Chapter 7
Epidemiology of Delirium in Children: Prevalence, Risk Factors, and Outcomes

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Introduction

Although the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) established diagnostic criteria for delirium in 1980, delirium research in the pediatric population has lagged significantly behind the mounting evidence in adults. A 2009 systematic review of the literature on delirium in children and adolescents identified only case series and a few case reports totaling 217 children or adolescents [1]. However, the last decade has seen an explosion in pediatric delirium research resulting from the introduction of validated pediatric-specific delirium screening tools [2]. Several research groups have shown that the prevalence of delirium in critically ill children approaches estimates in adults, and a growing body of literature has begun to identify the risk factors and outcomes associated with delirium development in children. While many of these risk factors and outcomes are parallel to those adults, there are specific predictors unique to the pediatric population.

In the latest edition of the DSM (DSM-5), the definition of delirium was modified to emphasize the cardinal features of diagnosis: (1) disturbances in attention or awareness, (2) changes in cognition, and (3) fluctuation in symptoms [3]. However, even this definition can be challenging to apply in the pediatric setting given

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substantial variability in the premorbid neurocognitive state and language abilities of children. Neither the DSM-5 nor International Classification of Diseases (10th edition) definitions include pediatric-specific delirium definitions [4], highlighting the importance of having validated pediatric-specific delirium screening tools, as was discussed in Chap. 6.

In order to understand the clinical burden and implications of delirium in children, it is imperative to review the epidemiology of delirium including prevalence, risk factors, and outcomes in a vulnerable group of patients undergoing active neurocognitive development.

Description of Studies

While there are a small number of studies that have examined delirium in the pediatric emergency department [5], neonatal intensive care unit [6] (NICU), and children with oncological disease [7], delirium in children is most frequently studied in the pediatric intensive care unit (PICU). A recent systematic review on pediatric delirium from Holly et al. identified 21 studies investigating how delirium is recognized in hospitalized children [8]. The overwhelming majority (90%) of these studies included PICU patients. Furthermore, only a small number of studies were prospective, with many case reports and case series included, providing a window into the current status of pediatric delirium research and future opportunities.

Prevalence

Prevalence is defined as the number of existing cases at a single point in time, while incidence is defined as the number of new cases population at risk in a given time period. Historically, the prevalence of delirium in children was largely extrapolated from referrals to child psychiatry services [9]. Children and adolescents accounted for 10% of consultation-liaison psychiatry services and between 17% and 66% of psychiatry referrals from PICUs. Furthermore, early case reports seemed to underestimate the burden of delirium in critically ill children with an incidence of 4–5%, likely due to under diagnosis [1]. The introduction of validated pediatric-specific delirium screening tools has propelled the field of pediatric delirium research into the modern day. The majority of literature describes the prevalence of delirium in critically ill children often admitted to the PICU.

In 2011, Smith et al. introduced one of the first validated pediatric-specific delirium screening tools [10]. In this study, a total of 68 pediatric critically ill patients, at least 5 years of age, were included in a prospective study to validate the Pediatric Confusion Assessment Method for Intensive Care Unit (pCAM-ICU). As detailed in Chap. 6, the pCAM-ICU was adapted from the well-established Confusion Assessment Method-ICU (CAM-ICU). The pCAM-ICU validation study identified

a prevalence of 13.2% among a mixed population of pediatric intensive care patients including medical, surgical, and cardiac diagnoses. Recognizing the pCAM-ICU was excluding a large population of critically ill children, Smith et al. went on to create and validate the Preschool Confusion Assessment Method for the ICU (psCAM-ICU) in 2016 [11]. This study included 281 critically ill children aged 6 months to 5 years admitted to the PICU. In this younger population, the overall delirium prevalence was 44%. Interestingly, rates of delirium were 53% in patients <2 years of age versus 33% in patients 2–5 years of age.

The other major validated pediatric-specific delirium screening tool is the Cornell Assessment for Pediatric Delirium (CAPD). In the initial validation study by Silver et al. in 2014 [12], 111 patients of ages ranging from 0 to 21 years admitted to a tertiary PICU were found to have a delirium prevalence of 20.6%. Other notable findings from this study include higher prevalence for delirium in critically ill children with developmental delay and higher severity of illness. The authors noted that children with developmental delay were diagnosed with delirium almost three times as often as children without delay (38.8% vs 13.9%). Additionally, those with a higher severity of illness, as determined by the Pediatric Index of Mortality II score, were also noted to have a higher likelihood of being diagnosed with delirium (29.7% vs 12.3%).

The largest study to establish the prevalence of delirium in the pediatric population was published by Traube et al. in 2017 [13], with an overall objective to determine the prevalence of delirium in critically ill children and explore associated risk factors. The study was a multi-institutional point prevalence study including 25 pediatric critical care units in the United States, the Netherlands, New Zealand, Australia, and Saudi Arabia. The majority of units were affiliated with universities; however, three were part of community hospitals. At the conclusion of the study, 994 subjects were enrolled, and an overall point prevalence was 25%. These findings were consistent with those of prior single-center studies that reported pediatric delirium rates ranging from 10% to 30% [14–16]. Of note, the delirium prevalence increased significantly (up to 38%) for those children admitted to the PICU for 6 or more days.

Risk Factors

Current literature has identified many risk factors for the development of delirium in critically ill children (Fig. 7.1). Despite the physiological and developmental differences between children (i.e., infants, toddlers, school age children, and adolescence), there is significant overlap in the risk factors for developing delirium across these groups.

The point prevalence study described above is one of the largest studies examining pediatric delirium to date, identifying many risk factors included in Fig. 7.1. These include age (less than 2 years), mechanical ventilation, exposure to vasopressor medications (potentially a marker for severity of illness), and antiepileptics.

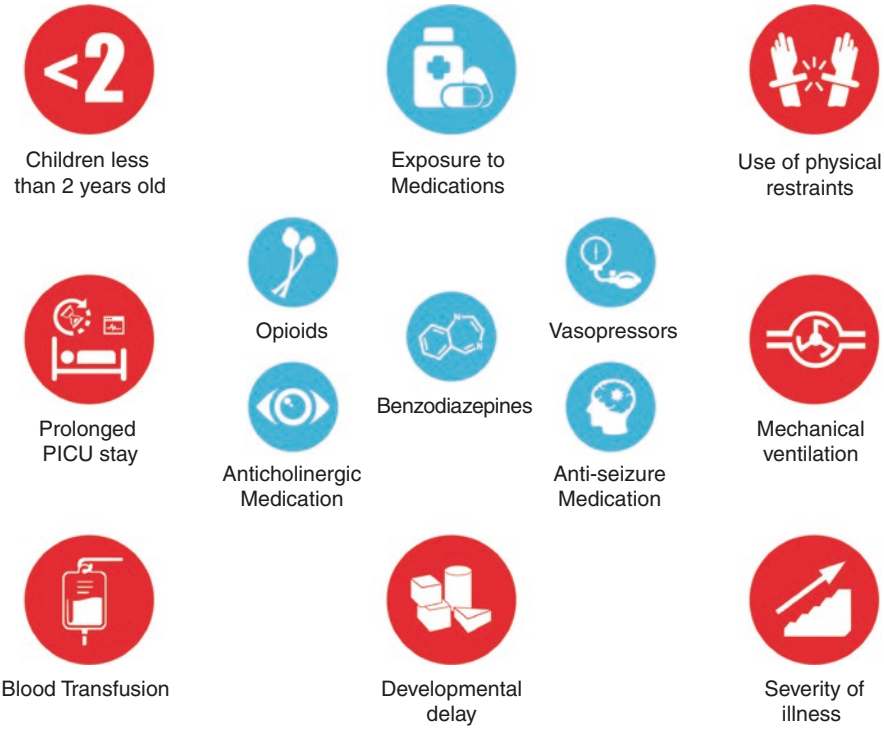

Fig. 7.1 Risk factors associated with delirium in critically ill children

Additionally, exposure to benzodiazepines, opioids, and use of physical restraints was strongly associated with delirium. Furthermore, the point prevalence study noted that the risk for developing delirium increased with the length of PICU admission [17]. Children admitted to the PICU with an infectious or inflammatory disorder had the highest rate of developing delirium (42%). These risk factors highlight how the most vulnerable patients are susceptible to developing delirium. In adults, the elderly are often most at risk for developing delirium; however, in children, it is the youngest who are most at risk. Similar to adults, those receiving mechanical ventilation are at significant risk for developing delirium. While adult studies are conflicting, early pediatric studies have shown that blood transfusions in the critically ill child are independently associated with the development of delirium.

A recent study by Nellis et al. identified that children who were transfused red blood cells (RBCs) were more than twice as likely to develop delirium during their admission compared with children who were never transfused. The authors observed a temporal relationship among transfused children, and for each additional 10 mL/kg of RBCs transfused, recipients were 90% more likely to develop delirium [18].

Medication exposure can also be a risk factor for the development of delirium in critically ill children. Fortunately, medication exposure is also one of the most common potentially modifiable risk factors.

Approaches in minimal but effective sedation in pediatric critical care have lagged behind adults. Many PICUs around the world still implement a combination of opioid and benzodiazepine as the primary sedatives for critically ill children [19]. Both opioids and benzodiazepines are known independent risk factors for the development of delirium in children. Traube et al. demonstrated that benzodiazepines were strongly associated with transition from normal cognitive status to delirium. In a retrospective observational study, they found that benzodiazepine use more than quadrupled delirium rates with an odds ratio of 4.4 [20]. In a secondary analysis of the psCAM-ICU validation study, Smith et al. demonstrated that greater benzodiazepine exposure was significantly associated with a lower likelihood of ICU discharge, longer delirium duration, and increased risk for delirium the following day [21]. Additionally, exposure to anticholinergic drugs may potentiate the effects of benzodiazepines and increase the risk of developing delirium [22]. While sedatives are often needed for mechanical ventilation in postoperative pediatric patients, the postoperative period in and of itself is a known risk factor for the development of delirium.

In fact, the postoperative period is a particularly vulnerable time for children to develop delirium. Meyberg et al. have published two articles on the same cohort of children investigating delirium in the postoperative period [23, 24] and identified specific risk factors for developing delirium in the postoperative period. Younger children develop delirium more frequently and with more pronounced symptoms. Interestingly, the number of preceding operations did not influence the risk of delirium. Of note, the authors identified that patients receiving total intravenous anesthesia had a lower risk of developing delirium than those who had received inhalational anesthesia. Lastly, invasive catheters, respiratory devices, and the development of an infection all increased the risk of developing delirium. A secondary analysis of this cohort described two different patterns of delirium in postoperative children admitted to the PICU. One pattern was an early short-lasting delirium (24 h), and the other was a longer more severe course. Overall the incidence of delirium was 66%, and the group was evenly split in each pattern.

There are special pediatric populations that are more likely to develop delirium. Two notable populations are children requiring extracorporeal membrane oxygenation (ECMO) and cardiac surgery. In a prospective observational longitudinal cohort study, Patel et al. describe delirium in children requiring ECMO [25]. In this study, eight patients accounted for 72 days of ECMO, and all patients developed delirium. The authors found that only 13% of ECMO days were categorized as delirium-free and coma-free, and the majority of patient days on ECMO were spent in coma (65%). Children undergoing cardiac surgery, and specifically surgery with cardiopulmonary bypass, are particularly susceptible to development of postoperative delirium [26]. In a prospective observational single-center study, Patel et al. report delirium prevalence of 49% in children after cardiac surgery with cardiopulmonary bypass [27]. The authors note that delirium often lasted 1–2 days and developed within the first 1–3 days after surgery. Similar to other postoperative pediatric

delirium studies, age less than 2 years was a risk factor for developing delirium. Other unique risk factors included developmental delay, higher Risk Adjustment for Congenital Heart Surgery-1 (RACHS-1) score, cyanotic disease, and albumin less than 3 g/dL.

Outcomes

There is a paucity of studies examining outcomes in pediatric delirium. However, emerging literature would suggest that children share many of the same unfavorable outcomes associated with delirium as adults (Fig. 7.2). In a prospective longitudinal cohort study of 1547 consecutive patients, Traube et al. characterized the epidemiology and outcomes of pediatric delirium [28]. In this study, delirium was diagnosed in 17% of all subjects and lasted a median of 2 days. Similar to adults, most cases of delirium were of the hypoactive and mixed subtypes, 46% and 45%, respectively. Core outcome measures such as length of stay were increased in children with

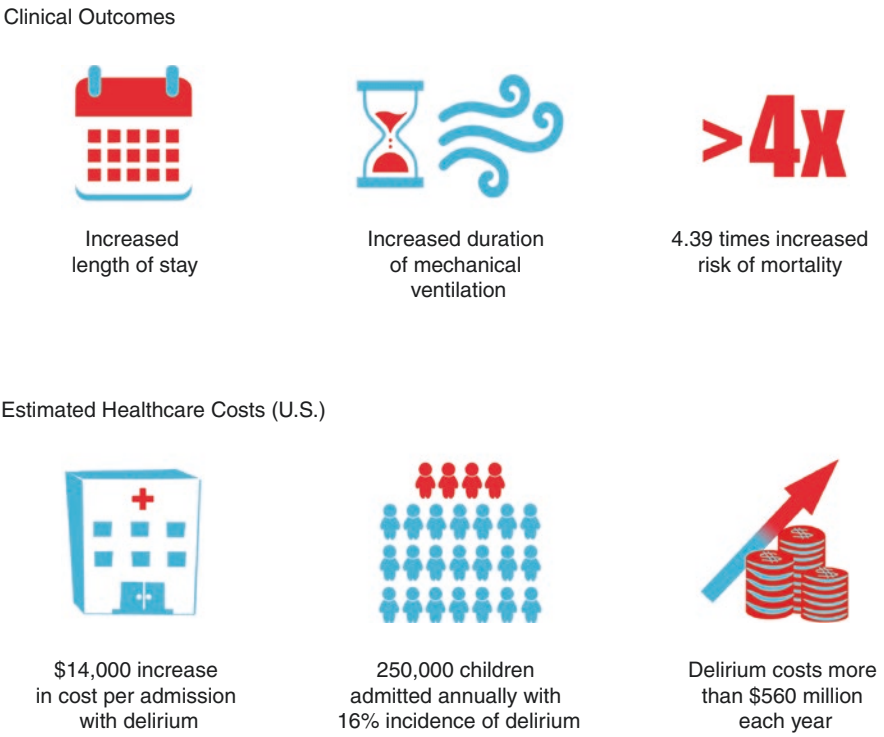

Fig. 7.2 Outcomes associated with delirium in children in the ICU

delirium, as was duration of mechanical ventilation. Finally, the authors identified that delirium was a strong and independent predictor of mortality with an adjusted odds ratio of 4.39. While other studies had identified that prolonged stay in the PICU was associated with delirium, this is one of the first studies to highlight the impact of delirium on mortality.

Another emerging outcome of interest in the study of delirium is the cognitive and behavioral consequences of delirium. Recent evidence supports the concern that adults who develop delirium are at an increased risk for a decline in cognitive and adaptive functioning. To begin to explore this topic in critically ill children, Meyburg et al. conducted a single-center point prevalence study to investigate the long-term neurocognitive impact of delirium on children [29]. Contrary to the findings in adults, the authors found no clear association between pediatric delirium and long-term neurocognitive outcomes. Larger multicenter studies are now required to further evaluate this relationship.

An often overlooked outcome in delirium is healthcare costs. Delirium in adults has been associated with an increase in healthcare costs, with some estimates at over 4 billion dollars annually [30]. While on a smaller scale, pediatric delirium likely contributes to an overall increase in healthcare costs in the United States. In a single-center study, Traube et al. found that a diagnosis of delirium is associated with an 85% increase in PICU costs, and at their institution, this increase in cost was approximately $14,000 per admission [31]. With an incidence of delirium of 16% (in their cohort) and roughly 250,000 children admitted to critical care units in the United States annually, this would translate into an increase in hospital charges of more than $560 million each year.

Conclusion

Much has been learned about the epidemiology of pediatric delirium over the last decade. Due to advances in delirium screening methods in children, we now know that one in four children admitted to the PICU are likely to suffer from delirium. Delirium itself significantly impacts length of stay in the hospital and dramatically increases overall hospital cost. The prevalence is even higher in special pediatric populations, such as those who require ECMO or cardiac surgery. However, much less is known about delirium in children outside the PICU. With emerging literature on the benefits of the ABCDEF bundle and extrapolated data from our adult colleagues, Fig. 7.3 highlights potential practices for prevention and management of delirium in children. Significant contributions have been made to the study of pediatric delirium, but much work is still to be done.

Fig. 7.3 Potential practices for prevention and management of delirium in children

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