Association of timing, duration, and intensity of hyperglycemia with intensive care unit mortality in critically ill children

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LEARNING OBJECTIVES

On completion of this article, the reader should be able to:

1. Recall the diseases in critically ill adults and children in which hyperglycemia is associated with a poor outcome.
2. Identify that both peak blood glucose level and duration of hyperglycemia are associated with increased risk of mortality in critically ill children.
3. Identify potential biological mechanisms by which hyperglycemia can be detrimental in critically ill infants and children.

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Objective: **To study the association of timing, duration, and intensity of hyperglycemia with pediatric intensive care unit (PICU) mortality in critically ill children.**

Design: **Retrospective cohort study.**

Setting: **PICU of a university-affiliated, tertiary care, children's hospital.**

Patients: **A total of 152 critically ill children receiving vasoactive infusions or mechanical ventilation.**

Interventions: **None.**

Methods: **With institutional review board approval, we reviewed a cohort of 179 consecutive children, 1 mo to 21 yrs of age, treated with mechanical ventilation or vasoactive infusions. We excluded 18 with $<3\ \mu g \cdot kg^{-1} \cdot min^{-1}$ dopamine only, diabetes, or solid organ transplant and nine who died within 24 hrs of PICU admission. Peak blood glucose (BG) and time to peak BG during PICU admission, duration of hyperglycemia (percentage of PICU days with any BG of >126 mg/dL), and intensity of hyperglycemia (median BG during first 48 PICU hours) were analyzed for association with PICU mortality using chi-square, Student's *t*-test, and logistic regression.**

Measurements and Main Results: **Peak BG of >126 mg/dL occurred in 86% of patients. Compared with survivors, nonsurvivors had higher peak BG (311 ± 115 vs. 205 ± 80 mg/dL, $p < .001$). Median time to peak BG was similar in nonsurvivors (23.5 hrs; interquartile ratio, 5–236 hrs) and survivors (19 hrs; interquartile ratio, 6–113 hrs). Duration of hyperglycemia was longer in nonsurvivors (71% ± 14% of PICU days) vs. survivors (37% ± 5% of PICU days, $p < .001$). Nonsurvivors had more intense hyperglycemia during the first 48 hrs in the PICU (126 ± 38 mg/dL) vs. survivors (116 ± 34 mg/dL, $p < .05$). Univariate logistic regression analysis showed that peak BG and the duration and intensity of hyperglycemia were each associated with PICU mortality ($p < .05$). Multivariate modeling controlling for age and Pediatric Risk of Mortality scores showed independent association of peak BG and duration of hyperglycemia with PICU mortality ($p < .05$).**

Conclusions: **Hyperglycemia is common in critically ill children. Peak BG and duration of hyperglycemia are independently associated with mortality in our PICU. A prospective, randomized trial of strict glycemic control in this subset of critically ill children who are at high risk of mortality is both warranted and feasible. (Pediatr Crit Care Med 2004; 5:329–336)**

KEY WORDS: hyperglycemia; children; pediatrics; mortality; survival; mechanical ventilation; vasopressor infusions; logistic model

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Hyperglycemia is often perceived as a stress response that reflects the severity of acute illness. Physicians typically treat hyperglycemia only after blood glucose concentrations exceed the renal threshold for resorption of glucose (200–250 mg/dL [11.1–13.8 mmol/L]), resulting in an osmotic diuresis (1). This is frequently due to the perception that avoidance of hypoglycemia and its potential consequences are more important than glycemic control while patients are hospitalized (2).

Several clinical studies indicate that hyperglycemia is a risk factor for adverse outcomes during acute illness. In adults who had experienced ischemic stroke, glucose values in excess of 108–144 mg/dL (6.0–8.0 mmol/L) were associated with a 3-fold increase in risk of mortality (odds ratio, 3.1; 95% confidence interval [CI], 2.5–3.8) and seem to be related to the degree of permanent disability after the stroke (3). Likewise, in adults who had just experienced myocardial infarction, glucose values greater than 110–144 mg/dL (6.1–8.0 mmol/L) were associated with at least a 3-fold increase in risk of mortality (odds ratio, 3.9; 95% CI, 2.9–5.4) and a higher risk of heart failure (4). Hyperglycemia has also been shown to be an independent predictor of poor outcome in patients with severe head injury (5) and multiple-system trauma (6). Similarly, in children, hyperglycemia, and especially its persistence over time, seems to be an important negative prognostic factor in those with head injury (7, 8). Hyperglycemia has also been associated with death after gunshot wounds to the brain in children (9). Similarly, hyperglycemia has been shown to be associated with diminution in pulmonary function, even in nondiabetic adults (10). Hyperglycemia also results in delayed gastric emptying and decreased small intestinal motility in adults (11, 12). Other studies have demonstrated the association of hyperglycemia with infections both in adults and children (13–15).

Control of hyperglycemia during acute illness in adults has been associated with improved outcomes (16–18). There are, however, no studies that have examined the frequency and association of hyperglycemia with mortality in critically ill children in the intensive care unit (ICU) who are mechanically ventilated or receiving vasoactive agents and, more importantly, the effect of glycemic control on mortality in such children. A reduction in mortality in acutely ill children from strict glycemic control (similar to the results obtained in adults) would represent a major advance in pediatric critical care. We hypothesize that hyperglycemia is common in acutely ill children and that timing, duration, and intensity of hyperglycemia are associated with mortality. We also propose that it is feasible to examine the effect of control of hyperglycemia on mortality in acutely ill children admitted to intensive care.

MATERIALS AND METHODS

The hospital institutional review board approved the study with waiver of informed consent. The setting for the study was a 38-bed pediatric ICU (PICU) at a tertiary care children's hospital, which has approximately 2,700 admissions every year. The study design consisted of a retrospective review of consecutive children admitted to the PICU in a 6-mo period from December 2001 to May 2002. Eligible patients were identified through a combination of the databases of the PICU, pharmacy, and respiratory therapy divisions. Patients were eligible for inclusion if they were between the ages of 1 mo and 21 yrs and if they were critically ill (defined as the need for mechanical ventilation or vasoactive infusions for a period of >24 hrs). We excluded patients with a diagnosis of diabetes mellitus requiring insulin replacement, those who had undergone solid organ transplants, and those who were exclusively receiving low-dose dopamine infusions (defined as infusion rates of $\leq 3\ \mu g \cdot kg^{-1} \cdot min^{-1}$). We also excluded those patients who died within 24 hrs of ICU admission. In addition, all postoperative cardiac surgery patients were cared for in a separate cardiac ICU and were not included for analysis in the study.

For the purpose of this study, we defined normoglycemia as a blood glucose level of <110 mg/dL (6.1 mmol/L) and hyperglycemia as a blood glucose level of >126 mg/dL (7.0 mmol/L). This was based on criteria for the diagnosis of diabetes mellitus as determined by the National Diabetes Data Group and the World Health Organization (19). Blood glucose levels between 110 and 126 mg/dL (6.1–7.0 mmol/L) were considered to represent a state of abnormal glucose tolerance. Blood glucose values included both whole-blood bedside glucometer (Surestep Flexx, Lifescan, Milpitas, CA) and chemistry laboratory serum glucose values (Vitros 950, Ortho-Clinical Diagnostics, Rochester, NY). The bedside glucometer is calibrated and checked daily, and the laboratory glucose analyzer is calibrated every 6 mos and checked daily. We defined peak blood glucose levels as the highest blood glucose levels measured during PICU admission, timing of hyperglycemia as time to peak blood glucose levels from admission to the PICU, duration of hyperglycemia as the percentage of PICU days with any measured blood glucose level of >126 mg/dL (7.0 mmol/L), and intensity of hyperglycemia as median blood glucose levels during the first 48 hrs of PICU admission. Demographic data, diagnoses at admission to the PICU, data on mechanical ventilation and vasoactive infusions (including type of drug), serial blood glucose levels, times and dates of collection, and use of steroids (including types and doses) were obtained from review of individual charts. Pediatric Risk of Mortality (PRISM) scores at 12 and 24 hrs (based on PRISM III guidelines) and highest blood glucose levels at 12 and 24 hrs used in calculation of PRISM scores were obtained from the PICU database.

The data are presented as mean ± SD or median (interquartile range). Normally distributed continuous variables were compared using the Student's *t*-test, and non–normally distributed variables were compared by the Mann-Whitney *U*-test. Categorical variables were compared using the chi-square test or Fisher's exact test. After determination of individual factors associated with mortality by univariate analysis, a multiple logistic regression model of important factors associated with mortality was developed. The results of the regression are presented as adjusted odds ratios with 95% CIs. In all comparisons, $p < .05$ is considered significant. Finally, based on the prevailing PICU mortality rate, a power analysis was performed to calculate the sample size for a prospective, randomized trial to study the effect of strict glycemic control on mortality. The feasibility of performing such a study in a single large center was then determined by observing the frequency of patients eligible for such a trial and calculating the time needed for their enrollment.

RESULTS

A total of 1,350 patients were admitted to the PICU during the 6-mo period between December 2001 and May 2002. A review of these patients revealed that 179 patients were eligible for inclusion into the study. Of these 179 patients, 12 were on exclusive low-dose dopamine, four were recipients of solid-organ transplants, and two had diabetes mellitus requiring insulin; these patients were excluded from the study. Another nine died within 24 hrs of PICU admission and were excluded, leaving 152 patients for analysis. The characteristics of these patients are shown in Table 1.

PICU mortality in the study population was 15% (23/152), which conformed to mortality predicted by PRISM scores at

24 hrs (15%; chi-square goodness of fit, $p = .85$). The subgroup of patients who were managed with both mechanical ventilation and vasoactive infusions had a mortality of 55% (17/31; mortality predicted by PRISM scores for this group at 24 hrs was 50%).

Survivors and nonsurvivors (in the ICU) were comparable with regard to demographic variables such as age, weight, and sex (Table 2). There was no significant difference in the institution and mean duration of mechanical ventilation between the two groups, nor was there any difference with regard to steroid use or dose of steroids used. Nonsurvivors were significantly more likely to receive more vasoactive infusions than survivors (2 vs.1, $p < .001$). Nonsurvivors were also significantly more likely to have been receiving epinephrine or norepinephrine than survivors.

Prevalence and Timing of Hyperglycemia. At 24 hrs after PICU admission, hyperglycemia was present in 54% of patients, whereas only 35% were normoglycemic. The remaining 11% had values that represented abnormal glucose tolerance. Peak blood glucose levels in the hyperglycemia range occurred in 86% of patients during their PICU admission, whereas only 7% of patients had peak blood glucose levels in the normoglycemic range. Seven percent of patients had peak blood glucose levels that represented abnormal glucose tolerance. Nonsurvivors had higher mean blood glucose levels at 24 hrs (173 ± 110 mg/dL) than survivors (129 ± 40 mg/dL, $p < .001$). Blood glucose levels of >150 mg/dL (8.3 mmol/L) at 24 hrs were associated with almost a 3.5-fold increase in risk of mortality (odds ratio, 3.4; 95% CI, 1.4–8.6, $p < .01$). This level of hyperglycemia was

Table 1. Characteristics of study patients ($n = 152$)

Variable	Median (IQR) or n (%)
Age, yrs	6 (1–12)
Weight, kg	20 (9.5–40)
Sex	
Males	85 (56)
Females	67 (44)
Ethnicity	
White	73 (48)
Black	43 (28)
Hispanic	13 (9)
Asian	7 (5)
Other	16 (10)
Admission diagnoses	
Respiratory	35 (23)
Cardiac (nonsurgical)	7 (5)
Infections	38 (25)
Trauma	13 (9)
Other (oncology, renal, etc.)	59 (38)
Mechanical ventilation	
Yes	116 (76)
No	36 (24)
Duration of ventilation, days	5.5 (3–10)
Vasoactive infusions	
Yes	67 (44)
No	85 (56)
Number of infusions	2 (1–2)
Steroids	
Yes	75 (49)
No	77 (51)
PRISM score at 12 hrs	9 (5–15)
PRISM score at 24 hrs	11 (6–18)

IQR, interquartile range; PRISM, Pediatric Risk of Mortality.

Table 2. Comparison of survivors ($n = 129$) and nonsurvivors ($n = 23$)

Variable	Survivors	Nonsurvivors	p Value[a]
Age, yrs[b]	6.6 ± 5.7	8.4 ± 6.7	.18
Sex (% boys)	75/129 (58)	10/23 (43)	.28
Weight, kg[b]	20 ± 17.4	33.4 ± 24.6	.15
Mechanical ventilation	98/129 (76%)	18/23 (78%)	1
Duration of mechanical ventilation, days[b]	10 ± 8.4	9.6 ± 8.6	.9
Vasoactive infusions	49/129 (38%)	18/23 (78%)	<.001
Epinephrine	16/129 (12%)	14/23 (61%)	<.001
Norepinephrine	2/129 (2%)	3/23 (13%)	<.01
No. of vasoactive infusions[c]	1 (1–2)	2 (2–3)	<.001
Steroids used	61/129 (47%)	14/23 (61%)	.33
Steroid dose (expressed in terms of hydrocortisone equivalent), mg/kg	22.9 ± 3.4	24.3 ± 11	.84
PRISM score at 12 hrs[b]	9.6 ± 6.8	18.3 ± 11	<.001
PRISM score at 24 hrs[b]	11.1 ± 8	21.4 ± 10	<.001

PRISM, Pediatric Risk of Mortality.

[a]$p < .05$ considered significant; [b]data represented as mean ± SD; [c]data represented as median (interquartile range).

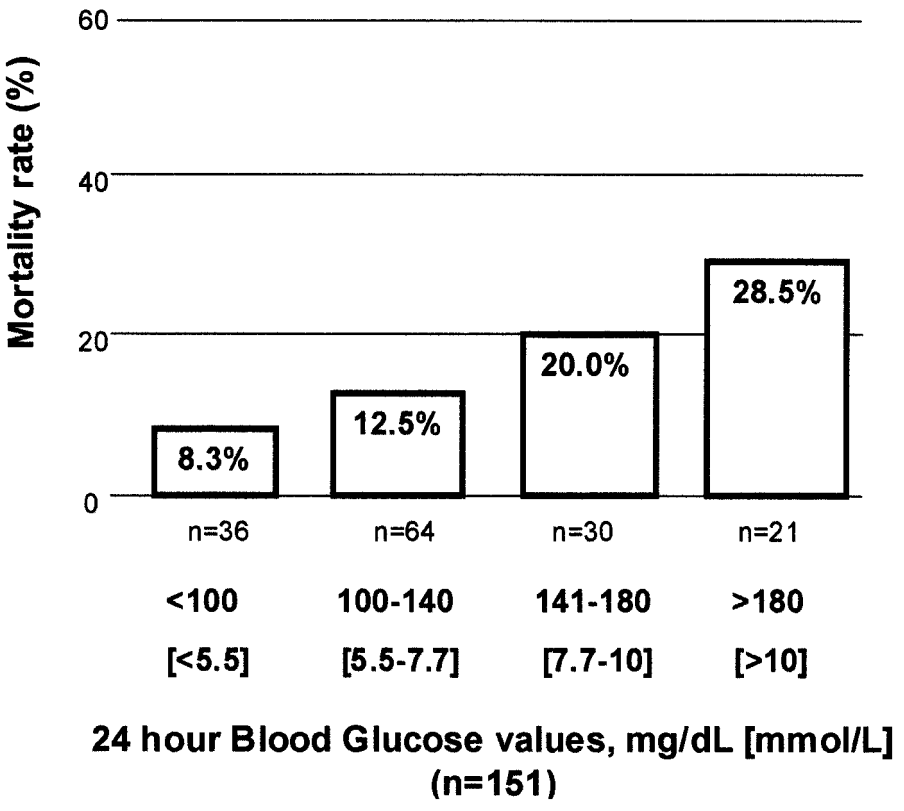

Figure 1. Correlation of blood glucose levels (mg/dL) at 24 hrs with mortality rates ($p < .001$, $r^2 = .18$, Spearman's rank-correlation coefficient). The *numbers* in *brackets* refer to values in mmol/L.

chosen based on similar levels examined in adults (3, 4). There was a positive correlation between blood glucose levels at 24 hrs and PICU mortality, which is illustrated in Figure 1 ($p < .001$, $r^2 = .18$, Spearman's rank-correlation coefficient). Compared with survivors, nonsurvivors had higher peak blood glucose levels (311 ± 115 mg/dL vs. 205 ± 80 mg/dL, $p < .001$). Median time to peak blood glucose levels was similar in both groups (Table 3).

Duration of Hyperglycemia. Duration of hyperglycemia was longer in nonsurvivors (71% ± 14% of PICU days) vs. survivors (37% ± 5% of PICU days, $p < .001$) (Table 3), with the mean duration for the entire cohort being 46% ± 9% of PICU days. Exposure to hyperglycemia for more than half of PICU days in which blood glucose was measured was associated with almost a 6-fold increased risk of mortality compared with exposure to hyperglycemia for less than half of measured PICU days (odds ratio, 5.9; 95% CI, 2.4–14.7; $p < .001$).

Intensity of Hyperglycemia. Nonsurvivors had significantly more intense hyperglycemia than survivors at all times during PICU admission (Table 3). Median blood glucose levels of >150 mg/dL (8.3 mmol/L) during the first 48 hrs of PICU admission were associated with a 3-fold increased risk of mortality compared with median levels of <150 mg/dL (odds ratio, 2.96; 95% CI, 1.06–8.33; $p < .05$). This level of hyperglycemia was chosen based on similar levels examined in adults (3, 4).

Blood glucose levels at 24 hrs ($p < .01$), peak blood glucose levels ($p < .001$), duration of hyperglycemia ($p < .001$), and intensity of hyperglycemia during the first 48 PICU hours ($p < .05$) were all associated with mortality by univariate logistic regression analysis (Table 4). Multivariate logistic regression analysis controlling for age, severity of illness, and epinephrine infusion demonstrated the independent associations of peak blood glucose levels and duration of hyperglycemia (percentage of PICU days with blood glucose of >126 mg/dL [7.0 mmol/L]) with mortality (both $p < .05$) (Table 5).

Hypoglycemia and Insulin Infusions. Hypoglycemia, defined as blood glucose of <50 mg/dL (2.8 mmol/L) occurred in 8% of the study population (12/152), with 17% of these patients (2/12) treated for symptoms (lethargy and tachycardia). Interestingly, 50% of hypoglycemic episodes (6/12) occurred in infants <1 yr of age. Insulin infusions for glucose control were used in 6% of the cohort (9/152); of these, 23% (2/9) developed hypoglycemia, but none were symptomatic. Insulin infusion use was not associated with a significantly higher risk of hypoglycemia of <50 mg/dL (2.8 mmol/L; odds ratio, 3.8; 95% CI, 0.7–14.0; $p = .2$) compared with those who did not receive insulin.

The feasibility of performing a prospective, randomized, controlled trial of strict glucose control comparable with recent adult studies was examined based on the estimate of prevailing PICU mortality of 20% (32/161) in the eligible study population (adjusted to include the nine patients who died within 24 hrs of admission and who were excluded from the review but would likely be included in a prospective trial of strict glucose control). To detect a 40% relative decrease in mortality similar to adult data (16) (i.e., absolute mortality risk decrease from 20% to 12%), a total of 518 patients (259 in the conventional treatment group and 259 in the strict glucose control group) would need to be enrolled, assuming a power of 80% and a significance level of 5%. Based on the hyperglycemia exhibited by eligible patients observed in this study and assuming 80% enrollment (dropouts, lack of consent, breach of protocol, etc.), such a study would be projected to take 2–3 yrs in a single large center such as ours.

DISCUSSION

The findings of our study emphasize higher than expected prevalence of hyperglycemia in critically ill children and, in particular, the independent association of peak blood glucose levels and duration of hyperglycemia of >126 mg/dL (7.0 mmol/L) with mortality. Although other studies have affirmed the association of hyperglycemia with poor outcomes in specific disease states (3–9), this is the first study that has demonstrated these associations in critically ill children needing mechanical ventilation or vasoactive infusions, independent of disease category.

The association of hyperglycemia with organ/tissue dysfunction and poor outcomes has been well documented in laboratory research settings. Findings in both focal and global models of cerebral ischemia have revealed that hyperglycemia exacerbates intracellular acidosis (20–22), accumulation of extracellular glutamate (23), brain edema formation (24), blood–brain barrier disruption (25), and a tendency toward hemorrhagic transformation of ischemic infarcts (26). In the setting of ischemic brain injury, hyperglycemia may worsen injury via promotion of anaerobic metabolism and intracellular metabolic acidosis. Hyperglycemia-induced reduction of cerebral adenosine production may also play a role in ischemic brain injury (27). Hyperglycemia also has deleterious effects on the rat myocardium, as evidenced by enhanced inducible nitric oxide synthase gene expression. Up-regulation of inducible nitric oxide synthase and raised nitric oxide generation are accompanied by a

Table 3. Characterization of blood glucose levels in study population

Variable	Survivors (n = 129)	Nonsurvivors (n = 23)	*p* Value[a]
BG level at 12 hrs, mg/dL (mmol/L)[b]	149 ± 64 (8.2 ± 3.4)	178 ± 94 (9.8 ± 4.8)	.06
BG level at 24 hrs, mg/dL (mmol/L)[b]	129 ± 40 (7.1 ± 2.3)	173 ± 110 (9.6 ± 6.2)	<.001
Peak BG level, mg/dL (mmol/L)[b]	205 ± 80 (11.3 ± 4.6)	311 ± 115 (17.2 ± 6.2)	<.001
Median time to peak BG, hrs (IQR)	19 (6–113)	23.5 (5–236)	.3
Duration, % PICU days >126 mg/dL[b]	37 ± 5	71 ± 14	<.001
Median BG levels in first 24 PICU hrs, mg/dL (mmol/L)[b]	130 ± 41 (7.2 ± 2.3)	166 ± 76 (9.2 ± 4.3)	<.05
Median BG levels in first 48 PICU hrs, mg/dL (mmol/L)[b]	116 ± 34.2 (6.4 ± 2.3)	126 ± 38.4 (7 ± 1.9)	<.05
Median BG levels in entire PICU stay, mg/dL (mmol/L)[b]	113 ± 26.2 (6.3 ± 3.4)	140 ± 37 (7.7 ± 1.9)	<.001
Median frequency of BG sampling, times/day (IQR)	2 (1–5)	4 (1–6)	.26

BG, blood glucose; IQR, interquartile range; PICU, pediatric intensive care unit.
[a]$p < .05$ was considered significant; [b]data represented as mean ± SD.

Table 4. Univariate analysis of factors[a] associated with mortality

Variable	Adjusted Odds Ratio	95% Confidence Interval	*p* Value[b]
Age	1.05	0.98–1.13	.18
Mechanical ventilation[c]	0.96	0.33–2.82	.94
Vasoactive infusions[c]	5.88	2.05–16.84	<.001
Epinephrine[c]	11	4–29.5	<.001
Steroids[c]	1.73	0.7–4.29	.23
Steroid dose	1.01	0.99–1.02	.26
12-hr PRISM score	1.13	1.07–1.20	<.001
24-hr PRISM score	1.14	1.08–1.20	<.001
Blood glucose level at 12 hrs	1.00	0.99–1.01	.07
Blood glucose level at 24 hrs	1.01	1.00–1.02	<.01
Peak blood glucose	1.01	1.00–1.02	<.001
Time to peak blood glucose	1.00	0.99–1.01	.06
Duration of hyperglycemia	1.03	1.02–1.05	<.001
Median blood glucose during first 48 PICU hrs	1.01	1.00–1.02	<.05

PRISM, Pediatric Risk of Mortality; PICU, pediatric intensive care unit.

[a]All continuous variables, unless otherwise specified; [b]$p < .05$ was considered significant; [c]dichotomous variables.

Table 5. Multivariate analysis of factors[a] associated with mortality

Variable	Adjusted Odds Ratio	95% Confidence Interval	*p* Value[b]
Age	0.96	0.87–1.06	.4
24-hr PRISM score	1.08	1.01–1.16	<.05
Epinephrine[c]	4.09	1.22–13.75	<.05
Peak blood glucose	1.01	1.00–1.02	<.05
Time to peak blood glucose	1.00	0.99–1.00	.71
Duration of hyperglycemia	1.03	1.01–1.05	<.05
Median blood glucose during first 48 PICU hrs	0.99	0.98–1.01	.61

PRISM, Pediatric Risk of Mortality; PICU, pediatric intensive care unit.

[a]All continuous variables, unless otherwise specified; [b]$p < .05$ was considered significant; [c]dichotomous variable.

marked concomitant increase of superoxide production, a condition favoring the production of peroxynitrite. This is a powerful pro-oxidant that can mediate the toxic effects of high glucose on the myocardium by itself or via the formation of nitrotyrosine, as suggested by the detection of cell apoptosis (28). Myocardial cell apoptosis is also mediated, at least in part, by activation of the cytochrome c-activated caspase-3 pathway, which may be triggered by reactive oxygen species derived from high levels of glucose (29).

Other studies have demonstrated the adverse effects of hyperglycemia on pulmonary and renal tissue through mechanisms involving nonenzymatic glycosylation of collagen, activation of protein kinase C resulting in production of reactive free radical production, and by increased production of sorbitol with concomitant depletion of intracellular glutathione (30–33). *In vitro* studies have shown that exposure of monocytic cell lines to hyperglycemia results in the elevation of nuclear factor-κB and activator protein-1 (a transcription factor that regulates the expression of metalloproteinases) with an increase in the expression of tumor necrosis factor-α, a proinflammatory cytokine (34). Figure 2 depicts the different pathways by which hyperglycemia is postulated to cause damage at the cellular level.

We found hyperglycemia (blood glucose level of >126 mg/dL [7.0 mmol/L]) to be surprisingly frequent, occurring in more than half of our study population at 24 hrs. In adults, hyperglycemia (defined as >126 mg/dL [7.0 mmol/L]) was present in 38% of patients admitted to the general hospital wards (one third of these patients had no history of diabetes) (35). In our study, 25% had blood glucose levels of >150 mg/dL (8.3 mmol/L) at 24 hrs. In comparison, hyperglycemia (defined as >150 mg/dL [8.3 mmol/L]) occurred in 3.8% of children presenting to an urban pediatric emergency department (36). Similarly, hyperglycemia (defined as >180 mg/dL [10.0 mmol/L]) was present in 2.7% of children at admission to a rural district hospital (37), whereas another study concluded that transient hyperglycemia of >150 mg/dL (8.3 mmol/L) occurred in 4.7% of children with acute illness (38). The strikingly high prevalence of hyperglycemia in our critically ill study population underscores the need to recognize that hyperglycemia is common in such acutely ill children.

Our study also demonstrates the independent association of hyperglycemia with mortality in critically ill children receiving mechanical ventilation or vasoactive infusions. Blood glucose levels at 24 hrs in excess of 150 mg/dL (8.3 mmol/L) on univariate analysis were associated with almost a 3.5-fold increase in risk of mortality (odds ratio, 3.4, 95% CI, 1.4–8.6; $p < .01$). Likewise, intense exposure to median blood glucose levels of >150 mg/dL (8.3 mmol/L) during the first 48 hrs of PICU admission was associated with a 3-fold increased risk of mortality. This association of hyperglycemia with increased mortality risk is similar to the data from adult studies on ischemic stroke and acute myocardial infarction (3, 4). Interestingly, prolonged duration (>50% of measured PICU days) of exposure to hyperglycemia was associated with almost a 6-fold increase in risk of PICU mortality. The association of peak blood glucose levels and duration of hyperglycemia with mortality was independent of age, severity of illness, epinephrine infusion, or steroid use, suggesting that hyperglycemia may not be just an epiphenomenon, but a maladaptive response to stress. Our study suggests that there is significant rationale to question the traditional approach of permissive hyperglycemia with blood glucose levels maintained just below the renal threshold (180–200 mg/dL [10.0–11.1 mmol/L]) in children receiving mechanical ventilation and/or vasoactive infusions.

Of interest, we observed a significant association between epinephrine use and mortality in the multivariate regression model of factors associated with mortality in this cohort. Several studies have documented that excessive vasoconstriction produced by epinephrine in the setting of post–cardiac arrest resuscitation worsens myocardial dysfunction and results in higher mortality (39, 40). We speculate that there might be similar mechanisms involved in this setting.

Steroid use was common in this cohort (50%) and most often in the setting of severe asthma, prevention of postextubation stridor, raised intracranial pres-

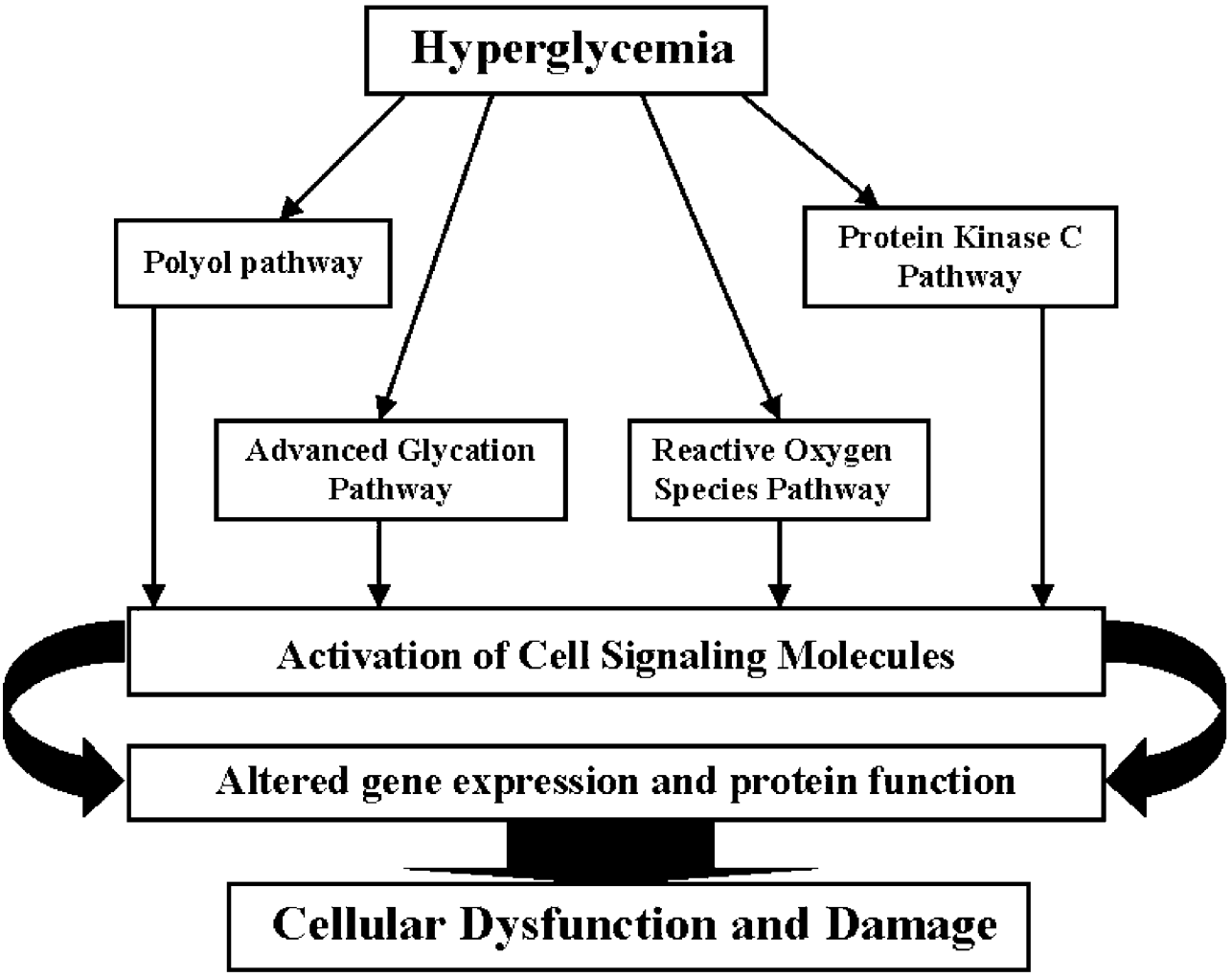

Figure 2. Overview of signaling mechanisms involved in cellular damage caused by hyperglycemia.

sure, and adrenal insufficiency (proven or suspected). We certainly could not rule out the possibility of steroids exacerbating hyperglycemia, and eventually outcome.

The findings of our study suggest that critically ill children in the ICU who are mechanically ventilated or receiving vasoactive infusions have a significant association of hyperglycemia with mortality, and they warrant consideration of a trial of strict glycemic control. A recent randomized trial in mechanically ventilated adults in a surgical ICU compared strict glycemic control (goal blood glucose levels of 80–110 mg/dL [4.4–6.1 mmol/L]) with conventional therapy to maintain blood glucose levels of 180–200 mg/dL (10–11.1 mmol/L). Strict glycemic control significantly reduced ICU mortality by 43% (death odds ratio, 0.52; 95% CI, 0.33–0.81), hospital mortality by 34%, mean ICU stay by 22%, and prevalence of bacteremia and hemodialysis by 50% (16). Another randomized trial of intensive insulin therapy (from admission to 3 mos after discharge) in diabetic patients after myocardial infarction (DIGAMI trial) demonstrated that the 1-yr mortality rate was 29% lower in patients receiving intensive insulin therapy than in the standard treatment group (17). Similarly, the risk of sternal wound infections after coronary artery bypass graft surgery was reduced by 58% with glycemic control of 150–200 mg/dL (8.3–11.1 mmol/L) (18).

Our power analysis demonstrates that such a prospective randomized trial of strict glycemic control (to a target range of 80–110 mg/dL [4.4–6.1 mmol/L]) in the pediatric population would be feasible to perform over 2 to 3 yrs in a single large center or shorter time period for a multiple center study. The adult study of intensive insulin therapy clearly demonstrates the reduction in both ICU and hospital mortality and associated morbidities with strict glycemic control (16). A similar reduction in PICU mortality in children would represent a tremendous advance in pediatric critical care. Furthermore, the adult trial by Van den Berghe et al. (41) suggests that it was feasible and safe to achieve and maintain blood glucose levels at <110 mg/dL (6.1 mmol/L) within 24 hrs by using a titration algorithm.

It is controversial whether the potential benefits are due to glycemic control or due to the correction of relative insulin deficiency. Normalization of glucose levels may restore immune function and limit the extent of ischemic damage to endothelial and neural tissues. In the study by Van den Berghe et al. (41), multivariate logistic regression analysis indicated that it was the lowered blood glucose level rather than the insulin dose that was related to reduced mortality (*p*

Peak blood glucose and duration of hyperglycemia are independently associated with mortality in our pediatric intensive care unit.

$< .0001$) and reduction in critical illness polyneuropathy ($p < .0001$), bacteremia ($p = .02$), and inflammation ($p = .0006$). Alternatively, administration of insulin may improve outcome by enhancing energy delivery to the ischemic myocardium (42, 43) and act as a positive inotropic agent, especially when used in conjunction with glucose and potassium (44). Insulin may also normalize endothelium-nitric oxide–dependent vasodilation by decreasing circulating fatty acids that are often elevated in insulin-resistant states, resulting in vascular oxidative stress and endothelial dysfunction (45). In addition, insulin may promote tissue repair through its anabolic effects and prevent or minimize critical illness neuropathy (46).

The main limitations of our study pertain to those of a retrospective cohort study. The method of blood glucose collection and analysis was not standardized. The timing of blood glucose estimation was also not standardized, limiting the estimated time interval patients were exposed to different blood glucose concentrations. Our study did not account for glucose infusion rates or hyperalimentation in the development of hyperglycemia, a matter of considerable importance in our study population. Most importantly, our study demonstrates an association between hyperglycemia and mortality that does not necessarily imply causation, and we cannot entirely exclude the interdependence of different variables related to glycemia such as epinephrine infusions or steroids. Cellular and tissue injury markers were not collected, and therefore, could not be examined to identify specific mechanisms of tissue damage related to glycemic control. A prospective, randomized trial of strict glycemic control is certainly needed to address these issues.

CONCLUSIONS

Hyperglycemia is common yet often underappreciated in critically ill children receiving mechanical ventilation or vasoactive infusions in the PICU. Intense hyperglycemia of >150 mg/dL (8.3 mmol/L) in the first 48 hrs in the PICU was associated with a 3-fold increase in mortality risk in such critically ill patients. Prolonged duration (>50% of measured PICU days) of hyperglycemia of >126 mg/dL (7.0 mmol/L) during the course of the PICU admission was associated with a 6-fold increase in mortality risk in the study population. Peak blood glucose levels and duration of hyperglycemia are independently associated with PICU mortality. In light of adult studies that demonstrate a similar association with mortality in patients with ischemic stroke and myocardial infarction, we believe that this is a valid association of sufficient concern. Based on the data presented in this study, a prospective, randomized trial of strict glycemic control in this subset of critically ill children who are at high risk of mortality is both warranted and feasible.

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