Pediatric Delirium and Associated Risk Factors: A Single-Center Prospective Observational Study*

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Objective: To describe a single-institution pilot study regarding prevalence and risk factors for delirium in critically ill children.

Design: A prospective observational study, with secondary analysis of data collected during the validation of a pediatric delirium screening tool, the Cornell Assessment of Pediatric Delirium.

Setting: This study took place in the PICU at an urban academic medical center.

Patients: Ninety-nine consecutive patients, ages newborn to 21 years.

Intervention: Subjects underwent a psychiatric evaluation for delirium based on the *Diagnostic and Statistical Manual* IV criteria.

Measurements and Main Results: Prevalence of delirium in this sample was 21%. In multivariate analysis, risk factors associated with the diagnosis of delirium were presence of developmental delay, need for mechanical ventilation, and age 2–5 years.

Conclusions: In our institution, pediatric delirium is a prevalent problem, with identifiable risk factors. Further large-scale prospective studies are required to explore multi-institutional prevalence, modifiable risk factors, therapeutic interventions, and effect on long-term outcomes. (*Pediatr Crit Care Med* 2015; 16:303–309)

Key Words: critical care; delirium; pediatric critical care; pediatrics; prevalence; risk factor

***See also p. 375.**

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This study was performed at Weill Cornell Medical College/NY Presbyterian Hospital.

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Delirium is the behavioral manifestation of acute cerebral dysfunction associated with serious underlying medical illness. It presents as an acute and fluctuating change in mental status, with disordered attention and cognition (1). It is a well-known and prevalent problem in adult intensive care, linked to short- and long-term morbidity (2), increased mortality (3), and astronomical healthcare costs (4).

The pathophysiology of ICU delirium is complex and multifactorial. It is the end result of diffuse cerebral metabolic abnormality. Broadly, alterations in neurotransmission, cerebral blood flow, energy metabolism, and disordered cellular homeostasis all play a role (5–7). Although it can occasionally be traced to a single etiology (e.g., alcohol toxicity or delirium tremens), in the ICU, it is frequently a result of three synergistic events: the underlying disease process, side-effects of treatment, and the highly abnormal critical care unit environment (8, 9).

As an example, let us consider the patient admitted to the ICU with pneumonia and associated acute hypoxemic respiratory failure. The inflammatory process associated with the infection and hypoxia predisposes the patient to delirium. The benzodiazepine prescribed to facilitate patient-ventilator synchrony is itself deliriogenic. The prolonged period of immobilization in the ICU bed, the presence of invasive catheters and monitors, and the disruption of the patient's sleep-wake cycle all contribute to the evolving delirium (9, 10).

It is important to recognize that delirium is a medical diagnosis and not simply a constellation of symptoms. Delirium is not untreated pain, oversedation, sleep deprivation, or withdrawal (although any of these may contribute to the development of delirium) (11, 12). Delirium is a syndrome that is the final common pathway of many factors. It represents acute nontraumatic brain injury and must be recognized as such to allow for proper treatment and prevention (13–16).

Epidemiology and risk factors for pediatric delirium are not yet well described, due in part to the absence of widespread screening, underrecognition, and lack of evidence-based data (17–19). The recent development of validated screening tools for use in critically ill children is a promising step (20–23). With

heightened awareness and detection of pediatric delirium, we can identify and address modifiable risk factors, investigate treatments, and assess the effects of delirium on long-term health and quality of life of PICU survivors.

The objective of this pilot study is to describe the prevalence and risk factors for delirium in critically ill children in our ICU over a 10-week time period. In this brief report, we present a secondary analysis of data prospectively collected during the validation of the Cornell Assessment of Pediatric Delirium, a rapid observational tool used by the bedside nurse to screen for delirium in PICU patients of all ages (21).

METHODS

This is a prospective observational study, conducted over 10 weeks in an urban academic tertiary care PICU. All patients were eligible for inclusion, regardless of age or diagnosis. Parent or guardian was approached by study investigators for consent, and if consent was granted, the child was enrolled. When appropriate, assent was obtained from the child as well. Consent rate was 88.5%.

Subjects were assessed for delirium by a child psychiatrist at approximately noon each day. Sedation was not interrupted for the assessment, as our unit standard-of-care is to keep all patients as lightly sedated as possible given their underlying medical condition. Subjects' level of consciousness ranged from moderately sedated (arousable to verbal stimulation), to awake, and to agitated. Patients who were deeply sedated—defined here as unarousable to verbal stimulation—were excluded as they could not be assessed for delirium. In our institution, we assess sedation status using the widely-accepted (although not yet validated in pediatrics) Richmond Agitation Sedation Scale (RASS) every 4 hours (24). All subjects with scores of –3 (movement or eye opening to voice) or higher were included. All children diagnosed with delirium were reported to the medical team so that appropriate treatment could be initiated.

Enrolled subjects were assessed for delirium daily, taking into consideration the past 24-hour period. The child psychiatrist completed a detailed interview and examination, utilizing the gold-standard DSM-IV diagnostic criteria (1). Six child psychiatrists participated in these 252 assessments, and four training sessions took place to establish group consistency in concepts and vocabulary. Using a developmental framework, the child psychiatrists were able to reliably diagnose delirium even in the youngest of children (25).

Children with developmental delay (defined as severe impairment in ability to communicate in age-appropriate way with caregiver at prehospital baseline) were assessed for delirium by these seasoned clinicians, who took into account the child's baseline and assessed for a fluctuating change in consciousness and cognition consistent with delirium (acute brain dysfunction, due to the underlying medical illness). With careful attention to baseline, the psychiatrist was able to make a determination as to presence or absence of delirium in these subjects.

Demographic and clinical data were collected upon enrollment, including age, gender, diagnosis, severity-of-illness score using Pediatric Index of Mortality II (PIM2), and history of prematurity. Severe impairment in the child's ability to communicate with caregiver at baseline was used as a proxy for severe developmental delay. Clinical data were collected daily, including need for oxygen and mechanical ventilation. Hospital length of stay (LOS) was calculated from day of hospital admission to day of hospital discharge. This study was approved by the Institutional Review Board at Weill Cornell Medical College.

Enrollment goal was 100 individual subjects and 250 encounters (each subject could be assessed up to a predetermined maximum of five times to avoid biasing the results). Sample size was determined by a conservative assumption of 15% delirium prevalence overall and to allow for exploratory subgroup analysis of delirium by age and presence or absence of significant developmental delay.

STATISTICAL METHODS

Normality tests were first performed to assess whether continuous covariates were normally distributed. If covariates were normally distributed, *t* tests were used. For covariates not normally distributed, the nonparametric Wilcoxon rank-sum test was used to compare the median differences of covariates by delirium status (yes or no). For discrete covariates, the chi-square test and Fisher exact test were used to compare the frequencies/proportion of covariates by delirium status. Multivariable logistic regression was performed to evaluate the independent associations between potential confounding factors and risk factors with delirium status. Any bivariate association that achieved a *p* value of less than 0.2 was entered into the multivariate model. The odds ratios (OR), 95% CIs, and *p* values of the covariates were reported. In order to correct for more than one delirium diagnosis within some individuals, generalized estimating equation (GEE) analysis was performed to determine if results obtained using the standard logistic regression analysis materially changed. All statistical tests were two-sided, and *p* value of less than 0.05 was considered statistically significant. All analyses were performed in SAS version 9.3 (SAS Institute, Cary, NC) and figures generated in STATA 13 (StataCorp LP, College Station, TX).

RESULTS

Characteristics of Study Population and Observation of Delirium

One hundred eleven subjects were enrolled. Ninety-nine subjects completed at least one psychiatric diagnostic interview and examination and are included in data analysis (12 subjects were unavailable for assessment: nine subjects were either off the unit [in surgical or radiologic suites] or involved in clinical care that could not be interrupted at the time the psychiatrist was available; three subjects were transferred out of the PICU prior to the psychiatrist's availability) (**Fig. 1**). These 12 subjects did not differ from the included patients with respect to demographics, diagnoses, or severity-of-illness categories.

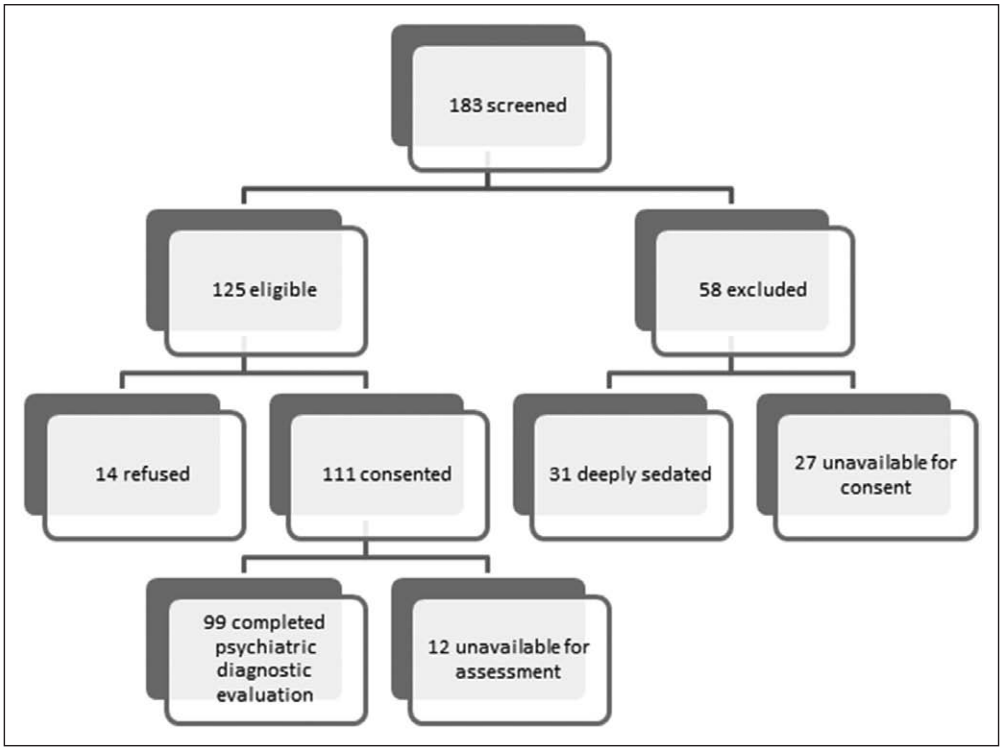

Figure 1. Patient flow of screening, eligibility, exclusions, and inclusions.

A total of 252 psychiatric diagnostic interviews and examinations were completed as part of this study. Each subject was assessed between one and five times. **Table 1** shows the demographics by subject (n = 99), and **Table 2** shows the clinical characteristics by encounter (n = 252).

Sixty percent of the subjects were boys, 54% were under 5 years old, and 18% were characterized as developmentally delayed (**Table 1**). Developmental delay was defined as severe impairment in ability to communicate in age-appropriate way with caregiver at prehospital baseline. Eighteen subjects had developmental delay: seven had an underlying genetic disorder, seven had complications of prematurity, two had hypoxic-ischemic encephalopathy, one had a history of stroke, and one had autism. These were diagnoses made prehospitalization and not by the study investigators. These subjects did not differ from the overall population with respect to demographics or severity-of-illness categories.

During daily assessments, 54% were on supplemental oxygen and 25% were mechanically ventilated. Six percent were moderately sedated (arousable to voice; RASS level –3), 8% were lightly sedated (briefly awaken to voice; RASS level –2), and 11% were drowsy (RASS level –1) (**Table 2**).

The prevalence of delirium was 21%. Ninety percent of subjects diagnosed with delirium had a fluctuating course; 10.5% of subjects diagnosed with delirium remained delirious throughout the course of the study. The average number of delirium diagnoses per patient was 2.52. There was a significant association with observations of pediatric delirium and developmental delay ($p < 0.0001$), need for oxygen ($p < 0.0001$), use of mechanical ventilation ($p < 0.0001$), and deeper sedation level ($p < 0.0001$) (**Fig. 2**). Median severity-of-illness score (PIM2)

TABLE 1. Subject Demographics and Delirium Status (n = 99)

Characteristic	No. of Subjects (%)	Average No. of Assessments per Subject	Delirium Diagnosis During Study (%)	No Delirium Diagnosis During Study (%)
n	99	2.5	21 (21.2)	78 (78.8)
Gender				
Male	59 (59.6)	2.6	12 (57.1)	47 (60.3)
Female	40 (40.4)	2.4	9 (42.9)	31 (39.7)
Age, yr				
0–2	34 (34.3)	2.3	8 (38.1)	26 (33.3)
2–5	19 (19.2)	2.6	6 (28.5)	13 (16.7)
5–13	21 (21.2)	3.2	6 (28.5)	15 (19.2)
> 13	25 (25.3)	2.2	1 (4.8)	24 (30.8)
Developmental delay				
No delay	81 (81.8)	2.3	13 (61.9)	68 (87.2)
Delay	18 (18.2)	3.6	8 (38.1)	41 (20.6)

TABLE 2. Clinical Characteristics by Encounter and Delirium Status ($n = 252$)

Characteristic	No. of Observations (%)	Delirium (%)	No Delirium (%)	*p*
n	252	53	199	
Age, yr				< 0.0001
0–2	77 (30.6)	16 (30.2)	61 (30.7)	
2–5	50 (19.8)	20 (37.8)	30 (15.1)	
5–13	69 (27.4)	15 (28.3)	54 (27.1)	
> 13	56 (22.2)	2 (3.8)	54 (27.1)	
Developmental delay				< 0.0001
No delay	184 (73.0)	26 (49.0)	158 (79.4)	
Delay	68 (27.0)	27 (51.1)	41 (20.6)	
Oxygen				< 0.0001
No	117 (46.4)	7 (13.2)	110 (55.3)	
Yes	135 (53.6)	46 (86.8)	89 (44.7)	
Mechanical ventilation				< 0.0001
No	190 (75.4)	24 (45.3)	166 (83.4)	
Yes	62 (24.6)	29 (54.7)	33 (16.6)	
Richmond Agitation Sedation Scale[a] ($n = 249$)				< 0.0001
0, 1, 2, 3	187 (75.1)	23 (44.2)	164 (83.2)	
–1	27 (10.8)	7 (13.4)	20 (10.2)	
–2	20 (8.0)	11 (21.2)	9 (4.6)	
–3	15 (6.0)	11 (21.2)	4 (2.0)	
Pediatric Index of Mortality II (median)		2.8	1.1	0.01

[a]See text for description of levels.

was significantly higher in the group with pediatric delirium (2.8 vs 1.1, $p = 0.01$).

Factors Predicting Pediatric Delirium

Multivariable logistic regression analysis predicting pediatric delirium (**Table 3**) indicated that when adjusting for prognostic variables, preschool age (2–5 yr old) was found to be statistically significant in predicting pediatric delirium when compared with adolescents (> 13 yr old, OR = 8.80; 95% CI, 1.82–42.53; $p = 0.007$) and when compared with infants (0–2 yr old, OR = 2.57; 95% CI, 1.11–5.93; $p = 0.027$). Compared with children with typical development, children with developmental delay had a 3.45 greater likelihood of having a diagnosis of delirium (OR = 3.45; 95% CI, 1.54–7.76; $p = 0.003$). Requirement for mechanical ventilation was also found to be statistically significant in predicting pediatric delirium (OR = 3.86; 95% CI, 1.81–8.24; $p = 0.0005$). Mechanical ventilation was highly associated with both need for oxygen ($p < 0.0001$) and depth of sedation ($p < 0.0001$); therefore, we did not enter these as independent variables in the multivariate model. Severity-of-illness (as determined by PIM2 score) and gender were not independent predictors of pediatric delirium.

GEE was performed to adjust for individuals who had more than one diagnosis of delirium. The statistical significance of the primary predictors in the model (**Table 3**) did not materially change. For example, the *p* value for developmental delay went from 0.003 to 0.021 and mechanical ventilation went from 0.0005 to 0.004.

Possible Association Between Diagnosis of Delirium and Hospital LOS

Hospital LOS for children diagnosed with delirium during this study was significantly higher than hospital LOS for children who were not diagnosed with delirium (median = 3 d vs 18 d; $p < 0.0001$) (**Fig. 3**). This association remained highly significant even when controlling for severity-of-illness.

DISCUSSION

Delirium is prevalent in the PICU. Children with significant developmental delay are at highest risk for developing delirium during their ICU stay. An atypical brain at baseline may

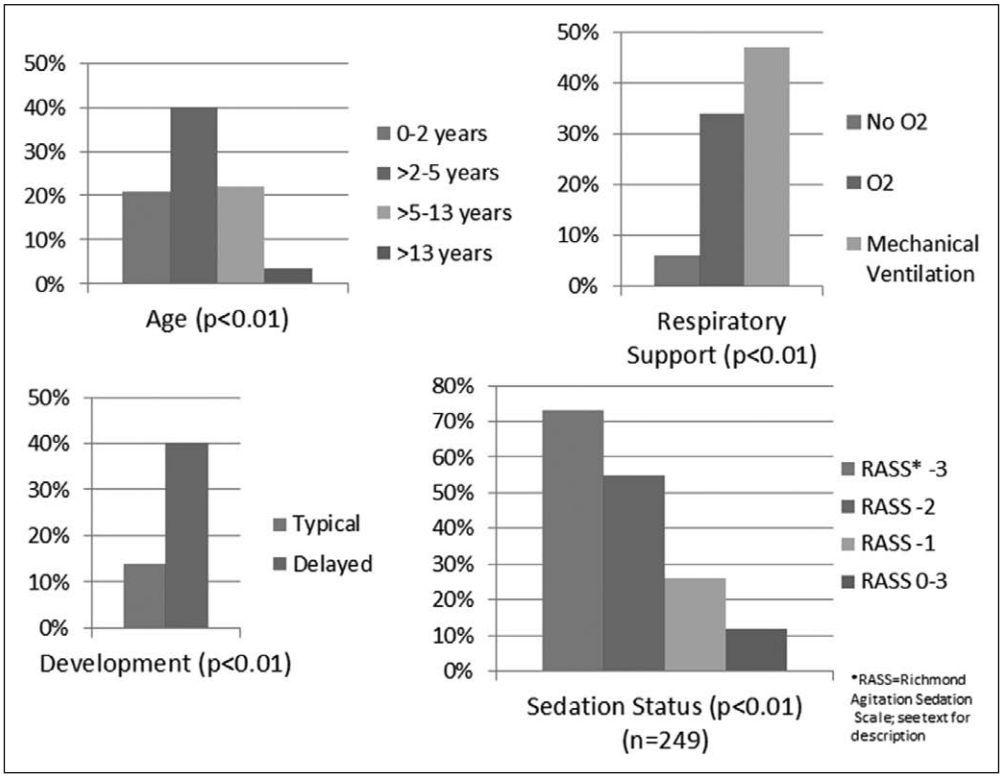

Figure 2. Risk factors associated with diagnoses of delirium. Data reported as percentage of entire sample (total n = 252 encounters).

be more vulnerable to the toxic/metabolic effects of critical illness through any number of proposed pathways associated with delirium. In this respect, children with developmental delay may be most analogous to adults with dementia, a well-described high-risk group in adult critical care (4).

This highlights a current area of debate in pediatric delirium research. Children with developmental delay are notoriously hard to assess in the acute care setting (24). As the diagnosis of delirium requires alteration from baseline, what is often required is a comprehensive and time-consuming history to establish the particular child's baseline prior to definitively diagnosing delirium. It would be more efficient to exclude these difficult-to-assess children from ongoing delirium research, but that would exclude an important high-risk population.

Consistent with adult delirium research (5), we have demonstrated a higher risk for delirium in subjects who required supplemental oxygen and the highest risk with need for invasive mechanical ventilation. We did not capture data regarding duration or severity of hypoxia (as measured by Po_2). This is an interesting area for further research; a study investigating the association between brain tissue oxygen tension, as measured by noninvasive oximetry, and development of delirium may be warranted.

Not surprisingly, we found that deeper levels of sedation were highly correlated with mechanical ventilation ($p < 0.0001$). An emerging literature in adult delirium research has identified a subset of delirium, sedation-induced delirium, which resolves shortly after sedative interruption. This delirium subtype does not seem to have the same poor prognosis when compared with persistent delirium in adults (26). If the increased prevalence of delirium noted in mechanically ventilated children is at least partially due to sedation, this may have a better long-term prognosis than delirium of other etiologies. Further research is needed.

When assessed by age subgroups, in multivariate analyses that control for severity-of-illness, preschool-age children (2–5 yr old) seem to be at highest risk for developing delirium in this cohort. The etiology of this increased risk has not been determined and needs to be reproduced in larger studies.

A possible contributing factor is the reliance of the 2- to 5-year-old child on constant stimulation from the environment (27). The developmentally inappropriate immobility in the PICU may be extremely disruptive to this particular age group. Interventions designed at increasing mobilization may be therapeutic, or even prophylactic, as found in the adult population (28). Prospective studies are required to assess this possibility.

Another factor may be that these preschool-age children are exquisitely sensitive to disruption of their sleep-wake cycles (29, 30). School-age children and adolescents are, in general, less sensitive to sleep disruption. Infants may be somewhat protected as their circadian rhythm is incompletely established, whereas preschool-age children have newly acquired consolidation of sleep at this developmental stage (31). This potential mechanism requires further study.

Importantly, these data show a possible association between the diagnosis of delirium and increased hospital LOS, even when controlling for severity-of-illness. This is consistent with previous pediatric delirium research (32) and suggests that pediatric delirium is associated with substantial increase in medical costs. Effectively managing delirium in children presents a significant opportunity for healthcare savings (33).

Limitations of this study involve its pilot nature, as it was a secondary aim of a validation study for a delirium screening tool. As such, it presents only a cross-section of pediatric delirium over a finite period in a single PICU. The data reported here are novel and represent an important contribution to pediatric delirium research. However, it is important not to overconclude based on these findings (34).

In this pilot study, although we captured level of sedation, we did not collect data regarding particular sedation agents used or doses. This is a limitation as the effects of

TABLE 3. Multivariable Logistic Regression Analyses Predicting Delirium (*n* = 252)

Predictor Variable	Adjusted OR (95% CI)	*p*
Age category (yr)		
0–2	Reference	
2–5	2.57 (1.11–5.93)	0.027
5–13	0.87 (0.33–2.33)	0.79
> 13	0.29 (0.06–1.43)	0.13
0–2	3.43 (0.70–16.78)	0.13
2–5	8.80 (1.82–42.53)	0.007
5–13	2.99 (0.58–15.41)	0.19
> 13	Reference	
Developmental delay		
Yes	3.45 (1.54–7.76)	0.003
No	Reference	
Mechanical ventilation		
Yes	3.86 (1.81–8.24)	0.0005
No	Reference	

OR = odds ratio.

Analysis controlled for potential confounders including severity-of-illness and gender.

particular sedatives (particularly benzodiazepines), and their doses, may be important. A large-scale, prospective observational longitudinal study is necessary to determine the association between delirium and modifiable risk factors, such as medications (particularly anticholinergics, sedatives, and steroids) and targeted interventions (both behavioral and pharmacologic). Preparation for such a study is underway.

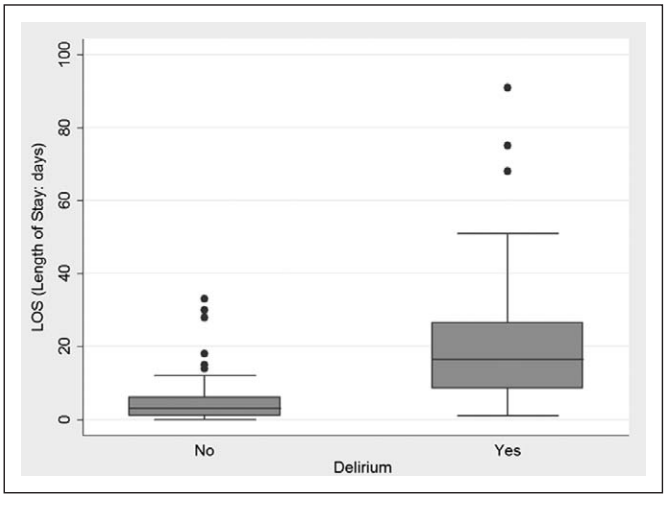

Figure 3. Associations between subjects diagnosed with delirium during this study and hospital length of stay (LOS). One outlier (LOS = 267 d) was included in analysis but removed from this figure.

CONCLUSION

Critically ill children are at risk for developing delirium during the course of their stay in the ICU. Our preliminary data suggest that there are clearly identifiable subgroups at higher risk. With heightened awareness to this prevalent problem, many PICUs are implementing delirium screening as standard-of-care. This will allow for a multi-institutional collaborative approach to furthering pediatric delirium research and improving the care we provide to these vulnerable children.

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