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Neurologic Outcomes Following Care in the Pediatric Intensive Care Unit

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Opinion statement

Purpose of review With increasing survival of children requiring admission to pediatric intensive care units (PICUs), neurodevelopmental outcomes of these patients are an area of increased attention. Our goal was to systematically review recently published literature on neurologic outcomes of PICU patients.
Recent findings Decline in neurofunctional status occurs in 3–20% of children requiring PICU care. This proportion varies based on primary diagnosis and severity of illness, with children admitted for primary neurologic diagnosis, children who suffer cardiac arrest or who require invasive interventions during the PICU admission, having worse outcomes. Recent research focuses on early identification and treatment of modifiable risk factors for unfavorable outcomes and on long-term follow-up that moves beyond global cognitive outcomes and is increasingly including tests assessing multidimensional aspects of neurodevelopment.
Summary The pediatric critical care research community has shifted focus from survival to survival with favorable neurologic outcomes of children admitted to the PICU.

Introduction

Advances in science, technology, and systems of care in emergency medicine and pediatric critical care medicine over the last several decades have led to significantly improved survival of children with critical illness [1–3]. This trend of improved survival has been widely described in the overall pediatric intensive care unit (PICU) population [1] as well as in children with specific diagnoses, including sepsis [4], cardiac arrest [5, 6], acute respiratory distress syndrome (ARDS) [7], and oncologic disorders [8]. However, increased survival has also translated to increased morbidity among survivors [2, 9]. Therefore, post-discharge morbidity, and specifically, new neurologic morbidity, has become a more relevant and meaningful outcome than mortality in the contemporary era of PICU care. In this systematic review of the literature, we discuss results of studies published in the last 5 years that focus on neurofunctional outcomes following PICU care, as well as some of the standardized outcome measures most commonly used in these studies.

Methods

Electronic searches of PubMed and EMBASE were conducted in January 2017 using heading terms and keywords to define concepts of pediatric critical care and neurologic outcomes (Supplemental Digital Content 1). The search was limited to publications between 2012 and 2016. Two reviewers (S.D.C., M.M.B) reviewed all citations independently, and disagreements were resolved by a third reviewer (S.R.K.). Eligible studies included children <18 years of age admitted to a PICU, and evaluated neurofunctional outcomes using standardized outcome measure tool(s). Studies were excluded if they met any of the following criteria: (1) subjects were cared for in the neonatal or pediatric cardiac intensive care unit exclusively; (2) included an adult-only population or a mixed population with the inability to separate data for children; (3) case reports or case series with <10 subjects; (4) animal studies; (5) non-original data; or (6) studies published in language other than English.

Results

Search results are presented in Fig. 1. The patient populations and/or pathologies evaluated in the 66 studies included in the final review were: general PICU patients (n = 15 studies) [9–23], seizures and/or status epilepticus (SE) (n = 7) [24–30], traumatic brain injury (TBI) (n = 17) [31–47], cardiac arrest (n = 22) [48–69], and infectious diseases (n = 5) [70–74].

The most commonly used outcome measure was the Pediatric Cerebral Performance Category (PCPC) [75, 76]. The PCPC was developed to evaluate the global cognitive impairment; it ranges from 1 to 6 with 1 being normal, 2 mild disability, 3 moderate disability, 4 severe disability, 5 coma or vegetative state, and 6 brain death [75, 76]. In most studies, PCPC is assessed at baseline (preadmission) and at hospital discharge, via medical record review or caregiver interview, and has very good to excellent interrater reliability, making it amenable to research [76]. The second most commonly used outcome measure was the Glasgow Outcome Scale (GOS) and its extensions, GOS-Extended (GOS-E) and GOS-E Pediatric Revision (GOS-E Peds) [77–79]. The GOS describes a range of disability, ranging from good recovery to death, and is administered as

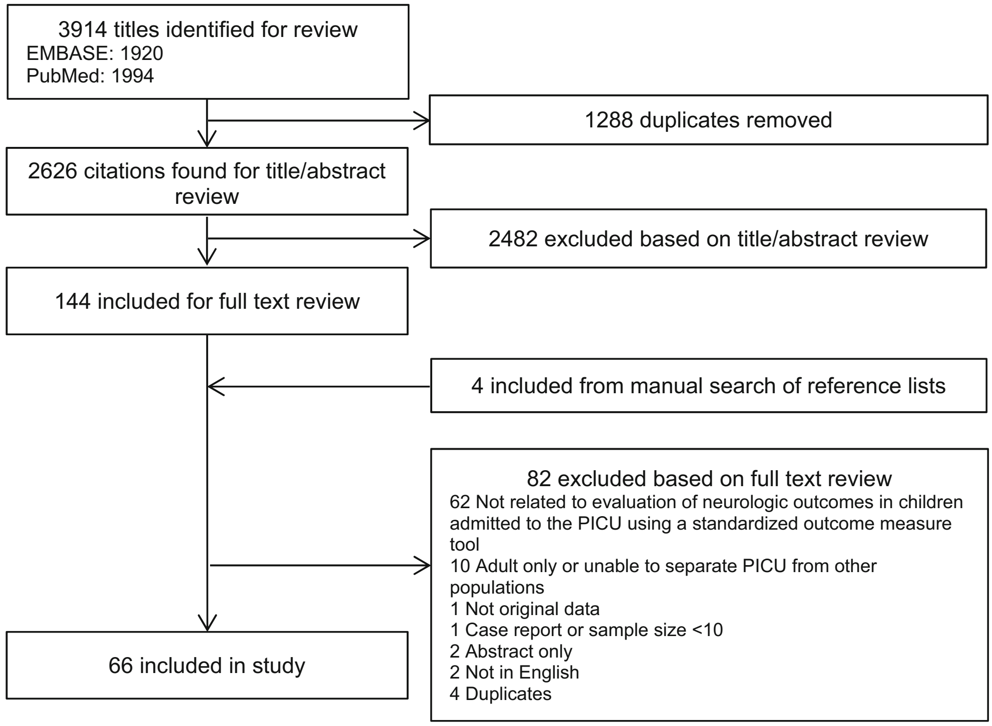

Fig. 1. Study flowchart.

a semi-structured interview [79]. Its pediatric version, GOS-E Peds, has recently been validated in children with TBI [78]. The full list of outcome measures identified in this systematic review is listed in Table 1. While some variability is to be expected given the wide range of age and pathology of critically ill children, the large number of measures used to evaluate short- and long-term outcomes of children after PICU discharge is also reflective of the lack of consensus on a core group of measures that should be used for outcome research in the PICU population.

Neurologic outcomes following PICU care

General PICU population

A decline in neurofunctional status following pediatric critical illness has been described in multiple recent studies. New morbidity occurs in up to 4.8% PICU patients, with higher rates (7.3%) seen in children with critical neurologic conditions [3, 20]. In a retrospective analysis of 29,352 admissions to 24 PICUs submitting data to the Virtual PICU Performance System network, 3.4 and 10.3% of participants acquired global cognitive or functional disability, respectively, as measured by PCPC and Pediatric Overall Performance Category (POPC) at the time of hospital discharge [19]. Risk factors for acquiring functional and cognitive disability were trauma, oncologic and neurologic primary diagnoses, unscheduled admission to the PICU, need for mechanical ventilation, renal replacement therapy, cardiopulmonary resuscitation, or extracorporeal membrane oxygenation [19].

Table 1. Outcome measures used in pediatric critical care studies

Outcome measure	No. of studies
PCPC	25
GOS[a]	16
WIQS	6
POPC	5
CBCL	5
FSS	4
CMS	4
BBDT	3
HUI	3
PedsQL	3
VABS-II	2
CHQ	2
WRIT	2
CNTAB	2
ANT	2
IES	2
Other[b]	20

PCPC Pediatric Cerebral Performance Category, *GOS* Glasgow Outcome Scale, *WIQS* Wechsler Intelligence Quotient Scales, *POPC* Pediatric Overall Performance Category, *CBCL* Child Behavior Checklist, *FSS* Functional Status Score, *CMS* Children's Memory Scale, *BBDT* Beery-Buktenica Development Test of Visual-Motor Integration, *HUI* Health Utilities Index, *PedsQL* Pediatric Quality of Life Inventory, *VABS-II* Vineland Adaptive Behavior Scale-II, *CHQ* Child Health Questionnaire, *WRIT* Wide Range Intelligence Test, *CNTAB* Cambridge Neuropsychological Test Automated Battery, *ANT* Amsterdam Neuropsychological Tasks, *IES* Impact of Events

[a]GOS includes GOS (n = 12 studies), GOS-Extended for Pediatrics (n = 2), and modified GOS (n = 2)

[b]Other outcome measures used in one study each: *ABAS* Adaptive Behavior Assessment System, *ABQ* A Behavioral Questionnaire, *ASDS* Acute Stress Disorder Scale, *BDI-II* Beck Depression Inventory: II, *BRIEF* Behavior Rating Inventory of Executive Function, *CPMS* Childhood Psychopathology Measurement Schedule, *CSDC* Child Stress Disorders Checklist, *CSHQ* Child Sleep Habits Questionnaire, *DP3* Development Profile 3, *HADS* Hospital Anxiety and Depression Scale, *HSUI* Health State Utilities Index, *KOSCHI* King's Outcome Scale for Childhood Head Injury, *MAQ* Multidimensional Anxiety Questionnaire, *MISIC* Malin's Intelligence Scale for Indian Children, *PTSDC-C* PTSD Checklist-Civilian, *RAH MOF* Royal Alexandra Hospital for Children Measure of Function, *SCORE* Subtest "SCORE" of the Test of Everyday Attention for Children, *SDQ* Strength and Difficulties Questionnaire, *TRF* Teacher Report Form, *YSR* Youth Self Report

Children admitted to the PICU remain fragile for long periods of time following their critical illness. In a single center prospective observational study of 91 children who required urgent PICU admission and were followed up to 1 month after discharge, 22% of subjects had PCPC ≥3 and 28% had poor adaptive behavior functioning (defined as a Vineland Adaptive Behavior Scale—Second Edition [VABS-II] composite score ≤70) [16]. A greater PCPC at baseline, neurologic illness and longer ECMO duration were associated with worse PCPC [16]. A greater PCPC at baseline, longer chest compression duration, lower oxygen saturations, and circulatory compromise on admission were associated with worse VABS-II composite scores [16]. In a single-center prospective longitudinal cohort of PICU patients followed up to 3-year post-discharge, the Functional Status Scale (FSS) worsened in 37.7% of subjects, remained unchanged in 44.1%, and improved in only 9% of subjects [20].

Patients with unfavorable 3-year neurofunctional outcomes were more likely to have required vasoactive medications and mechanical ventilation and to have had longer duration of mechanical ventilation and PICU length of stay (LOS) [20]. As a likely surrogate for severity of illness, LOS is consistently reported as a risk factor for unfavorable neurofunctional outcomes in PICU patients. Prolonged PICU admissions beyond 28 days are followed by moderate or severe disability as defined by a modified Glasgow Outcome Scale in as many as 67% of survivors [13].

Studies obtaining detailed neuropsychological testing in PICU survivors are somewhat limited by sample size, heterogeneity of primary diagnoses, cost, and loss to follow-up. Cohorts developed in Europe suggest that cognition, adaptive behavior, and verbal and visual memory in children who survive critical illness are within normal range, but tend to be significantly lower compared to healthy controls [22, 70]. Multiple contributing factors have been studied or are currently under study, including glucose control, sedation strategies, overall PICU LOS, and pre-PICU co-morbidities [22, 70, 72].

The impact of ICU care on development of short- and long-term psychiatric symptoms has been well documented in adult and pediatric ICU patients. In the ICU, delirium affects up to 80% of critically ill adults, and a recent international point prevalence study of critically ill children revealed that delirium was present in 25% of all children [80]. In children admitted to the PICU greater than 6 days, prevalence increased to 38% [80]. Similar to adults, independent risk factors for delirium in the PICU include benzodiazepines, use of physical restraints, and mechanical ventilation [80]. PICU length of stay is increased in children with delirium, as is duration of mechanical ventilation [81]. Despite the availability of validated screening tools for ICU setting in infants and children of all ages [82–84], however, routine delirium screening is not yet the PICU standard of care [85].

The link between ICU delirium and long-term neurologic outcomes is an emerging area of interest to both the adult and pediatric critical care community. While delirium affects patients during their ICU admission, a strong foundation of evidence on sequelae of ICU survivorship in adults has led to the definition of post-intensive care syndrome, or PICS [86]. PICS is defined as "new or worsening impairments in physical, cognitive, or mental health status arising after critical illness and persisting beyond hospitalization." A systematic review by Herrup et al. synthesizing the available pediatric evidence on morbidities within the construct of PICS found 19 studies which encompassed the characteristics of PICS, including nine studies on psychological morbidity after PICU admission [87]. Anxiety and depression, culminating in post-traumatic stress disorder, has been well documented in adult survivors of critical illness [88]. In children, limited evidence suggests that post-traumatic stress symptoms after PICU admission, including delusional memories, intrusive thoughts, and avoidance, occur in up to 32% of PICU survivors [18, 23]. Septic illness, increased numbers of invasive procedures, and benzodiazepines have been implicated as risk factors [18, 89–92], and psychoeducational tools have been piloted with some success [12]. Pediatric PICS is an important and rapidly growing area of research with results of ongoing multicenter studies expected to be published in the next few years [93]. Additionally, nine US PICUs have joined together as part the Society of Critical Care Medicine (SCCM) Pediatric ICU Liberation Collaborative to investigate approaches to multicomponent, interdisciplinary care using the "ABCDEF" bundle to improve outcomes for critically ill children through analgesia (A), ventilator management (B = breathing), sedation titration (C = coordination), delirium (D) prevention and treatment, early mobilization (E), and family engagement (F) [94, 95].

Neurocritical care

As many as 61% of children with neurocritical illness have unfavorable outcomes at hospital discharge, defined as PCPC 4–6 [28]. Among children with neurocritical illness, outcomes tend to be worse in children with stroke, cardiac arrest, and SE, compared to TBI [24, 27, 28].

Seizures and clinical or electrographic SE are reported in 10–40% of children in the PICU [26–29]. An increasing and impressive body of literature on the prevalence and adverse outcomes associated with seizures and SE in the PICU has been published by multidisciplinary groups composed of pediatric intensivists, neurologists, and neurophysiologists in the last years, as part of the pediatric Status Epilepticus Research Group (pSERG), the Critical Care Electroencephalography (EEG) Monitoring Research Consortium, the Approaches and Decisions in Acute Pediatric TBI Trial (ADAPT), and others [96–99].

In a retrospective observational cohort of children admitted to the ICU at a single institution, Payne et al. recently reported that as many as 93/259 (36%) experienced seizures and 23/259 (9%) experienced SE [26]. Children who spent more time per hour with a seizure (increased seizure burden) were younger, had a longer ICU LOS, and had larger decline in PCPC score at discharge compared to baseline [26]. Patients with a decline in PCPC at discharge compared to baseline were more likely to have a history of epilepsy, seizure on presentation, increased seizure burden during the ICU stay, unreactive EEG background, and a discharge diagnosis of acute brain injury [26]. In a distinct cohort of 200 children with acute encephalopathy admitted to the PICU and who underwent continuous EEG monitoring, Topjian et al. determined that 84 (42%) had seizures, categorized as electrographic seizures in 41 (20.5%), and electrographic SE in 43 (21.5%) [30]. After accounting for potential confounders, electrographic SE was significantly associated with increased risk of mortality and decline in PCPC at hospital discharge compared to baseline [30]. Electrographic seizures without SE were not associated with worse outcomes [30].

Electrographic SE appears to be a significant risk factor for unfavorable outcomes beyond the time of hospital discharge. In a cohort of 137 children who were neurodevelopmentally normal prior to PICU admission and who underwent clinically indicated EEG monitoring while critically ill, unfavorable outcomes based on the GOS-E Peds obtained at median time of 2.7 years after PICU discharge were found in 21/60 (35%) of subjects seen in follow-up [25]. Electrographic SE during the PICU stay was associated with unfavorable outcomes while electrographic seizures were not [25]. Children who experienced electrographic SE during the PICU stay also had a significantly worse quality of life at follow-up [25]. In this same cohort, Abend et al. reported that, in multivariable analysis, both electrographic seizures and electrographic SE during the PICU stay were significantly associated with lower adaptive behavior global composite scores compared to subjects with no seizures [29].

Similarly, *TBI* represents a significant cause of morbidity and mortality in children admitted to the PICU [31, 36, 42, 100]. As shown in other fields, protocolized care and adherence to guidelines, even if of low evidence level, can be associated with improved outcomes. O'Lynnger et al. evaluated the institution of protocolized therapy for TBI in a single center and demonstrated a significant decrease in mortality, but no significant difference in GOS scores among survivors, after vs before protocol institution [43]. In a study evaluating adherence to the 2003 Pediatric TBI guidelines in children with severe TBI who survived past 48 h of admission, for every 1% increase in adherence there was a 1% decrease in the chance of a poor outcome at discharge [42]. Multiple predictors of unfavorable neurologic outcome following pediatric TBI have been described, including elevated intracranial pressure and decreased cerebral perfusion pressures [37, 42, 101], low Glasgow Coma Scale (GCS) on admission [40, 41, 44, 46], subarachnoid hemorrhage and abnormal basal cisterns [35, 44], and cerebral edema [35, 41, 46] on neuroimaging. However, several randomized controlled trials in pediatric TBI investigating therapies, such as hypothermia [102], decompressive craniectomy [103], or immune-enhancing diet [104], have failed to improve patient outcomes. Enrolling children in moderate to severe TBI trials has also been shown to be extremely challenging, due to heterogeneity of injury, early availability of guardians for informed consent, and the need for large number of centers requiring significant efforts in training and coordination [105]. Using alternative approaches to randomized controlled trials, two large ongoing multicenter studies are starting to challenge paradigms of pediatric trauma systems and clinical care. Preliminary results have already been published, with more publications systematically addressing pediatric trauma guideline adherence (the Pediatric Guideline Adherence Outcomes [PEGASUS] study) and specific aspects of pediatric TBI care (ADAPT Trial; www.ADAPTTrial.org) are expected in the near future [106–110]. ADAPT is an observational cohort study of 1000 children comparing the effectiveness of the following therapeutic strategies employed in severe TBI: first-line intracranial pressure management (cerebrospinal fluid diversion and hyperosmolar therapies), mitigation of secondary insults (hyperventilation without intracranial hypertension and hypoxia detection/treatment using interstitial brain oxygen monitoring), and metabolic support (nutritional support and glucose management) [106]. Detailed neurodevelopmental follow-up data will be available in survivors from multiple international participating sites [106].

Cardiac arrest

Major progress has been achieved in the contemporary cardiopulmonary resuscitation of children after cardiac arrest. Using data from the American Heart Association Get With The Guidelines—Resuscitation (AHA GWTG-R) registry, Berg et al. demonstrated in a study published in 2013 that the ratio of PICU vs general ward cardiopulmonary resuscitation events in 315 US hospitals has significantly increased over the study period of 2000–2010, a phenomenon thought to be linked to the successful implementation of rapid response teams in hospitals around the country, with earlier recognition and transfer of patients with deteriorating clinical status to the PICU [111, 112]. A parallel increase in survival and survival with good neurologic function has also been described [5, 6, 51, 112]. In a 1997 study conducted in 32 North-American PICUs, the incidence of cardiopulmonary resuscitation events >2 min in PICU patients was 205/11,165 (1.8%)—only 13.7% survived to hospital discharge [5]. While the incidence of cardiac arrest in the PICU has not changed significantly since the 1990s, outcomes have certainly seen a remarkable improvement. In a recently published large prospective multicenter study that took place at 11 National Institute of Child Health and Human Development's Collaborative Pediatric Critical Care Research Network (NICHD/CPCCRN) academic children's hospitals, the incidence of cardiac arrest in the PICU was similar, 139/10078 (1.4%) [51]. However, of the 139 children who required cardiopulmonary resuscitation ≥1 min and/or defibrillation in the PICU, 78% had return of circulation, 45% survived to hospital discharge, and 89% of survivors had favorable neurologic outcome, defined as PCPC at hospital discharge 1–3 or no decline from baseline PCPC [51].

In contrast, out-of-hospital pediatric cardiac arrest is still fraught with poor outcomes. The results of a major randomized controlled trial of therapeutic hypothermia after out-of-hospital pediatric cardiac arrest (THAPCA-OH) were published in 2015 [67•]. There were 295 children who required cardiopulmonary resuscitation for ≥2 min, were comatose and mechanically ventilated after return of circulation, and who were randomized to therapeutic hypothermia vs therapeutic normothermia [67•]. Compared to therapeutic normothermia, therapeutic hypothermia did not improve survival with good functional outcome at 1 year post-arrest [67•]. Favorable neurobehavioral outcome at 1-year post-arrest, defined as VABS-II composite score >70, was present in 27/138 (20%) subjects in the hypothermia group and 15/112 (12%) subject in the normothermia group [67•]. Risk factors for poor long-term neurobehavioral function were acute life threatening event/sudden unexpected infant death, respiratory causes of arrest other than drowning, unknown causes of arrest, and duration of chest compressions >30 min [68]. There are significant ongoing efforts to optimize emergency medical systems of care and therapies aimed at improving outcomes after pediatric out-of-hospital cardiac arrest. Successes are starting to be reported in increased utilization of bystander cardiopulmonary resuscitation leading to improved overall survival and survival with favorable neurologic outcomes [69].

Drowning is the leading cause of accidental death among toddlers and continues to carry high morbidity in some children who survive [66, 113]. Our systematic review identified four articles published in the last 5 years which examined outcomes after drowning. Overall mortality from drowning remains high, recently reported as 17–73% [65, 66, 113]. Unfavorable outcome was associated with longer CPR time [64, 66, 113], CPR by emergency medical providers vs early initiation by bystander [65], more than four doses of epinephrine needed during cardiac arrest [64], lower base deficit and pH [65, 113], longer duration of mechanical ventilation [65], longer PICU LOS [65], and multiple failing organs [66]. Favorable outcomes have been associated with drowning in the winter [113].

Submersion for <10 min and drowning in water <6 °C has been associated with a normal full scale intelligence quotient [65]. Having a low intelligent quotient at median follow up of 8.5 years was associated with requiring CPR by emergency medical providers compared to those who received CPR only by a bystander [65]. In the THAPCA-OH trial, children who suffered drowning and required CPR for >30 vs ≤30 min had significantly lower VABS-II composite scores (median 41 vs 91) [64]. VABS-II is a caregiver report measure developed to assess communication, daily living, social, and motor domains of adaptive behavior [114]. The age-corrected composite score has a mean of 100 (standard deviation, 15) in the general population [114].

Infectious diseases

A large point prevalence study conducted in 128 international PICUs and published in 2015 showed that pediatric sepsis remains a significant public health challenge around the world [74]. In this study, 569 of 6925 PICU patients (8.2%) met diagnostic criteria for severe sepsis [74]. Hospital mortality was 25% and 17% of survivors had acquired moderate disability at hospital discharge, defined as discharge POPC ≥3 and increased ≥1 from baseline POPC [74]. Recent studies of long-term outcomes of children with severe sepsis showed that, at 3–9 months post-discharge, children with sepsis-associated encephalopathy had significantly decreased global and verbal intelligence quotient, compared to control sepsis patients not admitted to the PICU and to healthy controls [70–72]. Evaluation of academic performance also revealed that children with sepsis who required PICU care had significantly higher rates of difficulties in completing school work, deterioration in academic performance, dividing attention, and considering a variety of possible outcomes [70].

Acute respiratory distress syndrome

Outcomes of pediatric ARDS survivors have been comprehensively and systematically summarized by the Pediatric Acute Lung Injury Consensus Conference (PALICC) group [7]. In a multicenter randomized controlled trial of prone positioning, 16% of children who survived ARDS showed a decline in POPC and 11% showed a decline in PCPC at hospital discharge [115]. However, long-term outcomes of pediatric ARDS are difficult to ascertain given that most PICU studies do not separate children who meet ARDS diagnostic criteria [7]. The 2015 PALICC recommendations on long-term outcome assessment of children with ARDS of any etiology are to conduct physical, neurocognitive, emotional, family, and social function evaluation within 3 months of hospital discharge in children with moderate-to-severe pediatric ARDS and that the same evaluation should be conducted prior to school start in children who developed pediatric ARDS as infants or toddlers [116]. Future studies of neurocognitive outcomes after pediatric ARDS were recommended with strong agreement [116]. An ongoing large multicenter study is aiming to determine the association between sedative exposure and neurocognitive function at 2.5 years post-ICU discharge, in 500 subjects that had been enrolled in the Randomized Evaluation of Sedation Titration for Respiratory Failure (RESTORE) study [117, 118•].

Conclusions

Decline in neurofunctional status occurs in up to a quarter of children requiring PICU care. This proportion varies based on primary diagnosis and severity of illness, with children admitted for primary neurologic diagnoses, children who suffer cardiac arrest or who require invasive interventions during the PICU admission, having worse outcomes. Recent research focuses on early identification and treatment of modifiable risk factors for unfavorable outcomes and on long-term follow-up that moves beyond global cognitive outcomes and is increasingly relying on tests assessing multidimensional aspects of neurodevelopment.

Compliance with Ethical Standards

Conflict of Interest
Sherrill D. Caprarola declares that she has no conflicts of interest. Sapna R. Kudchadkar declares that she has no conflicts of interest. Melania M. Bembea reports support for this work included funding from the National Institute of Neurological Disorders and Stroke of the National Institutes of Health under Award Number K23NS076674 (MMB).

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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