Delirium is a Common and Early Finding in Patients in the Pediatric Cardiac Intensive Care Unit

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Objective To determine incidence, associated risk factors, and characteristics of delirium in a pediatric cardiac intensive care unit (CICU). Delirium is a frequent and serious complication in adults after cardiac surgery, but there is limited understanding of its impact in children with critical cardiac disease.

Study design Single-center prospective observational study of CICU patients ≤21 years old. All were screened for delirium using the Cornell Assessment for Pediatric Delirium each 12-hour shift.

Results Ninety-nine patients were included. Incidence of delirium was 57%. Median time to development of delirium was 1 day (95% CI 0, 1 days). Children with delirium were younger (geometric mean age 4 vs 46 months; $P < .001$), had longer periods of mechanical ventilation (mean 35.9 vs 8.8 hours; $P = .002$) and had longer cardiopulmonary bypass times (geometric mean 126 vs 81 minutes; $P = .001$). Delirious patients had longer length of CICU stay than those without delirium (median 3 (IQR 2, 12.5) vs 1 (IQR1, 2) days; $P < .0001$). A multivariable generalized linear mixed model showed a significant association between delirium and younger age (OR 0.35 for each additional month, 95% CI 0.19, 0.64), need for mechanical ventilation (OR 4.1, 95% CI 1.7, 9.89), and receipt of benzodiazepines (OR 3.78, 95% CI 1.46, 9.79).

Conclusions Delirium is common in patients in the pediatric CICU and is associated with longer length of stay. There may be opportunities for prevention of delirium by targeting modifiable risk factors, such as use of benzodiazepines. *(J Pediatr 2017;■■:■■-■■).*

Intensive care unit (ICU) delirium is a clinical syndrome with acute disturbance in consciousness and cognition that can fluctuates over the course of the day.[1-5] The etiology of delirium can be multifactorial including severe illness, its treatment, and the critical care environment.[6] Delirium occurs frequently in adults, and is known to be linked to poor outcomes including increased mortality, longer hospital length of stay, and long-term cognitive impairments in survivors.[7] Therefore, delirium has increasingly received attention as a significant entity in pediatric critical care.[8-13] However, investigations of the impact of delirium in critically ill children has been limited, until recently, by lack of a practical diagnostic tool. An international survey revealed that many pediatric intensive care units (PICUs) do not routinely screen for delirium.[9] Thus, little is known about the incidence, risk factors, presentation, time course, and outcomes of delirium in the PICU and pediatric cardiac intensive care unit (CICU).

Implementation of practical monitoring tools for diagnosis of delirium in the adult ICU has directly led to an understanding of the risk factors, morbidity associated with delirium, and strategies to prevent and treat this ICU complication.[1,7,14-29] To meet this need in children, researchers developed and validated practical bedside tools for the diagnosis of pediatric delirium.[30-32] As a result, there is now prospective literature that reports the prevalence of pediatric delirium in a general PICU population to range from 17% to 38%. There is evidence that pediatric delirium is associated with developmental delay; mechanical ventilation; young age; severity of illness; prior coma; a diagnosis of infection or inflammation; exposure to benzodiazepines, narcotics and anticholinergics; use of physical restraints; and exposure to vasopressors and antiepileptics.[11,33-35]

Presently, there is limited data on delirium in pediatric CICU patients.[11,30,31] We hypothesized that delirium is a common occurrence in the pediatric CICU, as these patients are exposed to many of the previously described risk factors for pediatric delirium. Pediatric CICU patients are often young, severely ill, deeply sedated,

CAPD	Cornell Assessment of Pediatric Delirium
CICU	Cardiac intensive care unit
CPB	Cardiopulmonary bypass
ICU	Intensive care unit
LOS	Length of stay
PICU	Pediatric Intensive care unit
RASS	Richmond Agitation Sedation Scale
STS-EACTS score	The Society of Thoracic Surgeons and the European Association for Cardiothoracic Surgery Congenital Heart Surgery Mortality Score

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and mechanically ventilated. In addition, many pediatric CICU patients are chronically cyanotic and/or experience hypoxia, which can further increase risk for cerebral dysfunction, and may present clinically as delirium. Therefore, we sought to determine the incidence of delirium, describe the course of delirium, associated risk factors, and short-term outcomes in a prospective cohort of pediatric CICU patients.

Methods

We conducted a prospective observational cohort study in the pediatric CICU of a tertiary care center. Delirium screening was instituted in the unit as part of a quality improvement initiative 6 months prior to the study. Approval of the study with a waiver of consent was granted by our Institutional Review Board. All patients from birth to 21 years old admitted over a 10-week period between June 2015 to August 2015 were included in the analysis. Patients were excluded if admitted to the pediatric CICU for less than 12 hours. In addition, patients admitted to the pediatric CICU >24 hours prior to first screening were excluded, to identify only new delirium diagnoses. Lastly, those under neuromuscular blockade and/or therapeutic hypothermia were excluded, as depth of sedation made it impossible to assess for delirium.

Delirium Screening

The Cornell Assessment of Pediatric Delirium (CAPD) was scored by the bedside nurse once per 12-hour shift. This is an 8-item tool, scored on a Likert scale, that uses the child's observable behavior to assess consciousness and cognition. A developmental anchor points chart was used as an aid to identify age appropriate behavior for each of the CAPD questions in the context of the ICU environment.[36] A CAPD score of ≥9 was defined as a positive screen for delirium. This is consistent with clinical practice guidelines that recommend routine use of the CAPD to detect delirium in critically ill children.[37]

The Richmond Agitation Sedation Scale (RASS) was used to assess sedation status and to determine delirium subtype. The RASS ranges from -5 (deeply sedated) to +4 (very agitated). Hypoactive delirium was defined as delirium with a negative RASS score. Hyperactive delirium was defined as delirium with a positive RASS score. Mixed delirium can present with a fluctuation between negative and positive RASS scores and/or a RASS of 0; an alert and calm patient. Withdrawal was defined as a Withdrawal Assessment Tool-1 score greater than 3.[38]

Children who were delirious on more than 1 assessment were categorized as follows: "continuous" if they remained delirious after onset; "intermittent" if they had multiple discrete episodes of delirium, and "recovery" if they were delirious but then recovered.

A delirium screening compliance goal of 80% was set a priori. The tool and supplemental developmental anchor points were previously incorporated into the electronic medical record for ease of use.

Data was collected from the electronic medical record for every day the patient was admitted to the pediatric CICU up to a maximum of 14 days. Patient characteristics collected included age, sex, race/ethnicity, date of admission, date and type of surgical procedure, and diagnoses. In patients who underwent surgical procedures, we collected The Society of Thoracic Surgeons and the European Association for Cardiothoracic Surgery Congenital Heart Surgery Mortality Score (STS-EACTS), which is used to estimate risk of in-hospital mortality by surgical procedure.[39] In addition, cardiopulmonary bypass (CPB) time, deep hypothermic circulatory arrest time, and cross-clamp time were collected. Clinical characteristics collected were type of respiratory support (both on admission and daily), use of vasopressor/inotrope, opiates, benzodiazepines, anticholinergics, steroids, Withdrawal Assessment Tool-1 scores, and CAPD score. In addition, the same clinical characteristics were collected for the 24 hours prior to the pediatric CICU admission if the patients were admitted from another hospital unit.

Statistical Analyses

The cohort and their outcomes were characterized using descriptive statistics. Clinical characteristics of the children who developed delirium were compared with those who did not develop delirium using 2-sample t tests, χ^2 tests, and Wilcoxon rank-sum tests for continuous, categorical, and continuous outcomes that were not normally distributed, respectively. Median time to delirium was calculated using the Kaplan-Meier method, with the log-log approach for CIs. Mixed logistic regression models, with a random intercept to account for correlation of outcomes within a subject, were used to assess the independent association between development of delirium and each relevant demographic and clinical factor: STS–EACTS score (>3 vs ≤3), bypass time (15-minute increments), cross-clamp time (minutes), age (months), mechanical ventilation on admission, any mechanical ventilation, benzodiazepine use, opioid use, drug exposure prior to admission, location prior to admission (home vs inpatient), and anticholinergics. These variables were chosen based on known clinical relevance and knowledge from previous studies.[8,9,30,31,40-49] Variables that were statistically significant in the individual models were included in a final multivariable mixed logistic regression model. Surgical subgroup analysis was planned a priori as this group would represent the largest proportion of patients admitted to the pediatric CICU and to determine whether there were unique risks for delirium among this group compared with medical patients. Missing data were excluded. Normality was visually assessed using histograms; outcomes were log transformed when necessary. All hypothesis tests were 2-sided with significance set at 0.05. R v 3.1.1 software (R Foundation for Statistical Computing, Vienna, Austria).

Results

A total of 145 patients were admitted to the pediatric CICU during the study period. Forty-six were excluded due to the following: 3 had no recorded delirium assessments, 5 were over 21 years old, and 38 were not evaluated for delirium within 24 hours of admission to the pediatric CICU. A total of 99 patients were analyzed, 88 surgical and 11 medical admissions.

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Table I. Demographic and clinical characteristics

Characteristics	All n (%)	No delirium (n = 43)	Delirium (n = 56)	*P* value
Sex				.071
Female	47 (47%)	25 (58%)	22 (39%)	
Male	52 (53%)	18 (42%)	34 (61%)	
Age				<.001
<1 mo	20 (20%)	2 (5%)	18 (32%)	
1 mo-1 y	24 (24%)	6 (14%)	18 (32%)	
1-5 y	29 (29%)	12 (28%)	17 (30%)	
6-12 y	13 (13%)	11 (26%)	2 (4%)	
13-21 y	13 (13%)	12 (28%)	1 (2%)	
Primary diagnosis				.216
Not cyanotic	59 (60%)	29 (67%)	30 (54%)	
Cyanotic	40 (40%)	14 (33%)	26 (46%)	
Comorbidities				.594
GI/GU	2 (14%)	1 (20%)	1 (11%)	
Infectious	3 (21%)	2 (40%)	1 (11%)	
Respiratory	2 (14%)	0 (0%)	2 (22%)	
Other	7 (50%)	2 (40%)	5 (56%)	
Admission type				.201
Medical	11 (11%)	7 (16%)	4 (7%)	
Surgical	88 (89%)	36 (84%)	52 (93%)	
Respiratory support on admission				.438
None	19 (19%)	9 (21%)	10 (18%)	
Low flow NC	19 (19%)	10 (23%)	9 (16%)	
High flow NC	3 (3%)	0 (0%)	3 (5%)	
NIV	2 (2%)	0 (0%)	2 (4%)	
Mechanical ventilation	56 (57%)	24 (56%)	32 (57%)	
Mechanical ventilation in pediatric CICU course				.055
No	33 (33%)	19 (44%)	14 (25%)	
Yes	66 (67%)	24 (56%)	42 (75%)	

GI, gastrointestinal; *GU,* genitourinary; *NC,* nasal cannula; *NIV,* noninvasive ventilation.

Compliance with use of the CAPD tool during the study period was 85%.

Table I shows demographics and clinical characteristics for the cohort. The distribution of female to male patients was approximately equal. The median cohort age was 24 months (IQR 2, 72 months); 44% of patients were ≤1 year of age and 26% were older than 5 years of age. Surgical patients accounted for 89% of the cohort, 78% of which had surgical procedures for their primary diagnosis, such as atrial septal defect repair or a Fontan procedure. Fifty-seven percent were admitted on mechanical ventilation and the rest required little to no oxygen. Ten children were intubated after admission to the pediatric CICU. Median length of stay for the cohort was 2 days (IQR 1, 4.5 days). There was no mortality in the study population during enrollment. Three patients died after completion of study.

Delirium Incidence and Characteristics

The incidence of delirium was 57%. The median time to delirium was 1 day (IQR 0, 1 day). 84% of patients who became delirious did so within the first 48 hours of admission.

The median number of positive assessments for patients who had delirium was 5 (IQR 3, 11), and the average proportion of positive assessments was 62% (SD 30). Seventeen (31%) patients exhibited a continuous pattern of delirium, 12 (22%) exhibited an intermittent pattern, and 25 (46%) exhibited a recovery pattern. Median duration of delirium was significantly different between the 3 patterns (continuous 45 hours [IQR 23, 216 hours] vs intermittent 181 hours [94, 212] vs recovery 22 hours [213, 24]; $P = .0026$. Two patients with delirium had only 1 assessment of delirium. Of the 56 patients with delirium, 3 (5%) had a hyperactive only pattern, 29 (52%) had a hypoactive only pattern, and 24 (43%) were of a mixed pattern. In the mixed subtype, 4 (7%) presented as alert and calm and 20 (36%) had fluctuation between hypoactive and hyperactive psychomotor activity. The psychomotor subtypes for each pattern of delirium are described in **Table II**. Out of 56 patients that had delirium, only 2 also had withdrawal symptoms during their pediatric CICU stay. Twenty-five children screened positive for delirium in their last assessment before transferring out of the pediatric CICU to a cardiac floor.

Associated Risk Factors

Demographic and clinical characteristics associated with a delirium diagnosis are shown in **Table I**. Children with delirium were more likely to be younger: 64% of children diagnosed with delirium were ≤1 year of age, and only 5% of

Table II. Psychomotor subtypes in delirium patterns

Subtypes	All (n = 56*)	Continuous (n = 17)	Intermittent (n = 12)	Recovery (n = 25)
Hyperactive	3 (5%)	1 (6%)	1 (8%)	0 (0%)
Hypoactive	29 (52%)	7 (41%)	6 (50%)	16 (64%)
Mixed	24 (43%)	9 (53%)	5 (42%)	9 (36%)

*Delirium course could not be assessed for 2 subjects.

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Table III. Surgical subgroup analysis

Characteristics	No delirium (n = 36)	Delirium (n = 52)	*P* value
Sex			.018
Female	24 (67%)	21 (40%)	
Male	12 (33%)	31 (60%)	
Age			<.001
<1 mo	2 (6%)	15 (29%)	
1 mo-1 y	5 (14%)	18 (35%)	
1-5 y	10 (28%)	17 (33%)	
6-12 y	10 (28%)	1 (2%)	
13-21 y	9 (25%)	1 (2%)	
Primary diagnosis			.048
Not cyanotic	26 (72%)	26 (50%)	
Cyanotic	10 (28%)	26 (50%)	
STS-EACTS score			.044
1	13 (48%)	9 (20%)	
2	9 (33%)	17 (39%)	
3	2 (7%)	2 (5%)	
4	3 (11%)	10 (23%)	
5	0 (0%)	6 (14%)	
CPB time (geometric mean)	81 min	126 min	.001

The Society of Thoracic Surgeons and the European Association for Cardiothoracic Surgery Congenital Heart Surgery Mortality Score (the STS–EACTS score).
STS-EACTS scores were not recorded for 17 patients.

Table IV. Multivariable mixed logistic regression model

Variables	OR (95% CI)	*P* value
STS–EACTS score >3	1.08 (0.25, 4.64)	.9125
CPB time (15 min)	1 (0.87, 1.16)	.9794
Age (mo)	0.35 (0.19, 0.64)	.0008
Mechanical ventilation	4.1 (1.7, 9.89)	.0017
Benzodiazepines	3.78 (1.46, 9.79)	.0061

Final model included STS-EACTS score, CPB time, age, mechanical ventilation, and benzodiazepines.

children diagnosed with delirium were >5 years old ($P < .001$). Although there was no statistical difference in delirium rates based on respiratory support on admission, it is interesting to note that all 10 patients who required initiation of mechanical ventilation after admission developed delirium. Thus, 64% of children who were ever mechanically ventilated while in the pediatric CICU were delirious compared with 42% of those not ventilated ($P = .055$). Median time to development of delirium was 2 days (95% CI 1, 4 days).

Subgroup analysis of the 88 surgical patients was performed (**Table III**); 59% (n = 52) of these children developed delirium. Those with delirium had longer CPB times (n = 61 bypass cases, 126 minutes (108, 147) vs 81 minutes (67, 99) respectively, ($P = .001$)). There were 9 patients who underwent deep hypothermic circulatory arrest; 8 (89%) subsequently experienced delirium. In the surgical subgroup, delirious children were more likely to be male ($P = .018$), younger ($P < .001$), and have cyanotic heart disease (50% vs 28%, $P = .048$). There was a statistically significant association between STS–EACTS score and delirium ($P = .044$). In fact, all patients in STS–EACTS category 5 were delirious as well as 77% of those in category 4. In bivariate analysis, there was a statistically significant association between STS–EACTS score >3, CPB time, age, mechanical ventilation at any point, benzodiazepines, opioids, ondansetron, and inpatient location prior to admission to the pediatric CICU. Ondansetron was associated with an 81% decrease in the odds of delirium ($P = .002$).

For multivariable analysis, using a mixed model with a random intercept, we considered those variables that achieved statistical significance in the individual models: STS–EACTS >3, bypass time (15-minute increments), age (months), mechanical ventilation at any point, location prior to admission (home vs inpatient), benzodiazepines, opioids, and anticholinergics. Though location prior to admission was independently associated with delirium, it was excluded from the final model as it is likely not a modifiable factor. Benzodiazepines and opiates were considered in separate models because of convergence issues when they were considered together. The model that included benzodiazepines had a lower Akaike information criterion; 183.7, relative to the model with opiates, 190, indicating the former as the better choice. Akaike information criterion permits comparison of the quality of a set of statistical models that do not comprise the same variables. The final model included STS-EACTS score, CPB time, age, mechanical ventilation, and benzodiazepines with a significant association between delirium and age, mechanical ventilation, and benzodiazepines (**Table IV**). On average, every additional month of age decreased the child's odds of delirium by 65%. Mechanical ventilation and benzodiazepines each independently increased the odds of delirium by approximately 400%.

Patients with delirium had longer periods of mechanical ventilation compared with those without delirium (mean 35.9 vs 8.8 hours; $P = .002$). Based on a Wilcoxon rank-sum test, length of stay (LOS) differed significantly between those with delirium (median LOS 3 days, IQR 2, 12.5 days), and those without delirium (median LOS 1 day, IQR 1, 2 days).

Discussion

In this study cohort, delirium in the pediatric CICU was common, occurred early in the hospital course, and was associated with worse clinical outcomes, as defined by increased duration of mechanical ventilation and increased length of CICU stay. The data presented in this study is both supportive of the existing pediatric evidence and contributes new knowledge regarding the unique presentation and risk factors in this cardiac specific population.

The incidence of delirium in our pediatric CICU cohort of 57% is higher than in some previous general PICU population studies[11,31,34,35,50] but consistent with the cardiac ICU studies.[51,52] This is physiologically plausible, as it is well known that complications of CPB include a generalized endothelial activation and systemic inflammatory response, nonpulsatile oxygen delivery, thromboembolic events,[53,54] and increased activity of the serotonergic system,[55-58] all of which may lead to brain injury and inflammation. In addition, increased serotonin has been implicated in the underlying neuropathophysiology of delirium.[6] The validation studies of the Pediatric Confusion Assessment Method for ICU and CAPD

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reported a prevalence of 11.8% and 21%, respectively. In these studies, patients with cardiac disease represented only a small proportion (18% and 11%, respectively).[30,31] In other studies that included a larger number of cardiac patients, pediatric delirium rates were higher, consistent with our findings. For example, delirium rates in a preschool aged population (with 31% cardiac patients) was 47% and delirium rates in a post-surgical ICU in Germany (with 58% cardiac patients) was 66%.[32,52] Another CICU study showed delirium incidence of 49% in children after cardiac bypass surgery.[51]

Risk factors for delirium in our cohort (younger age, mechanical ventilation during the pediatric CICU stay, benzodiazepine exposure, and cyanotic heart disease) are consistent with the literature. We found that the youngest children are at great risk of developing delirium. In the literature, there has been comparison of the youngest children to the elderly regarding the risk for delirium development.[43,59,60] Maldonado explains a relevant neuropathological hypothesis, neuronal aging, whereby changes in intracellular signal transduction, stress-regulating neurotransmitters, and blood flow to the brain all lead to neuron loss.[6] The neuronal aging hypothesis may have a counterpart in the other extreme of age, a vulnerable immature hypothesis. Considering the infant brain, continued central nervous system regional development, neurogenesis, migration, synaptogenesis, and myelination reflect the immature nature of the central nervous system. It is possible these young brains are particularly vulnerable to stress and illness. If so, then structural and molecular injury early in life may lead to significant neuropsychiatric morbidity. Further research is needed to investigate the pathophysiology of delirium in the youngest patients, and the effect of delirium on their long term neuropsychiatric health.

We also found 2 risk factors for delirium in our cohort that have not been previously described in the pediatric delirium literature. First, in the surgical subgroup, male sex was associated with delirium. This finding deserves further study. In addition, patients that were given the antiemetic ondansetron had an 81% decrease in the odds of delirium. This is consistent with adult delirium literature[61-63] but has not previously been reported in the pediatric population. Adult studies provide evidence that exposure to CPB could explain the higher incidence of delirium in the pediatric CICU compared with the PICU.[55-58] Ondansetron is a 5-HT3-receptor antagonist that has been shown to prevent development of delirium and effectively decrease its symptoms in CPB and postoperative adults.[61-63] We hypothesize that in children with increased serotonergic activity, 5-HT3-receptor antagonists will decrease the incidence of delirium and decrease delirium symptoms. It is also possible that untreated nausea contributes to the refractory agitation present in hyperactive delirium.[64] Further studies are needed to determine whether use of ondansetron is associated with decreased occurrence of pediatric delirium or whether it can be an effective treatment.

Pediatric delirium can be classified by subtypes based on the level of psychomotor activity. Hyperactive patients may have mood lability, agitation, restlessness, and are readily identified due to difficulties in caring for them. Hypoactive patients appear sluggish, lethargic, apathetic, and even stuporous. A normal level of psychomotor activity or fluctuating level of activity may occur in a mixed subtype. Hypoactive patients are at greatest risk of being missed as they are generally docile and often easy to care for. There is evidence that this subtype is likely associated with worse outcomes such as increased risk of mortality.[5,65,66] In this cohort, hypoactive delirium was the most common delirium subtype, followed by mixed delirium. Hyperactive delirium was by far the least common. This is consistent with other delirium studies, where hypoactive and mixed delirium are most commonly described.[11,34] This highlights the importance of routine screening, as otherwise only hyperactive delirium is reliably noted.

In our cohort, 46% of children had rapid resolution of delirium. These children exhibited delirium early on, followed by quick resolution. This early-onset, fast recovery delirium may represent sedation-induced delirium, or the lingering effects of anesthesia and/or cardiac bypass. Patel et al described rapidly reversible, sedation-related delirium in a subset of adult delirious patients that were identified as delirious while under sedation. Delirium symptomatology resolved after interruption of sedation.[26] This is similar to the findings of Meyburg et al.[52] However, it is notable that a significant proportion (31%) of children had persistent delirium, and possibly up to 45% of delirious children were transferred out of the pediatric CICU while still delirious. The scope of delirium in pediatric critical illness has only recently been appreciated and its significance is still being explored. The findings of this study would suggest a role for delirium screening and perhaps treatment for children transferred out of intensive care units. Further research following these children after transfer from the ICU to the inpatient services is warranted to determine duration of delirium, timing of resolution, and long-term effects of delirium. As of now, the new literature of pediatric delirium has been published in psychiatric and critical care journals and very little has been shared with other pediatric providers.

This study has several limitations. As a single-center study, findings may not be widely generalizable. Compliance with delirium screening was 85%, resulting in missing data. Therefore, the actual incidence and duration of delirium may have in fact been underestimated. Also, in children with severe developmental delay, the CAPD has less specificity so we may have overestimated delirium prevalence in this group. That said, children with severe developmental delay were a minority of our patient population and it is unlikely that this materially affected our results. It is also possible that we missed episodes of delirium that occurred after 14 days in the ICU, falsely lowering our measured delirium rates. In addition, we did not compare CAPD screening with the gold standard psychiatric evaluation. Also, although an association between delirium and benzodiazepines was reported, we were not powered to analyze the relationship between dosage and diagnosis of delirium. Lastly, causality cannot be inferred from this observational study. For example, it remains to be determined whether delirium impedes progress toward extubation or whether an extended course of mechanical ventilation leads to prolonged exposure to risk factors for delirium.

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In conclusion, we found that delirium is common and occurs early in the course of pediatric CICU patients. Delirium is associated with young age, mechanical ventilation and benzodiazepine exposure and is associated with increased length of mechanical ventilation and pediatric CICU LOS. These findings suggest that delirium is an important complication of critical illness in children with cardiac disease. Future studies of both medical and surgical cardiac patients are needed to further clarify this acute brain dysfunction and determine optimal strategies to prevent its occurrence. ■

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