Acute Neurologic Dysfunction in Critically Ill Children: The PODIUM Consensus Conference

Mark S. Wainwright, MD, PhD, FAAN,[a] Kristin Guilliams, MD,[b] Sujatha Kannan, MBBS,[c] Dennis W. Simon, MD,[d] Robert C. Tasker, MA, MD (Cantab), MBBS (Lond), DCH, FRCPCH, FRCP, FHEA (UK), AM (Harvard), MD (MA),[e] Chani Traube, MD,[f] Jose Pineda, MD[g] on behalf of the Pediatric Organ Dysfunction Information Update Mandate (PODIUM) Collaborative

abstract

CONTEXT: Acute neurologic dysfunction is common in critically ill children and contributes to outcomes and end of life decision-making.

OBJECTIVE: To develop consensus criteria for neurologic dysfunction in critically ill children by evaluating the evidence supporting such criteria and their association with outcomes.

DATA SOURCES: Electronic searches of PubMed and Embase were conducted from January 1992 to January 2020, by using a combination of medical subject heading terms and text words to define concepts of neurologic dysfunction, pediatric critical illness, and outcomes of interest.

STUDY SELECTION: Studies were included if the researchers evaluated critically ill children with neurologic injury, evaluated the performance characteristics of assessment and scoring tools to screen for neurologic dysfunction, and assessed outcomes related to mortality, functional status, organ-specific outcomes, or other patient-centered outcomes. Studies with an adult population or premature infants (≤36 weeks' gestational age), animal studies, reviews or commentaries, case series with sample size ≤10, and studies not published in English with an inability to determine eligibility criteria were excluded.

DATA EXTRACTION: Data were abstracted from each study meeting inclusion criteria into a standard data extraction form by task force members.

DATA SYNTHESIS: The systematic review supported the following criteria for neurologic dysfunction as any 1 of the following: (1) Glasgow Coma Scale score ≤8; (2) Glasgow Coma Scale motor score ≤4; (3) Cornell Assessment of Pediatric Delirium score ≥9; or (4) electroencephalography revealing attenuation, suppression, or electrographic seizures.

CONCLUSIONS: We present consensus criteria for neurologic dysfunction in critically ill children.

[a]*Division of Pediatric Neurology, Department of Neurology, School of Medicine, University of Washington, Seattle, Washington;* [b]*Division of Pediatric and Development Neurology, Department of Neurology and Division of Pediatric Critical Care Medicine, Department of Pediatrics, School of Medicine, Washington University in St Louis, St Louis, Missouri;* [c]*Department of Anesthesiology and Critical Care Medicine, School of Medicine, Johns Hopkins University, Baltimore, Maryland;* [d]*Department of Critical Care Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania;* [e]*Department of Anesthesiology, Critical Care and Pain Medicine, Harvard Medical School, Harvard University, Boston, Massachusetts;* [f]*Division of Critical Care Medicine, Department of Pediatrics, Weill Cornell Medical College, New York; and* [g]*Department of Anesthesiology Critical Care, Children's Hospital Los Angeles and Keck School of Medicine, University of Southern California, Los Angeles, California*

Drs Wainwright, Guilliams, Kannan, Simon, Tasker, Traube, and Pineda conceptualized and designed the study, collected data, conducted the initial analyses, drafted the initial manuscript, and reviewed and revised the manuscript; Dr Pineda coordinated data collection; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

The guidelines/recommendations in this article are not American Academy of Pediatrics policy, and publication herein does not imply endorsement.

DOI: https://doi.org/10.1542/peds.2021-052888E

Accepted for publication Sep 24, 2021

Children with acute brain injuries including cardiac arrest, traumatic brain injury (TBI), status epilepticus, central nervous system (CNS) infection, or stroke comprise 20% of admissions to the PICU. Neurologic complications of other organ injuries are also common.[1] Among all children admitted to the PICU, brain injury is the most common cause of death, with mortality of up to 24% after cardiac arrest.[2] Survivors of other common critical illnesses are at risk for neurologic complications, including seizures, during the ICU admission. Nonconvulsive seizures are detected in nearly 30% of critically ill children who undergo continuous EEG (cEEG) for any reason.[3] Children who survive critical illness may go on to experience a long-term combination of cognitive, affective, and physical symptoms that compromise their quality of life, a constellation characterized as post–intensive care syndrome-pediatric.

Accurate characterization of neurologic dysfunction in critically ill children has relied on a combination of the findings on the neurologic examination and invasive and noninvasive measures of neurologic function, including EEG, neuroimaging, biomarkers, near-infrared spectroscopy, optic nerve sheath, intracranial pressure, and brain tissue oxygen monitoring. A range of issues with each measure has limited their effective use in pediatric critical care, including developmental changes in the neurologic examination, the confounding effects of sedation on this examination, variable durations of outcome and measures of neurologic morbidity, and the heterogeneity of neurologic insults.

After a systematic review of the literature, the Neurologic Dysfunction workgroup of Pediatric Organ Dysfunction Information Update Mandate Consensus (PODIUM) created a set of criteria to define neurologic dysfunction in children with multiple organ dysfunction syndrome (MODS). These criteria include 2 composite measures of the neurologic examination, the Glasgow Coma Scale (GCS) score,[4] the Cornell Assessment of Pediatric Delirium (CAPD) score,[5] and noninvasive neuromonitoring by using the EEG.[6,7] The GCS was first described in the 1970s and is now used in 80% of PICUs for serial neurologic assessment.[8] Delirium, as reflected by the CAPD score, occurs in ~20% of critically ill children and is associated with increased mortality and morbidity.[9] Seizures and background EEG abnormalities are also common in critically ill children and have been associated with neurologic outcomes in range of neurologic insults, including encephalitis, TBI, and cardiac arrest.[10–12] The PODIUM criteria proposed here assign specific values of the GCS and CAPD and features of the EEG, which can be used to identify acute brain dysfunction in critically ill children.

METHODS

The PODIUM collaborative sought to develop evidence-based criteria for organ dysfunction in critically ill children. In the present article, we report a systematic review on neurologic dysfunction scoring tools performed as part of PODIUM, provide a critical evaluation of available literature, and propose evidence-based criteria for neurologic dysfunction in critically ill children as well as research priorities listed in the Supplemental Information. The PODIUM Executive Summary details Population, Interventions, Comparators, and Outcomes questions; search strategies; study inclusion and exclusion criteria; and processes for risk of bias assessment, data abstraction, and synthesis; and for drafting and developing agreement for criteria indicating neurologic dysfunction.[13]

RESULTS

Systematic Review

Of 7608 unique citations published between 1992 and 2020 identified, 199 studies were eligible for inclusion, as shown in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart (Fig 1). Studies conducted in pediatric TBI patients and published before March 2012 were excluded because they had been recently reviewed and summarized by the coauthors as part of the updates to the Brain Trauma Foundation recommendations for the management of pediatric severe TBI.[14] Data tables and risk of bias assessment are detailed in Supplemental Tables 1 and 2 and Supplemental Fig 1, respectively, in the Supplemental Information. Criteria for neurologic dysfunction in critically ill children informed by the evaluated evidence are presented in Table 1.

As presented in Supplemental Table 2, the majority (105) of the studies were prospective cohorts. A total of 72 studies were conducted by using a retrospective cohort design of a large database and 1 secondary analysis of a randomized controlled trial. The remainder included cases series with or without matched controls, observational studies, or another design.

A total of 31 studies were performed in a general, noncardiac PICU, 16 in a mixed pediatric noncardiac and cardiac ICU population and 24 in an emergency department alone or in combination

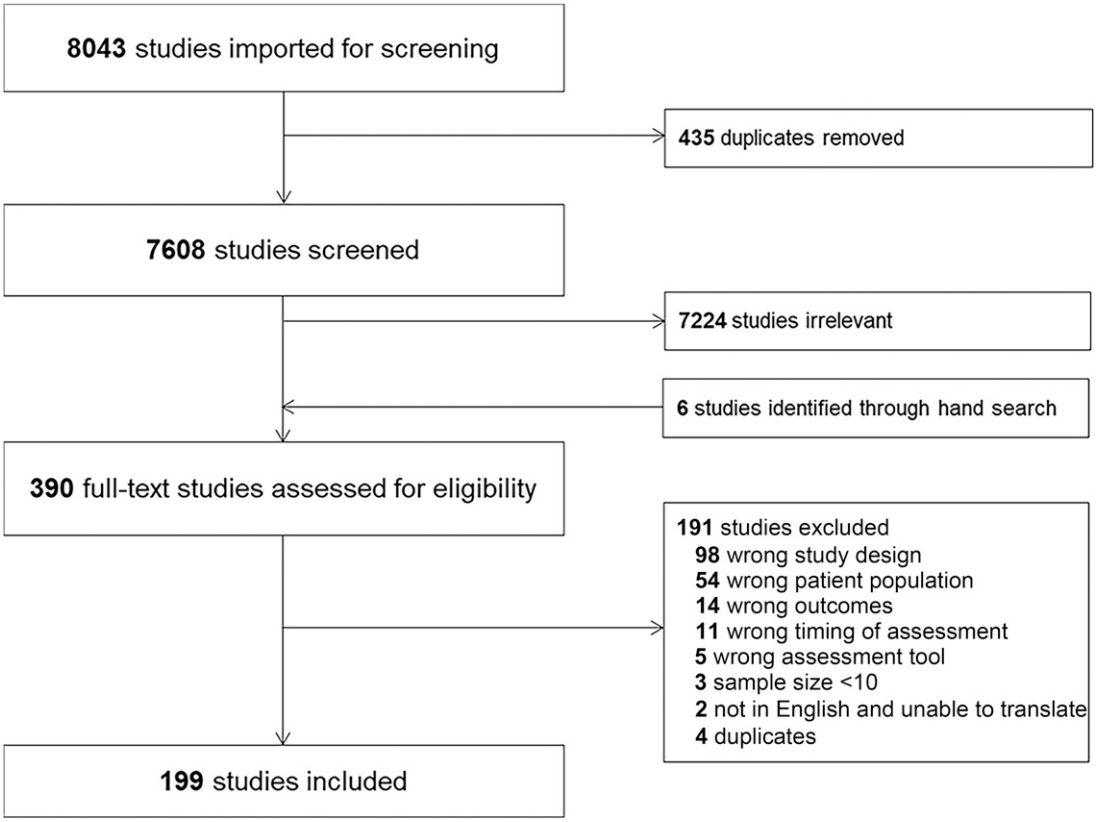

FIGURE 1
Study flow diagram according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis protocols recommendations.

with a PICU. The remaining studies were performed in newborn units, mixed inpatient settings that included PICU patients, or PICU populations of unknown composition. Sample sizes in each primary analysis ranged from 9 to 160 570.

The mechanism of injury was TBI in 67 studies; cardiac arrest or drowning in 22 studies; encephalitis, cerebral malaria, or meningitis in 8 studies; status epilepticus in 2 studies; stroke in 10 studies; or a general PICU population in 90.

Most of the studies included were a mixture of derivation or validation design. In 38 studies, researchers used mortality (death in the PICU or hospital, within 28 days of hospital discharge) as the primary outcome measure.

In 36 studies, researchers used functional outcomes including Pediatric Cerebral Performance Category (PCPC), Pediatric Overall Performance Category (POPC), Functional Status Scale, Functional Independent Measure for Children (WeeFIM), Pediatric Evaluation of Disability Inventory, cognitive (Mullen Scales of Early Learning, Wechsler Intelligence Scale for Children, and Bayley Scales of Infant Development) or adaptive measures (Vineland Adaptive Behavior Scales), or psychiatric diagnosis (depression). The majority (19) of the remainder included other

TABLE 1 PODIUM: Criteria for Neurologic Dysfunction in Pediatric Critical Illness

Criteria for Neurologic Dysfunction	Proposed Threshold	Exclusions	Severity
GCS	≤8	None	Not graded
GCS-m	≤4	None	Not graded
CAPD	≥9	None	Not graded
EEG background attenuation and suppression; electrographic seizures	NA	Not applicable in patients with history of seizures or acute neurologic injury on admission	Not graded

GCS-m, Glasgow Coma Score motor response; NA, not applicable.

outcome scores, such as the Liverpool Outcome Score, Glasgow Outcome Scale, diagnosis of delirium, and clinical and imaging signs of increased intracranial pressure.

In 25 studies, researchers evaluated the EEG for prediction of outcome. Researchers evaluated the GCS score in 50 studies, and delirium screening in 9 studies (CAPD; Pediatric Confusion Assessment Method for the ICU [pCAM-ICU] scores). The remainder comprised a mixture of imaging, biomarkers, and other clinical scores.

The timing of these measures was highly variable. In most (102) studies, researchers used information collected within the first 24 hours of ictus or admission, but the location of data collection varied from prehospital arrival to the emergency department, hospital, or ICU admission. In some studies, researchers performed serial measures, and these windows ranged from hours or daily during the hospital admission to intervals of months after discharge. Others used a single time point beginning between 1 to up to 10 days after ictus.

Criteria for Neurologic Dysfunction and Rationale

MODS-associated neurologic dysfunction is defined when a critically ill child meets any 1 of the criteria listed in Table 1.

Rationale: GCS Score

We reviewed 49 studies in which researchers evaluated the relationship between the GCS Score or the GCS-motor response (GCS-m) and mortality or functional outcome (Supplemental Table 1).

There were 14 studies ($N = 1547$ children; age range from neonates to 18 years) in which researchers assessed the relationship of the GCS score and functional neurologic outcome (Supplemental Table 1). All these studies comprised children with TBI. The majority of these studies were prospective cohorts and had single-center design, with 2 exceptions, which included 5 and 3 sites. The mean duration of follow-up was 7±5 years (range: 2–16). Most (12) of these studies were in a PICU, with 1 in a pediatric neurosurgical unit and 1 location not specified. In the majority (12), researchers studied the association of GCS and functional outcome in children after TBI. The timing of the GCS score was variable, with the authors of 8 studies using the admission score and others using the score assigned by emergency medical services, 6 hours post-TBI, or daily starting on day 1 in the PICU, within 24 hours of admission and during the acute phase in the ICU.

Other studies ($N = 5100$ children; age range neonates to 16 years) evaluated the association of the GCS score with a combination of functional outcome and mortality (Supplemental Table 1). The timing of assessment was both before[15,16] and at the time of admission. Neurologic insults included TBI, hypoxia-ischemia, CNS infection, or mixed PICU population, including status epilepticus and acute alteration in consciousness.

Studies in which researchers examined the association of the GCS with mortality or functional neurologic outcome and excluded neonates totaled 3929 children (Supplemental Table 1). In most of these studies, researchers were managing TBI. The remainder were a combination of a general PICU population, nontraumatic coma, or encephalopathy, CNS infection, or cardiac arrest.

Although the timing of neurologic assessment was variable and the outcomes combined both mortality and neurologic function, we found that these data reveal children with a GCS ≤8 before or within 24 hours of admission or a GCS-motor (GCS-m) score ≤4 (ie, failing to localize to a painful stimulus) not due to sedating medications should be considered to have MODS-associated neurologic dysfunction. Importantly, in research studies, researchers using the GCS score should also specify the GCS-m because, in some cases, this may be 5 with a total score of ≤8.

Rationale: CAPD Score

Delirium is defined as an acute and fluctuating change in consciousness and cognition that is the result of an underlying medical illness or its treatment.[16] The symptoms may be hyperactive hypoactive or mixed. In the CAPD screening test, the scores range from 0 to 32, with higher scores reflecting more severe symptoms of delirium.[5] This test can be applied to neonates and children up to 21 years. The pCAM-ICU is used to assess delirium in children ≥5 years of age.[18]

Pediatric delirium has been independently linked to poor outcomes in 7 prospective observational studies. All studies took place in either a PICU or pediatric cardiothoracic ICU and used a bedside pediatric delirium screening tool. Patients ranged in age from newborn to 21 years old. In 6 of the 7 studies, researchers used the CAPD; the operational definition of delirium was a CAPD score of ≥9. One study used the preschool version of the pCAM-ICU.

We reviewed 9 studies ($n = 2907$ children; age range neonates to 18 years) in which researchers examined the association of delirium

screening tools with outcome. Three studies included a general PICU population, whereas 2 included only patients with cardiac disorders. Three studies ($n = 93$, $n = 99$, $n = 1547$) revealed increased duration of invasive mechanical ventilation in children with delirium. One study ($n = 99$) revealed an independent association between delirium and increased hospital length of stay (LOS), and 5 studies ($n = 93$, $n = 99$, $n = 194$, $n = 300$, $n = 1547$) revealed an association between delirium and increased ICU LOS. In the largest study, the adjusted relative LOS for children with delirium was 2.3 (95% confidence interval [CI] 2.1 to 2.5; $P < .001$) after controlling for severity of illness and mechanical ventilation.[9] In this study, it was also established that delirium was a strong and independent predictor of in-hospital mortality (adjusted odds ratio: 4.39; 95% CI 1.96 to 9.99; $P < .001$).

In a single-center study in which researchers included 464 consecutive PICU admissions, it was indicated that, after controlling for age, severity of illness, and LOS, delirium was associated with an 85% increase in PICU costs (relative costs: 1.85; 95% CI 1.51 to 2.26, $P < .0001$). A pilot prospective cohort study ($n = 47$) did not reveal an association between pediatric postoperative delirium and cognitive and executive dysfunction at 18 months after PICU discharge.[18]

There are valid and reliable delirium screening tools available for use in the PICU.[19,20] Expert consensus recommends that all critically ill children be screened for delirium twice daily by using the CAPD as standard of care, throughout their PICU stay.[22] The CAPD has 8 domains (assessing eye contact, purposefulness, awareness, communication, restlessness, consolability, underactivity, and delayed response to interactions), scored on a Likert-type scale from 0 to 4; a score of ≥9 is consistent with the criterion standard delirium diagnosis by a child psychiatrist. This noninvasive, observational, cost-effective delirium screen has been validated for delirium diagnosis in children of all ages (0–21 years) and developmental stage.[5] It is important to recognize that bedside screening for delirium is highly feasible. As an example, an academic PICU implemented the CAPD as standard of care and revealed an overall compliance rate of 95% over a 22-month period.[23] As further evidence of feasibility, an international point-prevalence study including 25 separate PICUs successfully screened 835 children for delirium (84% of all patients) over 2 study days.[24]

We found that the presence of delirium, as defined by the CAPD score with a cutoff score of ≥9, was associated with greater risk for morbidity, LOS, and cost of care. We suggest that the score be performed twice daily at the end of each nursing shift by ICU bedside clinicians trained in its use. Patients who meet the screening threshold for delirium should then undergo an assessment for common treatable causes of delirium.

Rationale: EEG Background and Seizures

We reviewed 25 studies ($n = 2121$ subjects) in which researchers evaluated an association between EEG features (seizures or EEG background) alone (Supplemental Table 1) or in combination with other modalities including neuroimaging (head ultrasound, transcranial Doppler, computed tomography [CT], or MRI), neurophysiology (somatosensory evoked potential, or brainstem auditory evoked response), heart rate variability, and sleep-wake cycle (Supplemental Table 2). Three studies were focused exclusively on neonates.[25–27] In other studies, researchers included either neonates together with infants and older children up to adolescence or only children >2 months and ≤14 years of age.

The majority of studies were performed in patients after cardiac arrest. In other studies, researchers investigated outcome after TBI, CNS infection, status epilepticus or perinatal asphyxia, patients in coma and undergoing extracorporeal membrane oxygenation (ECMO) or cardiopulmonary bypass. Again, the timing was variable, with some performed within 24 hours of return of spontaneous circulation (ROSC) or ICU admission and others a range of days to up to a year after ictus. In only 1 study did researchers examine mortality exclusively whereas others combined mortality with functional outcome or residual morbidity. The remainder examined functional outcome or residual morbidity alone or brain imaging. The EEG characteristics examined in these studies included the background or changes in background or presence of seizures or status epilepticus.

Although some studies graded the severity of EEG background abnormalities, we did not find sufficient evidence to grade the degree of EEG abnormality of EEG burden. Accordingly, we found that a suppressed or attenuated EEG background not due to sedating medications or the presence of electrographic seizures should be considered evidence of neurologic dysfunction. This assessment cannot be made, however, in children with a history of seizures or in children with acute neurologic injury.

Neurologic failure in critically ill children may be a product of insults to cerebral gray or white matter, the brainstem, spinal cord, or the peripheral nervous system. The clinical signs of an insult will vary substantially with the location of the injury, and the impact on outcome may vary with the age of the child or may not be apparent for years after the insult. Improved identification of neurologic injuries in critically ill children will likely require a combination of clinical and EEG features and other diagnostic assessments, such as blood-based biomarkers, neuroimaging, and noninvasive neuromonitoring methods, including near-infrared spectroscopy and transcranial Doppler.

CONCLUSIONS

Neurologic failure is common in critically ill children and contributes to poor short and long-term outcomes and decisions to withdraw care. After a systematic review of 199 studies using a modified Delphi process, we propose clinical and EEG criteria for MODS-associated neurologic dysfunction. It is important to acknowledge that our ability to reliably identify critically ill children who develop neurologic failure or experience evolution of their initial brain injury in the ICU is limited. Development of improved clinical and neuromonitoring approaches (ie, blood-based biomarkers, neuroimaging, and noninvasive physiologic monitoring) to overcome this limitation is a necessary step toward the identification of specific pathophysiologic processes that result in neurologic failure, evaluating response to therapy, and further defining the effect of neurologic failure on long-term cognitive and psychological health.

ABBREVIATIONS

CAPD: Cornell Assessment of Pediatric Delirium
cEEG: continuous EEG
CI: confidence interval
CNS: central nervous system
CT: computed tomography
ECMO: extracorporeal membrane oxygenation
GCS: Glasgow Coma Scale
LOS: length of stay
MODS: multiorgan dysfunction syndrome
pCAM-ICU: Pediatric Confusion Assessment Method for the ICU
PCPC: Pediatric Cerebral Performance Category
PODIUM: Pediatric Organ Dysfunction Information Update Mandate Consensus
POPC: Pediatric Overall Performance Category
ROSC: return of spontaneous circulation
TBI: traumatic brain injury
WeeFIM: Functional Independent Measure for Children

Address correspondence to Mark S. Wainwright, MD, PhD, FAAN, Division of Pediatric Neurology, Department of Neurology, School of Medicine, University of Washington, 4800 Sand Point Way NE, Seattle, WA 98105. E-mail: mark.wainwright@seattlechildrens.org

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: Children's Hospital Los Angeles and Seattle Children's Hospital contributed to publication costs; this article was funded by National Institute of Neurological Disorders and Stroke grant K23NS099472 (Dr Guilliams) and National Cancer Institute grant R01CA244500 and *Eunice Kennedy Shriver* National Institute of Child Health and Human Development grant R01HD099284 (Dr Traube). The funding institutions had no role in the design and conduct of the study. Funded by the National Institutes of Health (NIH).

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

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