The Ideal Time Interval for Critical Care Severity-of-Illness Assessment

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Objective: Determine if the shortest sampling interval for laboratory variables used to estimate baseline severity of illness in pediatric critical care is equivalently sensitive across multiple sites without site-specific bias, while accounting for the vast majority of dysfunction compared with the standard 0- to 12-hour Pediatric Risk of Mortality III score.

Design: Prospective random patient selection.

Setting: General/medical and cardiac/cardiovascular PICUs in eight hospitals.

Patients: Patients younger than 18 years admitted to the PICU.

Interventions: None.

Measurements and Main Results: A total of 376 patients were included. Measurements for Pediatric Risk of Mortality III laboratory variables (pH, Pco_2, total CO_2, Pao_2, glucose, potassium, blood urea nitrogen, creatinine, total WBC count, platelet count, and prothrombin time/partial thromboplastin time) were recorded from 2 hours prior to PICU admission through 12 hours of PICU care except for data in the operating room. Decreasing the observation period from 0 to 12 hours post-PICU admission resulted in progressive decreases in the Pediatric Risk of Mortality III laboratory variables measured. However, allowing the observation period to start 2 hours prior to PICU admission to 4 hours reduced this loss to only 3.4%. Similar trends existed for each of the individual laboratory Pediatric Risk of Mortality III variables. There was a nearly identical distribution of laboratory Pediatric Risk of Mortality III points within the −2- to 4-hour period compared with the standard period. We did not detect any institutional bias using the −2- to 4-hour time period compared with the baseline.

Conclusions: Prognostically important laboratory physiologic data collected within the interval from 2 hours prior to PICU to admission through 4 hours after admission account for the vast majority of dysfunction that these variables would contribute to Pediatric Risk of Mortality III scores. There was no institutional bias associated with this sampling period. (*Pediatr Crit Care Med* 2013; 14:448–453)

Key Words: critical care; intensive care; outcome prediction; pediatric critical care; Pediatric Risk of Mortality score; pediatrics; scoring systems; severity of illness

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Supported, in part, by a grant from the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), Bethesda, MD.

Dr. Doctor consulted for TerumoBCT, iNO Therapeutics, Galleon Pharmaceuticals, Nitrox, and has patents with Nitrox. Dr. Berger received grant support from Actelion (grant for enrolling research subjects in unrelated area). Dr. Harrison received grant support from the University of Michigan and payment for lectures from UCLA Department of Pediatrics, Society of Critical Care Medicine. Dr. Shanley provides expert testimony to Sandberg, Phoenix & Von Gontard PC. Dr. Nicholson is employed by the NIH. The remaining authors have disclosed that they do not have any potential conflicts of interest.

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DOI: 10.1097/PCC.0b013e31828a7270

The assessment of severity of critical illness using physiologic-based profiles is a balancing act of choosing a measurement period that is long enough to include all appropriate measurements, sufficiently short to minimize the effects of therapy on the variable values to represent "true"

severity on ICU admission, and choosing a time period that does not impose institutional bias (1–5). First, the assessment period should be sufficiently long to enable the assessment of prognostically important physiologic variables. For some variables, such as heart rate or blood pressure, measurement is so frequent that short assessment periods will include these measurements. However, some laboratory variables with proven prognostic information are measured relatively infrequently, and this can lengthen the measurement period necessary to capture these variables. At the same time, though, the assessment period should be as short as possible to minimize the effects of therapy on the initial estimation of illness severity, especially if the purposes of the severity method include assessing quality of care. Finally, the time period should not impose biased estimates because of institutional practice patterns of laboratory testing. For example, some PICUs routinely use measurements done prior to admission as their admission labs and other routinely repeat these measurements after PICU admission.

The Collaborative Pediatric Critical Care Research Network (CPCCRN) undertook a study of the appropriate sampling time period for physiologic variables used to estimate baseline severity of illness in pediatric critical care. Our aim was to determine the shortest time period for collection of the laboratory variables that would be equivalently sensitive across all study sites without evidence of site-specific bias while accounting for the vast majority of dysfunction, compared with the 0- to 12-hour Pediatric Risk of Mortality (PRISM) III score for laboratory variables. This study was preparatory to a current study evaluating a new paradigm of quality assessment of critical care based on using initial severity of illness to predict functional status (other than survival) at PICU discharge or later.

METHODOLOGY

Patient Population

The CPCCRN is composed of seven sites and eight PICUs and admits approximately 17,000 patients per year (6). Patients from newborn to less than 18 years were selected according to a randomization scheme developed at the data coordinating center, for a total of approximately 50 subjects per PICU during a 1-month period. For enrollment days when more than the protocol-allocated number of patients was eligible at a center, the required number was selected using this prespecified random selection method. Both general/medical PICUs and cardiac/cardiovascular PICUs were included. There were no separate surgical or neurologic PICUs. The protocol was approved by the institutional review boards at all participating institutions.

Selected Physiologic Variables

Physiologic variables included in this assessment were the laboratory components of PRISM III because each had been previously associated with mortality in univariate and multivariate analyses (7). These included pH, P_{CO_2}, total CO_2, Pa_{O_2}, glucose, potassium, blood urea nitrogen, creatinine, total WBC count, platelet count, and PT/PTT. The measurement time was assessed as the time stamp associated with the measurement. All measurements were recorded from 2 hours prior to PICU admission through 12 hours of PICU care, except for data in the operating room. That is, pre-PICU laboratory data were included from the emergency department, from other care areas of the hospital, from the postanesthesia care unit, and/or from outside care facilities if available up to 2 hours prior to PICU admission.

TABLE 1. Descriptive Characteristics of the Study Population Overall and in the Participating Sites

Factor	Overall	Site Ranges
Median age (yr)[a]	4.8	1.65–8.3
0–1 mo (%)	4.8	0–8.2
> 1–3 mo (%)	4.5	0–8.3
> 3–6 mo (%)	6.1	2.0–16.3
> 6–12 mo (%)	8.5	6.0–16.7
> 12 mo–6 yr (%)	30.9	19.4–46.7
> 6–12 yr (%)	17.3	10.0–36.7
> 12 yr (%)	27.9	10.2–36.2
Diagnoses[b]		
Respiratory (%)	20	8–40
Neurologic system (%)	28	24–26
Cardiovascular (*n*, %)	35	24–57
Miscellaneous (%)	18	6–30
Operative status[b]		
Nonoperative (*n*, %)	208 (55.3)	40.8–72.0
Postoperative (*n*, %)	168 (44.7)	28.0–59.2
Cardiac surgery[c]		
Nonoperative (*n*, %)	301 (80.1)	57.1–93.3
Cardiac surgery (*n*, %)	75 (19.9)	6.7–42.9
Type of ICU[c]		
Medical (*n*, %)	275 (73.1)	55.1–95.7
Cardiovascular (*n*, %)	101 (26.9)	4.3–44.9
Median length of stay (d)[d]	4.4	3.2–5.2

[a] $p > 0.50$, Kruskal-Wallis test comparing distributions across sites.
[b] $p < 0.01$, chi-square test.
[c] $p < 0.001$, chi-square test.
[d] $p < 0.05$, Kruskal-Wallis test comparing distributions across sites.

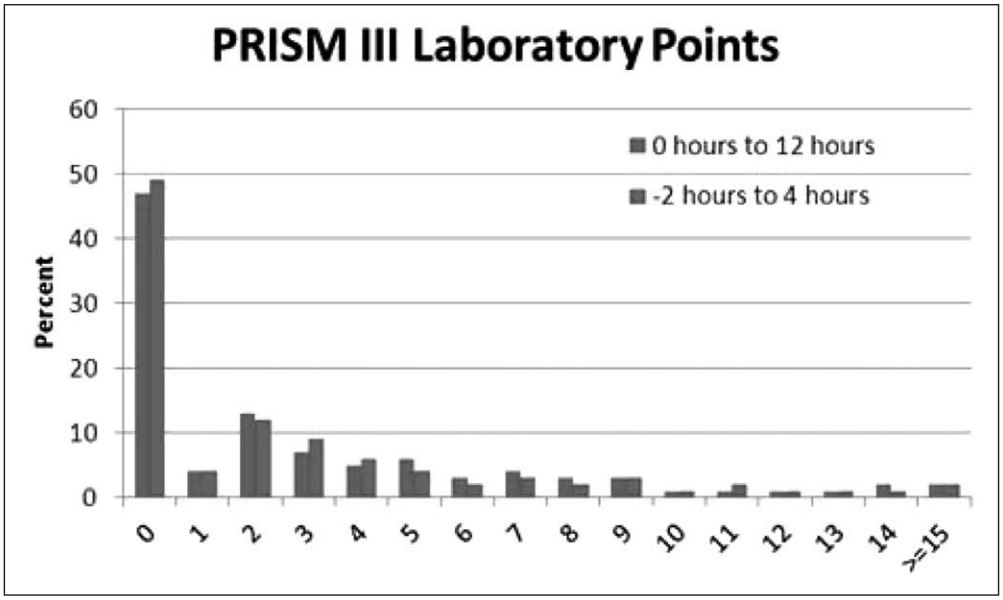

Figure 1. Distribution of Pediatric Risk of Mortality (PRISM) III laboratory points in the –2- to 4-hr interval and the 0- to 12-hr (baseline) interval. For each pair of bars, the first bar represents the baseline interval and the second bar represents the new time interval.

Although the data effort focused primarily on the laboratory variables, the most abnormal nonlaboratory variables in PRISM III, systolic blood pressure, heart rate, mental status/Glasgow Coma Scale, and temperature were also collected with the time of occurrence from 0 to 12 hours.

Data Analyses

The analysis focused on determining the shortest measurement interval for laboratory-based variables that would be sufficiently sensitive (overall and across all study sites without evidence of site-specific bias), measuring a comparable amount of dysfunction compared with the 0- to 12-hour PRISM III score for laboratory variables (gold standard) (7). We examined a variety of intervals beginning 2 hours prior to admission (–2 hr), 1 hour prior to admission (–1 hr), or at the time of admission (0 hr) and extending to postadmission times of 2, 4, 6, 8, and 12 hours. We evaluated the number of patients with any measurement available during the time interval, the number of patients with specific variables measured during the interval, and the PRISM III points generated from the laboratory variables (laboratory PRISM III) in the various candidate intervals. These were compared with the period of 0–12 hours, which is the standard period for data collection for PRISM III scoring.

Finally, we compared the availability of each of the laboratory variables during the intervals of interest at each institution. This comparison allowed us to assess if there was institutional bias due to including or excluding a disproportionate number of laboratory values across institutions. This analysis used chi-squared and Fisher exact testing to compare proportions of patients at each institution for whom laboratory value availability status changed when the interval was modified. This analysis (which is not reported in detail in the text) found no significant institutional bias after accounting for the multiple (12 laboratory values) comparisons that were performed.

Statistical analysis used the chi-square test for comparison of categorical variable distributions between centers and the Kruskal-Wallis test for comparing distributions of continuous variables between centers.

RESULTS

A total of 376 patients were included from the eight PICUs. **Table 1** shows the patient characteristics in the participating sites. The patients came from both medical PICUs (73.1%) and cardiovascular PICUs (26.9%). This differed significantly across the sites with as few as 4.3% and as many as 44.9% of institutional samples from cardiovascular units ($p < 0.001$). Median age was 4.8 years, and although it did not differ across the sites, the distribution of ages did vary. Median length of stay was 4.4 days and differed among the institutions ($p < 0.05$). Overall, 44.7% of patients were postoperative, and this varied from 28.0% to 59.2% ($p < 0.01$). The most common organ system of dysfunction based on the admitting diagnosis was the cardiovascular system followed by the neurologic and the respiratory systems. **Table 2** shows the number of individuals with a measurement of any PRISM III laboratory variable and the number of individuals with a measurement of each of the PRISM III variables in representative candidate intervals. Overall, 82 patients or 22% did not have any PRISM III laboratory measurement in the 0- to 12-hour (standard) period. A total of 6.5% more patients had laboratory variables measured in the –2- to 12-hour period than the standard period.

Decreasing the observation period from the standard period to 0–8, 0–6, 0–4, and 0–2 hours resulted in substantial decreases in the number of variables measured (Table 2). For example, reducing the time period to 0–8 hours resulted in a reduction of 8.2% of patients having any PRISM III laboratory variable measured. Reducing the laboratory observation period by 50% to 6 hours from 0 to 6 hours resulted in an 11.6% decrease. However, allowing the observation period to start 2 hours prior to PICU admission to 4 hours reduced this loss to 3.4%. Therefore, further analysis focused on the suitability of the –2- to 4-hour period compared with the standard 0- to 12-hour period.

Similar trends existed for each of the individual laboratory PRISM III variables as the overall measurement prevalence (Table 2). In 10 of the 13 laboratory variables, the time period most closely reflecting the standard was the –2- to 4-hour period. For the other three laboratory variables (pH, P_{CO_2}, P_{O_2}), the –2- to 4-hour period actually captured more measurements than the standard period, whereas 0- to 8-hour and 0- to 6-hour candidate time intervals were more comparable to the standard period. WBCs and platelets were also measured in more individuals in the –2- to 4-hour period compared with the standard period.

Figure 1 shows the very similar distributions of laboratory PRISM III points within the –2- to 4-hour period compared with the standard period. Some patients lost and some patients gained PRISM III laboratory points (**Fig. 2**) by using the –2- to 4-hour interval compared with the standard interval, but the mean laboratory PRISM III score only changed from 3.8 in the standard period to 3.6 in the –2- to 4-hour interval. Seventy percent of patients did not change their PRISM score at all; 13% of patients lost points and 18% of patients gained PRISM III points.

The most abnormal nonlaboratory PRISM III values in the first 12 hours were also assessed. The maximum dysfunction for systolic blood pressure, heart rate, temperature, and GCS/mental status occurred in 80%, 92%, 98%, and 96% of the patients, respectively, within the first 4 hours of PICU admission.

We did not detect any institutional bias using the –2 to 4-hour time period compared with the baseline. **Table 3** shows the change in the PRISM III laboratory score from the standard period to the –2- to 4-hour interval, for all sites and the individual sites. There was no significant institutional bias present (p = 0.42 for Kruskal-Wallis test comparing distributions of this change between centers). For some sites, variable measurement and PRISM III scores slightly increased, and for others, they slightly decreased.

DISCUSSION

We have demonstrated that prognostically important laboratory and nonlaboratory physiologic data collected within the interval from 2 hours prior to PICU admission through 4 hours after admission account for almost all of the dysfunction that these variables would contribute to PRISM III scores compared with the standard 0- to 12-hour time period. Data collection within this interval was not associated with significant inter-institutional bias, and this shortened interval (compared with the standard period of time of admission through 12 hr after admission) will minimize the effects of therapy on the initial estimation of disease severity. However, the PRISM III score using this revised time interval should not be used to represent risk of mortality or morbidity until formal validation studies are conducted.

The CPCCRN undertook this study in preparation for the Trichotomous Outcome Prediction in Critical Care (TOPICC) study, prospectively enrolling 10,000 patients admitted to CPCCRN PICUs and assessing the functional status at the time of PICU discharge with the goal of deriving and validating a statistical prediction model relating initial status to ultimate outcome. PRISM III and the Pediatric Index of Mortality have been used to assess and compare the quality of care received in PICUs by comparing observed and predicted mortality (7–10). However, the significant decrease in PICU mortality during the past several decades and the greater emphasis on preventing morbidity have reduced the relevance of mortality-based quality assessments. Therefore, quality of care assessments and comparisons should consider morbidities, such as functional status impairment, and mortalities.

The first step in accomplishing the goals of the TOPICC study was to develop a parsimonious instrument for assessing functional outcome of children at the time of PICU discharge. The CPCCRN developed the Functional Status Score for this purpose (11). The second step was the subject of the current report: to reassess the appropriate time interval for the measurement of severity of illness variables. Practice patterns have changed since the development of the PRISM III score in 1996. Initially, the 12-hour period for PRISM III was chosen because

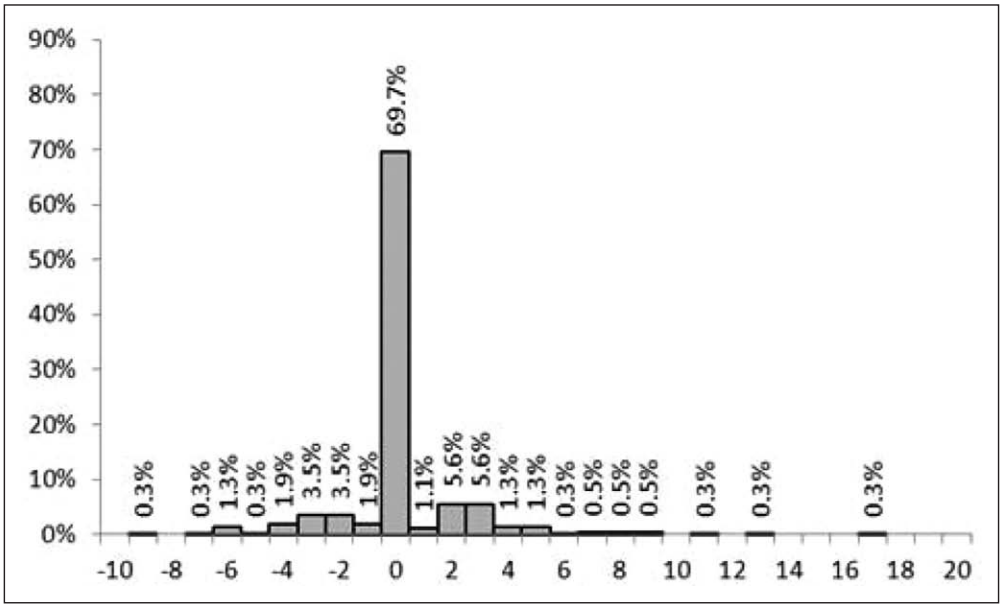

Figure 2. Distribution of the change in Pediatric Risk of Mortality (PRISM) III laboratory points when the observation interval is changed from the 0- to 12-hr (baseline) to the –2- to 4-hr interval. The vertical axis is the percent of the population and the horizontal axis is the change in the PRISM III laboratory points.

TABLE 2. Measurement of Pediatric Risk of Mortality III Laboratory Variables

Time Interval (h)	Any Pediatric Risk of Mortality III Laboratory Measurement	WBC	Acidosis	pH	Pco_2
−2 to 12	106.5	117.6	107.4	111.3	111.3
0 to 12 (baseline)	100 ($n = 294$)	100 ($n = 222$)	100 ($n = 282$)	100 ($n = 194$)	100 ($n = 194$)
0 to 8	91.8	86.0	90.1	97.4	97.4
0 to 6	88.4	81.1	86.5	94.8	94.8
0 to 4	84.4	76.6	83.0	91.2	91.2
0 to 2	72.4	63.5	70.6	78.4	78.4
−1 to 4	89.5	89.2	86.9	95.4	95.4
−2 to 4	96.6	101.8	95.0	105.7	105.7

The number of patients with a measurement of any Pediatric Risk of Mortality (PRISM) III laboratory variable and the number with a measurement of each of the PRISM III variables are shown as a percent of the baseline period (0–12 hr) for selected candidate intervals. The absolute number of patients with measurements is shown in the baseline period.

that time period was required to capture 90% of the variables that would be measured in the first 24 hours (12). This was done to assure that all 16 centers participating in the initial validation of PRISM III would have at least one measurement for variables, minimizing the potential for institutional bias. As part of this national study, PRISM III will be recalibrated to mortality and morbidity, which will enable adjustment for changes induced by the new sampling period from –2 to 4 hours post-PICU admission.

This study found that the time period of 2 hours prior to PICU admission and 4 hours after ICU admission provides a time interval resulting in sampling frequencies very similar to the original 12-hour time period used in the development of PRISM III and did not bias the laboratory PRISM III variables of any of the PICUs participating in the study (12). This time period accounts for the common practices of variable measurement, including not routinely repeating laboratory data at admission. It reduces the potential for lead time bias by reducing the PICU observation time from 12 to 4 hours, which is expected to more effectively separate the effects of therapy on physiologic functioning. Therefore, the TOPICC study investigating the relationship of severity of illness to the development of morbidity as well as mortality is using this shortened sampling interval.

ACKNOWLEDGMENTS

We thank the following individuals for their contributions in this study: Teresa Liu, University of Utah; Jean Reardon, Children's National Medical Center; Aimee Labell, Phoenix Children's Hospital; Jeffrey Terry, Children's Hospital Los Angeles; Ann Pawluszka, Children's Hospital of Michigan; Mary Ann DiLiberto, Children's Hospital of Philadelphia; Moni Weber, University of Michigan; Lauren Conlin, University of Michigan;

TABLE 3. Pediatric Risk of Mortality III Laboratory Score Change From the Standard Period to the –2- to 4-Hour Time Period by Site

Site	Score Increased by > 4 Points (%)	Score Increased Between 1 and 4 Points (%)	Score Remained the Same (%)	Score Decreased Between 1 and 4 Points (%)	Score Decreased by > 4 Points (%)
1	2	12	73	10	2
2	2	11	70	13	4
3	0	12	76	8	4
4	0	12	70	10	8
5	4	4	65	22	4
6	2	4	78	14	2
7	6	11	56	28	0
9	2	20	64	7	7
Total	2	11	70	14	4

Total CO_2	Pao_2	Platelets	Glucose	Potassium	PT/PTT	Blood Urea Nitrogen	Creatinine
110.9	109.1	117.6	110.9	110.2	116.1	111	110.8
100 ($n = 247$)	100 ($n = 132$)	100 ($n = 221$)	100 ($n = 247$)	100 ($n = 254$)	100 ($n = 137$)	100 ($n = 246$)	100 ($n = 249$)
83.4	96.2	86.0	84.6	83.9	91.2	82.9	83.1
77.3	90.9	81.0	77.3	77.2	87.6	76	76.3
71.3	84.1	76.5	68.8	71.3	77.4	69.9	70.3
56.7	70.5	63.3	56.7	57.5	68.6	56.5	56.6
81.0	90.2	89.1	77.3	79.9	89.1	78.9	79.1
89.9	95.5	101.8	86.2	89.4	98.5	87.4	87.6

Alan Abraham, University of Pittsburgh Medical Center; Jeri Burr, University of Utah; Tammara Jenkins, National Institutes of Health.

REFERENCES

1. Nielsen MS, Woodcock TE, Nolan KM, et al: Lead time bias and standardised mortality ratios in intensive care patients. *Anaesthesia* 1999; 54:399
2. Richardson D, Tarnow-Mordi WO, Lee SK: Risk adjustment for quality improvement. *Pediatrics* 1999; 103(1 Suppl E):255–265
3. Tunnell RD, Millar BW, Smith GB: The effect of lead time bias on severity of illness scoring, mortality prediction and standardised mortality ratio in intensive care–a pilot study. *Anaesthesia* 1998; 53:1045–1053
4. Vincent JL, Moreno R: Clinical review: Scoring systems in the critically ill. *Crit Care* 2010; 14:207
5. Harrison DA, Rowan KM: Outcome prediction in critical care: The ICNARC model. *Curr Opin Crit Care* 2008; 14:506–512
6. Willson DF, Dean JM, Meert KL, et al; Eunice Kennedy Shriver National Institute of Child Health, and Human Development Collaborative Pediatric Critical Care Research Network: Collaborative pediatric critical care research network: Looking back and moving forward. *Pediatr Crit Care Med* 2010; 11:1–6
7. Pollack MM, Patel KM, Ruttimann UE: PRISM III: An updated Pediatric Risk of Mortality score. *Crit Care Med* 1996; 24:743–752
8. Czaja AS, Scanlon MC, Kuhn EM, et al: Performance of the Pediatric Index of Mortality 2 for pediatric cardiac surgery patients. *Pediatr Crit Care Med* 2011; 12:184–189
9. Shann F, Pearson G, Slater A, et al: Paediatric index of mortality (PIM): A mortality prediction model for children in intensive care. *Intensive Care Med* 1997; 23:201–207
10. 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; 29:278–285
11. Pollack MM, Holubkov R, Glass P, et al; Eunice Kennedy Shriver National Institute of Child Health and Human Development Collaborative Pediatric Critical Care Research Network: Functional Status Scale: New pediatric outcome measure. *Pediatrics* 2009; 124:e18–e28
12. Pollack MM, Patel KM, Ruttimann U, et al: Frequency of variable measurement in 16 pediatric intensive care units: Influence on accuracy and potential for bias in severity of illness assessment. *Crit Care Med* 1996; 24:74–77