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Pediatrics 2006;118;173
DOI: 10.1542/peds.2005-1819

ARTICLE

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The authors have indicated they have no financial relationships relevant to this article to disclose.

ABSTRACT

OBJECTIVE. We evaluated retrospectively plasma glucose levels and the degree of hypoglycemia, hyperglycemia, and glucose variability in a PICU and then assessed their association with hospital length of stay and mortality rates.

METHODS. Electronic medical records at the Packard Children's Hospital at Stanford University were reviewed retrospectively for all PICU admissions between March 1, 2003, and March 31, 2004. Patients with a known diagnosis of diabetes mellitus were excluded. The prevalence of hyperglycemia was defined with cutoff values of 110, 150, and 200 mg/dL. Hypoglycemia was defined as ≤65 mg/dL. Glucose variability was assessed with a calculated glucose variability index.

RESULTS. In 13 months, 1094 eligible admissions generated 18 865 glucose values (median: 107 mg/dL; range: 13–1839 mg/dL). Patients in the highest maximal glucose quintile had a significantly longer median PICU length of stay, compared with those in the lowest quintile (7.5 days vs 1 day). Mortality rates increased as patients' maximal glucose levels increased, reaching 15.2% among patients with the greatest degree of hyperglycemia. Hypoglycemia was also prevalent, with 18.6% of patients (182 of 980 patients) having minimal glucose levels of ≤65 mg/dL. There was an increased median PICU length of stay (9.5 days vs 1 day) associated with glucose values in the lowest minimal quintile, compared with those in the highest quintile. Hypoglycemia was correlated with mortality rates; 16.5% of patients with glucose levels of ≤65 mg/dL died. Glucose variability also was associated with increased length of stay and mortality rates. In multivariate logistic regression analyses, glucose variability, taken with hyperglycemia and hypoglycemia, showed the strongest association with mortality rates.

CONCLUSIONS. Hyperglycemia and hypoglycemia were prevalent in the PICU. Hypoglycemia, hyperglycemia, and, in particular, increased glucose variability were associated with increased morbidity (length of stay) and mortality rates.

www.pediatrics.org/cgi/doi/10.1542/peds.2005-1819

doi:10.1542/peds.2005-1819

Key Words
hyperglycemia, hypoglycemia, glucose, variability, pediatric, intensive care, mortality, morbidity

Abbreviations
LOS—length of stay
IQR—interquartile range

Accepted for publication Jan 13, 2006

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RECENT STUDIES REVEALED a significant association between hyperglycemia and increased morbidity and mortality rates among adult patients, both diabetic and nondiabetic, in the ICU.[1–3] In particular, hyperglycemia has been shown to be a risk factor for poor outcomes in a variety of clinical settings, including trauma,[4,5] cardiac,[6–9] surgical,[10–14] head injury[15–17] and stroke[18,19] settings. Moreover, controlling hyperglycemia greatly improves the risk of morbidity and death among such critically ill adult patients. In a prospective randomized study, Van den Berghe et al[11,13] reported on 1548 patients admitted to an adult surgical ICU. During the admission, intensive treatment with intravenously administered insulin to control hyperglycemia (target range: 80–110 mg/dL) for both diabetic and nondiabetic patients reduced the risk of death in the ICU by 42%, the overall in-hospital mortality rate by 34%, the sepsis rate by 46%, the acute renal failure rate by 41%, and the median number of red blood cell transfusions by 50%. With less-stringent criteria for glycemic control (target range: 80–140 mg/dL), Krinsley[20] also reported that control of hyperglycemia greatly improved morbidity and mortality risks among critically ill adult patients. That study, in contrast to the predominantly postoperative, cardiothoracic, surgical population in the study by Van den Berghe et al,[11,13] was a historical control trial that included both medical and surgical patients. Recently, Van den Berghe et al[21] reported the results of a similarly designed, prospective, randomized study focusing on the effects of glycemic control (target range: 80–110 mg/dL) among medical, rather than surgical, ICU patients. Unlike in the surgical ICU study, tight glycemic control did not reduce the overall in-hospital mortality rate significantly. The mortality rate was reduced among patients with ICU admissions of >3 days, however. There was also a significant reduction in the morbidity rate, regardless of the number of days in the ICU.[21]

Less is known about the incidence of hyperglycemia, and its effects, in the PICU. Hyperglycemia is an important negative prognostic factor and an indication of poor neurologic long-term outcomes among pediatric patients with traumatic head injuries.[22,23] Among infants diagnosed as having necrotizing enterocolitis, hyperglycemia is common and is associated with longer lengths of stay (LOSs) and increased rates of late death in the NICU.[24] Srinivasan et al[25] focused on a subgroup of pediatric patients who received vasoactive infustions or mechanical ventilation. Those authors reported that peak blood glucose levels and duration of hyperglycemia were associated independently with PICU mortality rates. Recently, Faustino and Apkon[26] examined the prevalence of hyperglycemia among 942 nondiabetic patients and, with cutoff values of 120 mg/dL, 150 mg/dL, and 200 mg/dL, found a correlation between the relative risk of dying and hyperglycemia. To our knowledge, however, there has not been a study evaluating hypoglycemia, hyperglycemia, and glucose variability among critically ill children admitted to the PICU.

We performed a large, detailed, retrospective chart review of data for all pediatric patients admitted to our PICU during a 13-month period. This study was undertaken to gain a better understanding of glucose monitoring in the PICU and to broaden the understanding of how hypoglycemia and hyperglycemia, as well as glucose variability, are associated with morbidity (hospital LOS) and mortality rates for the PICU population.

METHODS

Study Design

In this single-center, institutional review board-approved, retrospective analysis, the computerized medical records system (MEDITECH, Westwood, MA) at the Lucile Packard Children's Hospital at Stanford University was reviewed. Electronic data from all PICU admissions between March 1, 2003, and March 31, 2004, were abstracted. The PICU is a hybrid unit with both medical and surgical patients. The unit includes an area devoted to cardiovascular surgical patients. All patients are treated by critical care physicians and nurses, with subspecialty consultation as needed. Only the last admission for an individual patient during the study period was analyzed, for complete assessment of mortality rates. Patients with a preexisting or new diagnosis of diabetes mellitus were excluded. In addition to all glucose values, patients' records were abstracted to determine general demographic information, admitting hospital service, and whether a surgical procedure was performed during the admission. During the study period, there was no glucose management protocol in place; therefore, all glucose values obtained were at the discretion of the treating physicians. Our main outcome measures were PICU LOS, overall hospital LOS, and mortality rate.

Glucose Parameters

Three methods for measuring glucose levels were used; plasma glucose levels were measured in the hospital clinical laboratory (Synchron LX20; Beckman, Fullerton, CA), whole-blood glucose levels were obtained in association with blood gas monitoring (Rapidlab 865; Bayer, Tarrytown, NY), and whole-blood glucose levels were measured with point-of-care devices (Precision PCx device and i-STAT 1 analyzer; Abbott Laboratories, Abbott Park, IL). Quality assurance for all 3 methods followed standard hospital laboratory procedures and included a 2-level protocol for liquid quality control. Control calibration was performed once per day and was repeated if the results were not within the prescribed range. System correlation calibration was performed every 6 months. All glucose values were reported as plasma equivalents. For each subject, the mean glucose level was calculated as the mean of all glucose measurements; the minimal

glucose level was the lowest and the maximal glucose level was the highest glucose measurement for the entire PICU admission. The glucose variability index was calculated for each patient as a measure of variability. This index was calculated for subjects with ≥3 glucose determinations, by dividing the absolute difference of sequential glucose values by the difference in collection time (in hours + 0.01). The mean of the ratios for each subject forms the variability index.[27] Patients were divided into quintiles on the basis of these glucose parameters, for evaluation of the association between these indices of glycemic control and PICU LOS, total hospital LOS, and mortality rate.

The formal definition of hypoglycemia in pediatrics varies depending on the age and fasting state of the individual. From a biochemical standpoint, counter-regulatory hormones are activated at levels between 65 and 68 mg/dL for pediatric patients.[28] On the basis of these findings, we chose to define hypoglycemia as a blood glucose concentration of ≤65 mg/dL.

There are no specific criteria for defining hyperglycemia among acutely ill, nondiabetic children. We chose hyperglycemia cutoff values of 110, 150, and 200 mg/dL for comparison, on the basis of both adult and pediatric studies.[1,8,11,25] Those reports included retrospective data as well as prospective interventional study data such as those obtained by Van Den Berghe et al[11] and Krinsley,[20] which demonstrated that maintaining tighter glucose control improved morbidity and mortality rates significantly among adult patients.

Statistical Analyses

Data analysis was performed with SAS software (version 9.1; SAS Institute, Cary, NC). Because many of the measures were not distributed normally, the median and interquartile range (IQR) (25th to 75th percentiles) are the main summary measures reported. When 2 variables were both ordinal (eg, LOS versus maximal glucose level quintile), significance was calculated with the nonparametric Wilcoxon rank-sum test. When quintiles were assessed, all 5 levels were used. When a variable was nominal (eg, death or glucose level above or below a certain cutoff value), significance was calculated with Pearson's χ^2 test. Multivariate logistic regression analysis was used to model the relationship between death and maximal glucose level, minimal glucose level, and glucose variability index (the 3 independent variables were rank-transformed). P values of $<.05$ were considered significant.

RESULTS

Patients

There were a total of 1275 patient admissions to the PICU at the Lucile Packard Children's Hospital between March 1, 2003, and March 31, 2004. Of these patients, 152 (11.9%) were admitted more than once during this period, 29 (2.3%) carried a known or new diagnosis of diabetes mellitus, and 7 were >21 years of age. After exclusion of these patients, 1094 patient admissions were included in subsequent analyses (Table 1).

Patient Demographic Features, LOS, and Mortality Rate

Among the 1094 eligible patient admissions, there were 492 girls (45%) and 602 boys (55%), ranging in age from 0 days to 21 years (median age: 2.8 years; IQR: 0.5–10.3 years) (Fig 1). Patient admissions according to subspecialty admitting service are listed in Table 2. For the total subject population of 1094, the median PICU LOS was 3 days (IQR: 1–7 days), and the median total hospital LOS was 7 days (IQR: 4–16 days). Of these patients, 764 (70%) underwent ≥1 surgical procedure during their admission, with a median PICU LOS of 3 days, compared with 1 day for the 330 patients (30%) without a surgical procedure. A total of 50 (4.6%) of the 1094 patients died during the study period (Table 1).

Glucose Data

In 13 months, the 1094 eligible patient admissions generated 18 865 glucose values (median: 107 mg/dL; range: 13–1839 mg/dL). Of these, 980 patients had ≥1 glucose measurement, whereas 114 patients had no glucose measurements during their admission. The median number of glucose values was 7 per patient admission (IQR: 3–19 measurements). All glucose values were expressed in plasma equivalents. Whereas 48.1% of the glucose testing was performed through standard laboratory blood draws, almost one half of the glucose values were obtained with point-of-care devices (i-STAT

TABLE 1 **Patient Demographic Features and General Study Categorization**

	No. (%)	PICU LOS, Median (IQR), d	Total LOS, Median (IQR), d	Deaths According to Demographic Factor, *n* (%)
Patient admissions	1094 (100)	3 (1–7)	7 (4–16)	50 (4.6)
Surgical[a]	764 (70)	3 (1–7)	8 (5–18)	22 (2.9)
Nonsurgical	330 (30)	1 (1–4)	5 (2–12)	28 (8.5)
Gender				
Male	602 (55)	3 (1–7)	7 (4–17)	28 (4.7)
Female	492 (45)	2 (1–6)	7 (4–15)	22 (4.5)

[a] Patient had ≥1 surgical procedure during admission.

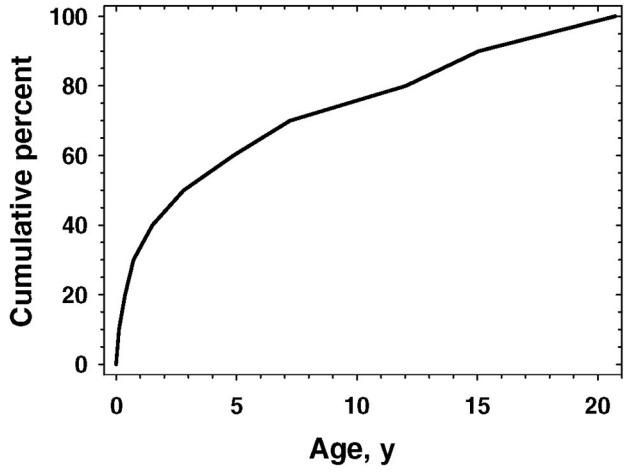

FIGURE 1
Subject population according to age.

TABLE 2 Patient Admissions According to Subspecialty Admitting Service

Subspecialty	No.	No. of Deaths
Intensive care	266	35
Cardiac surgery	237	4
Cardiology	130	1
Neurosurgery	91	1
General pediatrics	72	1
General surgery	49	0
Neonatology	48	2
Orthopedics	32	0
Ear, nose, and throat	28	0
Plastic surgery	28	0
Nephrology	24	0
Liver transplant	22	1
Hematology/oncology	20	3
Gastroenterology	14	1
Pulmonology	11	0
Other	22	1
Total	1094	50

1 Analyzer, 44.4%; Precision PCx, 1.3%); 6.1% of glucose values were obtained during blood gas analysis.

Hyperglycemia

Hyperglycemia was prevalent in our patient population. The maximal glucose levels were >110 mg/dL for 86.7% of patients ($n = 850$), >150 mg/dL for 61.0% of patients ($n = 598$), and >200 mg/dL for 35.2% of patients ($n = 345$).

We found an association between maximal glucose levels, LOS values, and mortality rates with each of these hyperglycemia cutoff values. Patients with maximal glucose levels of >110 mg/dL had a median PICU LOS of 4 days and a median total (hospital) LOS of 9 days, compared with 5 and 11 days, respectively, for those with glucose levels of >150 mg/dL and 6 and 14 days for those with levels of >200 mg/dL (all $P < .0001$, χ^2 test). In comparison, patients with maximal glucose levels of <110 mg/dL had a median PICU LOS of 1 day and a median total hospital LOS of 5 days (Table 3).

The effects of hyperglycemia on mortality rates were also quite significant, with 34 (68%) of the 50 deaths occurring among patients with maximal glucose levels of >200 mg/dL ($P < .0001$, χ^2 test). The mortality rate was 5.7% at glucose levels of >110 mg/dL ($P = .047$, χ^2 test), the mortality rate increased to 7.4% at glucose levels of >150 mg/dL ($P < .0001$, χ^2 test), and the mortality rate increased to 9.9% at glucose levels of >200 mg/dL ($P < .0001$, χ^2 test). In contrast, patients with maximal glucose levels of <110 mg/dL had a mortality rate of 1.5%, accounting for only 2 (4%) of 50 deaths in the study (Table 3).

When the data were analyzed with glucose level quintiles, to reduce the preselection bias related to our selection of glucose cutoff values, there was a comparable association between maximal glucose levels, LOS values, and mortality rates (Table 4). Both the median PICU LOS and total (hospital) LOS increased with greater maximal glucose levels. Moreover, death was associated with greater maximal glucose levels, with 30 deaths (15.2%) among 198 patients in the highest quintile ($P < .0001$, χ^2 test). This quintile accounted for 30 (60%) of 50 total patient deaths in our study.

Hypoglycemia

Hypoglycemia was also found to be prevalent among pediatric ICU patients, with 18.6% of patients ($n = 182$) having minimal glucose levels of ≤65 mg/dL (Table 4). Patients in the lowest quintile of minimal glucose levels (13–65 mg/dL) had a median PICU LOS of 9.5 days and a median total (hospital) LOS of 20 days; 30 (16.5%) of 182 patients in the lowest quintile died ($P < .0001$, χ^2 test). As the minimal glucose level quintiles increased, there was a reduction in LOS and mortality rate, except in the highest quintile. The patients in the highest minimal glucose level quintile (minimal glucose level range: 107–579 mg/dL) had an increase in mortality rate, compared with those in the middle 3 minimal glucose level quintiles. Interestingly, however, the LOS was lowest for this quintile.

Glucose Variability Data

To obtain an estimate of the effects of glucose variability on LOS and mortality rate, patients were divided into quintiles on the basis of their individual glucose variability index. The median LOS and mortality rate according to quintile increased as the glucose variability index increased (Table 4). For the most-variable subjects (highest quintile), the median PICU LOS was 5 days, with a median total hospital LOS of 11 days. The mortality rate was also the highest, with 23 deaths (15.1%) among 152 patients, compared with only 2 deaths (1.3%) among 151 patients in the least-variable quintile

TABLE 3 **Hospital LOS and Mortality Rates According to Glucose Cutoff Values**

Glucose Cutoff,[a] mg/dL	No.	PICU LOS, Median (IQR), d	Total LOS, Median (IQR), d	Deaths According to Quintile, *n* (%)
<65	182	9.5 (6–21)[b]	20 (11–38)[b]	30 (16.5)[b]
>65	798	2 (1–5)[b]	7 (4–14)[b]	20 (2.5)[b]
<110	130	1 (1–2)[b]	5 (3–9)[b]	2 (1.5)[c]
>110	850	4 (2–8)[b]	9 (5–19)[b]	48 (5.7)[c]
<150	382	2 (1–3)[b]	6 (3–12)[b]	6 (1.6)[b]
>150	598	5 (2–10)[b]	11 (5–25)[b]	44 (7.4)[b]
<200	635	2 (1–4)[b]	7 (4–13)[b]	16 (2.5)[b]
>200	345	6 (3–13)[b]	14 (6–32)[b]	34 (9.9)[b]

Analysis was performed with Pearson's χ^2 calculation.
[a] The 65 mg/dL cutoff values refer to subjects' minimal glucose values during the PICU stay. All other cutoff values refer to subjects' maximal glucose values.
[b] $P < .0001$.
[c] $P < .05$.

($P < 0.0001$, χ^2 test). The relationship between glucose variability and mortality rate was also demonstrated by the finding that 67% of the patients in the highest maximal glucose level quintile who died were also in the lowest quintile for minimal glucose level. In a multivariate logistic regression analysis, glucose variability ($P = .0002$), minimal glucose level ($P = .0006$), and maximal glucose level ($P = .0137$) each had an independent relationship with death.

DISCUSSION

Hyperglycemia in the ICU has been of increasing interest in pediatrics since several studies showed that hyperglycemia is associated with poor outcomes among children.[22–25] Several mechanisms for this association during critical illness have been proposed, including increased inflammatory cytokine production, acute dyslipidemia, endothelial dysfunction, hypercoagulation, and accelerated glucose toxicity leading to metabolic disturbances and increased cellular apoptosis.[29]

In a recent study analyzing hyperglycemia, the relative risk of dying was increased for PICU patients with glucose levels of >150 mg/dL within 24 hours after hospitalization and increased maximal glucose levels were associated with longer PICU LOS.[26] The prevalence rates of hyperglycemia in our study were 86.7%, 61.0%,

TABLE 4 **Hospital LOS and Mortality Rates According to Quintiles**

Quintile	Glucose Range, mg/dL	No.	PICU LOS, Median (IQR),[a] d	Total LOS, Median (IQR),[a] d	Deaths According to Quintile, *n* (%)[a]
Maximal glucose level quintile					
—[c]	0	114	1 (1–1)	2 (1–2)	0
1	69–122	191	1 (1–3)	5 (3–11)	4 (2.1)
2	123–151	197	2 (1–4)	7 (4–12)	2 (1.0)
3	152–192	195	3 (2–6)	7 (4–16)	9 (4.6)
4	193–259	199	4 (2–9)	10 (5–20)	5 (2.5)
5	261–1839	198	7.5 (4–20)	18 (9–38)	30 (15.2)
Minimal glucose level quintile					
—[c]	0	114	1 (1–1)	2 (1–2)	0
1	13–65	182	9.5 (6–21)	20 (11–38)	30 (16.5)
2	66–78	196	5.5 (3–10.5)	12 (6–22.5)	7 (3.6)
3	79–90	209	3 (2–6)	8 (5–16)	2 (1.0)
4	91–106	189	2 (1–3)	5 (4–11)	2 (1.1)
5	107–579	204	1 (1–2)	5 (3–8)	9 (4.4)
Glucose variability index quintile					
—[d]	0	339	1 (1–1)	2 (1–2)[b]	2 (0.6)
1	0.06–3.51	151	3 (2–7)	8 (5–15)[b]	2 (1.3)
2	3.51–9.14	150	4 (2–7)	9.5 (5–18)[b]	3 (2.0)
3	9.21–19.05	151	5 (2–12)	12 (6–25)[b]	4 (2.6)
4	19.14–45.30	151	6 (3–12)	12 (5–24)[b]	16 (10.6)
5	45.55–1246.66	152	5 (2–12.5)	11 (5–27.5)[b]	23 (15.1)

Analyses of LOS and individual quintiles were performed with the nonparametric Wilcoxon rank-sum test, and analyses of mortality rates were performed with Pearson's χ^2 test.
[a] All $P < .0001$ except where noted.
[b] $P < .05$.
[c] Patients with no glucose measurements obtained during admission.
[d] Patients without ≥3 glucose measurements obtained during admission.

and 35.2% for patients with maximal glucose levels of >110, >150, and >200 mg/dL, respectively. This is comparable to prevalence data presented by Faustino and Apkon,[26] that is, 75%, 50.1%, and 26.3% of patients with cutoff values of 120, 150, and 200 mg/dL. With these glucose cutoff values alone, we found a strong association of increasing LOS and mortality risk with increasing maximal glucose values. Our analysis showed an even stronger statistical association between hypoglycemia and glucose variability and their relationship with LOS and mortality risk, neither of which has been reported previously for the PICU population.

Analysis of the data according to quintile removes the bias associated with these somewhat-arbitrary hyperglycemia cutoff values. Our analysis displayed a significant increase in both PICU and total hospital LOSs with increasing maximal glucose levels. In a retrospective cohort study of PICU patients requiring mechanical ventilation or vasoactive infusions, Srinivasan et al[25] demonstrated a strong correlation between maximal glucose levels and mortality risk.

Our data on hypoglycemia and its association with LOS values and mortality rates are equally compelling. In our study, the prevalence of hypoglycemia (minimal glucose level of ≤65 mg/dL) was 18.6%, and we showed a strong association between hypoglycemia and mortality rates. Lower minimal glucose levels were also associated significantly with longer PICU LOS and total hospital LOS. Hypoglycemia has been considered to be a possible cause of long-term cognitive impairment among patients with early-onset diabetes mellitus and is considered to be a significant cause of death among such patients.[30–33] In addition, hypoglycemia was shown to be associated with increased mortality rates among adult hospitalized patients without diabetes mellitus.[34] Although no significant hypoglycemia was noted in the adult populations by Krinsley[20] or by Van den Berghe et al[11] in the surgical ICU study, hypoglycemia was found to be significantly more common among patients receiving intensive insulin therapy in the medical ICU study by Van den Berghe et al.[21] ICU mortality rates for patients with hypoglycemia (67% for the conventional treatment group and 46% for the intensive insulin treatment group) were notably higher than rates for patients without hypoglycemia (27% and 24%, respectively). These findings suggest that hypoglycemia may play a role as important as that of hyperglycemia in leading to increased morbidity and mortality rates and that more work needs to be performed to evaluate the significance of hypoglycemia.

Glucose variability had the strongest association with both LOS and mortality rates. As the glucose variability increased, both the PICU LOS and total hospital LOS increased. Mortality rates also increased, reaching a peak of 15.1% for patients in the highest quintile. When we evaluated subjects with glucose values in both the highest maximal glucose quintile and the lowest minimal quintile, we found, not surprisingly, this same strong association with increased mortality rates. These patients accounted for 40% of the total deaths in our study.

In addition to the potential effects of glucose variability on hydration and nutrition status, glucose variability, more than stable hyperglycemia, was shown indirectly to lead to increased oxidative stress, resulting in direct cellular damage and apoptosis.[35,36] The increased production of reactive oxygen species, such as peroxynitrite and superoxide, has been postulated to be the major underlying mechanism for glucose-induced vascular damage.[29,35,37] Through these microvascular effects, glucose variability may play a larger role than surmised previously in the acute physiologic changes that occur among critically ill patients.

Although we evaluated all eligible patients, our report has the typical limitations of a retrospective study. Statistical associations among glucose parameters, LOS, and mortality rates cannot be used to demonstrate causality. The lack of a glucose-monitoring protocol in our PICU during the study period might have affected our estimation of the incidence of both hyperglycemic and hypoglycemic glucose values; patients who were considered to be at high risk for hyperglycemia might have been preferentially monitored more closely, compared with those thought to be at low risk. An example of this involves the 114 patients who had no glucose monitoring performed during their hospitalization. Those patients were found to have the lowest PICU LOS and total hospital LOS values, as well as no deaths. When possible effects on our analysis are considered, however, this patient group constituted only 10.4% of the total studied. Considering the very low LOS and lack of deaths in this group, it is reasonable to assume that the group did not include patients who were significantly hyperglycemic. If all of these patients were considered to have normal blood glucose levels, then the prevalence of hyperglycemia would be altered by only a small percentage (77.7%, 54.7%, and 31.5% with cutoff values of 110 mg/dL, 150 mg/dL, and 200 mg/dL, respectively). When this same limitation is considered for our analysis of hypoglycemia, the prevalence decreases from 18.5% to 16.6%.

Our study demonstrates several important relationships among hypoglycemia, hyperglycemia, and glucose variability and their associations with morbidity (LOS) and mortality rates. Although hyperglycemia has been shown to be a negative prognostic indicator of poor outcomes among adult and pediatric patients, this study is the first to show that glucose variability and hypoglycemia have similar associations in the PICU population. Strict glucose control has been shown to improve morbidity and mortality rates significantly among adult surgical ICU patients.[11,20] However, its benefit in reducing mortality rates for adult medical patients is less impressive.[21] Additional studies in the pediatric popula-

tion, with due consideration of the risks of hypoglycemia and glucose variability, are needed to elucidate the effects that strict glucose control may have on morbidity and mortality rates in the PICU.

ACKNOWLEDGMENTS

This study was supported in part by a National Institutes of Health Training Grant (DK07217) given to the Division of Endocrinology and Diabetes at Stanford University. Dr Gandrud received research support from the Glaser Pediatric Research Network, the William E. and Aenid R. Weisgerber Foundation, and the Lucile Packard Foundation for Children's Health.

We gratefully acknowledge the statistical advice of Dr Richard Olshen, Department of Biostatistics, Stanford University. Special thanks go to Mary McIntyre, Barry Cooper, Christine Yang, and Loretta Jones for their kind assistance with data collection during the study.

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Pediatrics 2006;118;173
DOI: 10.1542/peds.2005-1819