subjects for the first 14 days of PICU admission, or until PICU discharge or death. We aimed to study 400 subjects in two months.

Glucose Measurement. Eight of nine units measured blood glucose using a blood gas analyzer, calibrated and maintained according to the manufacturer's instructions. The Women's and Children's Hospital, Adelaide, used a bedside glucometer, (Abbott MediSense Optium, Bedford, MA) calibrated daily according to the manufacturer's instructions. The Appendix shows details of each unit's device.

Data Collection and Entry. All PICUs routinely collected the ANZPIC Registry minimum dataset (30). We appended additional data specifically for glucose management and PELOD scores. Data were collected prospectively on specific study forms from PICU charts during the PICU admission. De-identified data were stored in a password-protected, Microsoft Access database. Ten percent of the data were recollected to check for completeness and accuracy. Data collected were as follows: glucose management plans (insulin use and target blood glucose range), all glucose measurements, measurement device used, concurrent insulin dose, and data necessary for PELOD scores. We calculated the scores for each day and used the worst day's score as the maximum score for the admission.

Outcome Measures

1. Exposure to hyperglycemia. This was measured by the area under the glucose-time curve for blood glucose above thresholds of 6.1 and 7.0 mmol/L, respectively, using a trapezoidal method. The first threshold was that used by Van den Berghe (5). The latter was chosen because time >7.0 mmol/L may be harmful (17) and because a low threshold may be problematic in a pediatric trial, given the concern about hypoglycemia. Hyperglycemic subjects are those in the upper half of the sample for AUC >6.1 mmol/L, unless stated otherwise.

2. Relationship between hyperglycemia and PELOD score. The primary outcome was

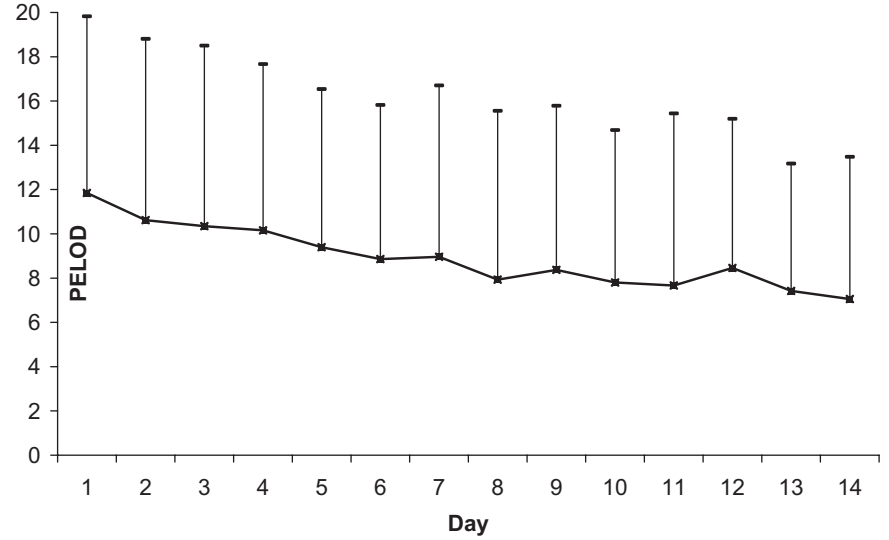

Figure 1. Mean Paediatric Logistic Organ Dysfunction (*PELOD*) score over time.

Table 3. Univariate analysis of variables associated with Paediatric Logistic Organ Dysfunction ≥10

Variable	OR	95% CI	*p*
Hyperglycemia	3.40	1.85 to 6.46	<.0001
PIM2	1.68	1.28 to 2.21	<.0001
Male gender	0.81	0.46 to 1.43	.44
Age (infant <1 yr)	1.40	0.80 to 2.46	.21
Recovery from procedure	1.00	0.57 to 1.76	1
Emergency admission	0.97	0.55 to 1.71	.93
Cardiopulmonary bypass	1.34	0.71 to 2.63	.35

OR, odds ratio; CI, confidence interval; PIM; Pediatric Index of Mortality.

whether hyperglycemic subjects are more likely than nonhyperglycemic subjects to have clinically significant organ failure, defined by PELOD ≥10. A patient with a PELOD ≥10 has severe organ dysfunction in at least one system. For example, a PELOD ≥10 for respiratory failure requires a Po_2 ≤70 mm Hg or a Pco_2 >88 mm Hg, while for renal failure (>12 yrs) a creatinine ≥140 μmol/L (1.6 mg/dL) is required.

3. Descriptive statistics on current Australasian PICU practice for glucose control, that is, thresholds for commencing insulin, target glucose level on insulin, and daily insulin dose.

Statistical Analysis. Data are presented as mean ± SD or median (interquartile range). Odds ratios (ORs) and the receiver operating characteristic are followed by their 95% confidence interval in brackets. Chi-square or Fisher's exact tests were used to assess the association between hyperglycemia and clinically significant organ failure. Spearman's ρ and Wilcoxon's rank sum test were used to test associations for skewed variables.

Table 4. Multivariate analysis of factors associated with death (n = 33)

Variable	OR	95% CI	*p*
Hyperglycemia	3.12	1.26–7.7	.013
Male gender	0.48	0.22–1.07	.07
PIM2	1.67	1.29–2.16	<.001
Emergency admission	2.78	0.88–8.78	.081

OR, odds ratio; CI, confidence interval; PIM, Pediatric Index of Mortality.

The PIM2 OR is that associated with a one-unit increase in the PIM2 logit, indicating increasing severity of illness.

To estimate the effect of hyperglycemia (exposure) on clinically significant organ failure (PELOD ≥10, outcome) adjusted for possible confounders, we used a multiple logistic regression model as follows (31). The variables initially included in the model were severity of illness (using Pediatric Index of Mortality 2, which does not contain glucose) (27), gender, age (infant or not), recovery from a procedure, emergency or elective admission, cardiopulmonary bypass, insulin therapy, and center. We included interaction terms with hyperglycemia for all these variables except center. All the possible confounders were selected in advance and were binary except Pediatric Index of Mortality 2 (continuous). Starting with the full model, we first excluded interactions as a group and then assessed confounding by the effect of each potential confounder on the OR for hyperglycemia on outcome. Variables which, when removed, altered the OR by >10% or increased precision for the OR were retained in the model (31). We used eight equal groups for Hosmer-Lemeshow goodness-of-fit tests.

For statistical analysis, we used Stata version 8.0 (32).

RESULTS

Demographics and PICU Outcomes. One center collected data for August and September 2004. The other eight collected data for September and October 2004. There were 410 children ventilated >12 hrs. One subject had no glucose measurement and was excluded from further analysis. Table 1 describes the sample and the ANZPIC Registry population for the same period. Subjects were grouped by principal diagnosis, based on ANZPIC Registry diagnostic categories (30), shown in Table 2. There were 33 PICU deaths (8%), and three subjects were still in a PICU at the end of the study. These three were treated as survivors for the purpose of analysis.

Glucose Measurements. From 409 subjects, there were 9,604 glucose measurements. The mean was 6.8, SD 2.7 mmol/L. Ninety-six (1%) measurements were <3.0 mmol/L, of which two (2%) were associated with concurrent insulin use; 4,870 (50.7%) and 3,092 (32.2%) measurements were >6.1 and >7.0 mmol/L, respectively. The median peak value for each subject was 9.0 (7.2–12.1) mmol/L. Of 409 subjects, 363 (89%) and 310 (76%) had peak values >6.1 and >7.0 mmol/L, respectively. The median time to peak was 7 (0–30) hrs, and 129 (32%) subjects' peak measurement was their first measurement. The median area under the glucose-time curve above a threshold of 6.1 mmol/L was 28.4 (5.7–87.8) $mmol \cdot L^{-1} \cdot hr^{-1}$. Most of the exposure to hyperglycemia occurred within the first 48 hrs; the median percentage of the total area from the first 48 hrs was 98% (38% to 100%). We recollected and re-entered the glucose measurements from day 1 for a random sample of 37 patients (165 measurements, one missing) and found a mean difference compared with the original data collection of −0.1, SD 0.9 mmol/L.

PELOD Scores. The median PELOD was 12 (11–21). Three hundred forty-two (84%) subjects had PELOD ≥10. PELOD ≥10 was associated with death ($p = .003$, Fisher's exact test). No subject with PELOD <10 died. The area under the receiver operating characteristic curve for PELOD as a predictor of death was 0.83 (0.76–0.90). Two hundred thirty (56%) subjects had PELOD ≥12. For 328 (80%) subjects, the maximum PELOD occurred on day 1. Overall, mean PELOD decreased over time (Fig. 1).

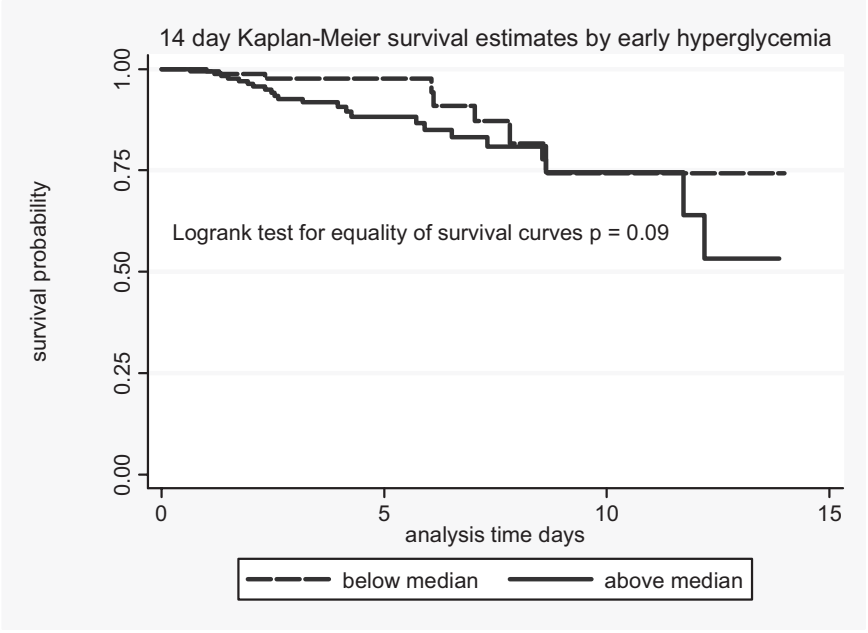

Figure 2. Fourteen-day Kaplan-Meier survival estimates by early hyperglycemia.

We recollected and re-entered day 1 organ data in 44 patients. Two would have changed category for PELOD ≥10.

Association Between Hyperglycemia and Clinically Significant Organ Failure (PELOD ≥10). Univariate analysis of the association between variables and clinically significant organ failure (PELOD ≥10) is shown in Table 3. There was a crude association between PELOD ≥10 and hyperglycemia.

When we adjusted for potential confounders, as specified previously, hyperglycemia remained strongly associated with clinically significant organ failure and PELOD ≥12: OR 3.41 (1.91–6.10), $p < .001$, and 3.48 (2.31–5.26), $p < .001$, respectively. The models included emergency admission, although not statistically significant ($p = .79$ and .75, respectively), because it increased the precision for the ORs for hyperglycemia. Insulin could not be fitted into a full model because few subjects received it. The models fitted well: Hosmer-Lemeshow chi-square = 0.61, $p = .74$, and .82, $p = .66$, respectively.

Hyperglycemic subjects had a crude mortality rate of 13% (26 of 208) vs. 3% (7 of 201) for nonhyperglycemic subjects ($p = .001$). Factors associated with death are shown in Table 4. The other variables were included in the model because of their effect on the OR for hyperglycemia or its precision. The model fitted well: Hosmer-Lemeshow chi-square = 5.66, $p = .46$.

Other Measures of Hyperglycemia. For PELOD ≥10, defining hyperglycemia as >7.0 mmol/L yielded similar results.

We also examined the effect of exposure to early hyperglycemia, defined by AUC >6.1 mmol/L in the first 48 hrs. For PELOD ≥10, PELOD ≥12, and death, the adjusted ORs were 2.11 (1.22–3.66), $p = .008$; 3.26 (2.08, 4.70), $p < .001$; and 2.86 (1.18, 6.92), $p = .02$, respectively. However, early hyperglycemia predicted neither an increase in PELOD from day 1 (OR 1.40, 0.86–5.6, $p = .18$) nor a PELOD ≥10 after day 2 (OR 1.70, 0.64–4.55, $p = .287$). Kaplan-Meier survival curves were similar for both early glycemia groups (Fig. 2). Early hyperglycemia was significantly but weakly associated with length of stay (Spearman's ρ 0.22, $p < .001$).

Dose-Response Relationship. We divided the total glucose-time AUC, without using a glucose threshold, into quarters categorized as dummy variables. The logistic model has PELOD ≥10 as the outcome and the lowest category as the reference. The ORs for the higher quarters in ascending order, compared with the lowest, were 0.80 (0.40–1.61), $p = .53$; 5.07 (1.99–12.9), $p = .001$; and 9.54 (2.97–30.6), $p < .001$, respectively. For PELOD ≥12, they were 0.98 (0.52–1.82), $p = .94$; 2.33 (1.25–4.34), $p = .008$; and 4.63 (2.36–9.07). However, there was no evidence for a dose-response relationship for death (results not shown).

Glucose Management. Twenty subjects (5%) had a documented glucose target range. Eighteen subjects received insulin infusions, seven without a documented target range. Two had subcutaneous insulin. One had both intravenous and subcutaneous insulin, and one had subcutaneous insulin only.

DISCUSSION

Hyperglycemia is common (>50% of all measurements are >6.1 and 89% subjects had at least one measurement >6.1 mmol/L) in ventilated children in the PICU and occurs early (median 7 hrs after admission). However, glucose control targets and insulin are seldom used in Australasian PICUs. Hypoglycemia is uncommon and infrequently associated with insulin use.

Hyperglycemia and organ failure, measured by PELOD, are independently associated. There is evidence for a dose-response relationship. Most (80%) of maximum PELOD scores are on day 1, and early hyperglycemia does not predict an increase in PELOD. There was an association between hyperglycemia and mortality, adjusted for other factors, including severity of illness, but this was not the primary study outcome.

The strengths of the study were as follows. We selected and studied prospectively a sick but readily identifiable sample (i.e., ventilated >12 hrs with a higher mortality than the overall PICU population). All glucose measurements were included, enabling us to measure time-weighted glucose exposure.

The weaknesses were as follows. First, the frequency of glucose measurement was not determined by protocol but by clinical practice, potentially introducing detection bias. However, this method reflects clinical practice, where glucose is measured as indicated. We cannot comment on the effect of insulin, as too few subjects had insulin. Second, the poor calibration of the PELOD score is a potential limitation; however, for models designed to describe the severity of organ failure, discrimination is more important than calibration (23). The discrimination of PELOD, both in the original report (22) and in this study, was adequate. Third, the observational design cannot prove causation but can only demonstrate association.

Our findings were similar to those of other adult and pediatric studies, in that hyperglycemia was associated with harm.

Our sample had the same mortality rate as the control group in the study by Van den Berghe et al. (8%) (5).

Five other PICU studies found harm associated with hyperglycemia, despite selecting different populations and using different definitions of hyperglycemia (16, 17, 28, 29, 33). Definitions of hyperglycemia were peak glucose (16, 17, 29), peak glucose exceeding thresholds (28, 33), and duration above a threshold (16, 17). One study also found that mortality was associated with hypoglycemia (33). The populations studied were unselected PICU patients (28, 33), those requiring mechanical ventilation or vasoactive infusions (17), postoperative cardiac infants (16), and those with septic shock (29). Hyperglycemia was associated with mortality whether adjusted for severity of illness (17, 29) or not (16, 28, 33). However, hyperglycemia was not independently associated with harm in children ventilated for bronchiolitis (34).

Mechanisms postulated for a harmful effect of hyperglycemia have been reviewed elsewhere (17, 35). Hyperglycemia may be toxic to cells from intracellular glucose overload, or the side effects of glycolysis and oxidative phosphorylation, particularly in cells where glucose uptake is insulin-independent. These include cells of the central and peripheral nervous systems, immune cells, epithelial cells, and endothelial cells and may explain the benefits of glucose control for preventing seizures, polyneuropathy, and sepsis. While benefits are probably from glucose control, insulin itself may confer a benefit through an anti-inflammatory effect, preventing endothelial dysfunction and hypercoagulability, and an antiapoptotic effect (35).

A randomized controlled trial of intensive insulin therapy in critically ill children is needed. However, since we found that the highest daily PELOD score occurs early, it is an unsuitable outcome measure, as it is unlikely to be influenced by therapy. Mortality remains the most appropriate and clinically important outcome and was associated with hyperglycemia, but power for a trial with this outcome is problematic. A 22% relative reduction as found by Van den Bergh et al. (5) means an absolute mortality reduction from 8% to 6% in our population, requiring a sample size of >5,000 for 80% power. Larger effect sizes may not be biologically plausible.

CONCLUSIONS

It is premature to conclude that treating hyperglycemia is beneficial in PICU patients, because we have shown only an association between hyperglycemia and organ failure and death, not proven causation. Both hyperglycemia and organ failure occurred early, and early hyperglycemia did not predict worsening or late development of organ failure. Hyperglycemia and organ failure are early, simultaneous markers of severity.

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Appendix. Methods for measuring blood glucose

	No. of Patients	Method	Device Name
Princess Margaret Hospital, Perth, WA	27	Blood gas analyzer	Bayer 865 Rapidlab
Women's and Children's Hospital, Adelaide, SA	24	Glucometer	Abbott MediSense Optium
Royal Children's Hospital, Melbourne, VIC	110	Blood gas analyzer	Bayer 865 Rapidlab
Children's Hospital at Westmead, Sydney, NSW	58	Blood gas analyzer	Radiometer ABL 625
Sydney Children's Hospital, Sydney, NSW	46	Blood gas analyzer	Radiometer ABL 725
Royal Children's Hospital, Brisbane, QLD	31	Blood gas analyzer	Radiometer ABL 700
Mater Miseracordiae Hospital, Brisbane, QLD	19	Blood gas analyzer	Radiometer ABL 700
Prince Charles Hospital, Brisbane, QLD	25	Blood gas analyzer	Radiometer ABL825 Flex
Starship Hospital, Auckland, NZP	70	Blood gas analyzer	Radiometer ABL 700