REVIEW ARTICLE

CONTINUUM AUDIO INTERVIEW AVAILABLE ONLINE

Neurologic Complications in the Pediatric Intensive Care Unit

By Mark S. Wainwright, MD, PhD

ABSTRACT

PURPOSE OF REVIEW: All critical care is directed at maintaining brain health, but recognizing neurologic complications of critical illness in children is difficult, and limited data exist to guide practice. This article discusses an approach to the recognition and management of seizures, stroke, and cardiac arrest as complications of other critical illnesses in the pediatric intensive care unit.

RECENT FINDINGS: Convulsive and nonconvulsive seizures occur frequently in children after cardiac arrest or traumatic brain injury and during extracorporeal membrane oxygenation. Seizures may add to neurologic morbidity, and continuous EEG monitoring is needed for up to 24 hours for detection. Hypothermia has not been shown to improve outcome after cardiac arrest in children, but targeted temperature management with controlled normothermia and prevention of fever is a mainstay of neuroprotection.

SUMMARY: Much of brain-directed pediatric critical care is empiric. Recognition of neurologic complications of critical illness requires multidisciplinary care, serial neurologic examinations, and an appreciation for the multiple risk factors for neurologic injury present in most patients in the pediatric intensive care unit. Through attention to the fundamentals of neuroprotection, including maintaining or restoring cerebral perfusion matched to the metabolic needs of the brain, combined with anticipatory planning, these complications can be prevented or the neurologic injury mitigated.

CITE AS:
CONTINUUM (MINNEAP MINN) 2018;24(1, CHILD NEUROLOGY): 288–299.

Address correspondence to Dr Mark S. Wainwright, Division of Neurology, Seattle Children's Hospital, 4300 Sand Point Way NE, Seattle, WA 98105, *Mark.Wainwright@seattlechildrens.org*.

RELATIONSHIP DISCLOSURE:
Dr Wainwright serves as a consultant for and on the clinical advisory board of SAGE Therapeutics.

UNLABELED USE OF PRODUCTS/INVESTIGATIONAL USE DISCLOSURE:
Dr Wainwright reports no disclosure.

INTRODUCTION

The lack of data from randomized controlled clinical trials to guide management of children with acute brain injuries or neurologic complications of critical illness occurs in striking contrast with the data available to neonatologists, adult neurointensivists, or adult stroke neurologists. Early recognition of changes in the neurologic examination is essential for brain-directed critical care for children. Therefore, neurologic management of the patient in the pediatric or cardiac intensive care unit (ICU) requires an interdisciplinary team involving neurologists, intensivists,

neurosurgeons, and allied disciplines, including physical medicine and rehabilitation and psychiatry.[1,2] Management should include anticipation of specific changes in the patient's examination, an understanding of the cellular mechanisms of injury causing that change, and a predefined intervention to address that mechanism.[3] This article discusses the approach to diagnosis and management of common neurologic complications in the pediatric ICU, including seizures, stroke, cardiac arrest, weakness, and sympathetic hyperarousal, as well as in two high-risk populations: children with acute liver failure and those supported with extracorporeal membrane oxygenation (ECMO).

GENERAL PRINCIPLES OF NEUROPROTECTION

All critical care is directed at maintaining brain health. In general, this means maintaining or restoring cerebral perfusion matched to the metabolic needs of the brain, whether this involves management of complications such as stroke, intracranial hemorrhage, cerebral edema, or refractory status epilepticus. The approaches needed to achieve this balance depend on the mechanism of the neurologic insult.

SEIZURES IN THE INTENSIVE CARE UNIT

Seizure management, or evaluation for suspected seizures or nonconvulsive seizures, is the most frequent reason for a request for neurologic evaluation in the ICU. Since many patients in the pediatric ICU or cardiac ICU have a risk factor for central nervous system (CNS) injury, the threshold for obtaining continuous EEG monitoring to characterize spells or to detect nonconvulsive seizures should be low. In the past decade, the burden posed by nonconvulsive seizures in critically ill children has increasingly been recognized, seen in approximately 30% of patients undergoing continuous EEG monitoring.[4]

Association of Seizures With Outcome

The rationale for the use of continuous EEG to detect nonconvulsive seizures is based on the hypothesis that seizures are a secondary insult and that treatment of these seizures will improve outcome. In a study of 259 pediatric ICU and cardiac ICU patients with a range of neurologic insults who underwent continuous EEG monitoring, seizure burden was defined as the maximum percentage of any given hour occupied by electrographic seizures.[5] The maximum total seizure burden was much greater in patients with neurologic decline than in patients without such alterations and was associated with greater risk for neurologic decline for every 1% increase in maximum hourly seizure burden. In a study of 300 children with an acute neurologic disorder (137 of whom were neurodevelopmentally normal) who underwent clinically indicated continuous EEG in the pediatric ICU, electrographic seizures and electrographic status epilepticus were associated with worse adaptive behavior after discharge than in children without seizures.[6] These studies suggest that seizures in critically ill children are associated with greater neurologic injury and may worsen outcome. This plausible hypothesis has not been tested in a prospective study.[7]

At-risk Populations in the Intensive Care Unit

Specific populations of children in the ICU who are at increased risk for nonconvulsive seizures have been identified. Nonconvulsive seizures were detected in approximately one-third of children with prior in-hospital convulsive seizures, structural brain injuries, or previous interictal EEG abnormalities.[8] In

KEY POINTS

- Neurologic management of the patient in the pediatric or cardiac intensive care unit (ICU) requires an interdisciplinary team involving neurologists, intensivists, neurosurgeons, and allied disciplines, including physical medicine and rehabilitation and psychiatry.
- Neuroprotection aims to match cerebral perfusion with the metabolic requirements of the injured brain.
- Electrographic seizures and electrographic status epilepticus have been associated with increased risk for neurologic morbidity after neurologic insults.
- Electrographic seizures may cause secondary injury and worsen outcome in critical illness.

KEY POINTS

- Continuous EEG monitoring for nonconvulsive seizures should be obtained for at least 12 to 24 hours in children with persistent altered mental status following generalized convulsive status epilepticus or other clinically evident seizures and after supratentorial brain injury with altered mental status.
- Many children in the intensive care unit have risk factors for ischemic or hemorrhagic stroke.

children supported by ECMO, nonconvulsive seizures were detected in 23%,[9] and in neonates after cardiac surgery with cardiac bypass, nonconvulsive seizures were detected in 8%.[10] Nonconvulsive seizures occurred in 36% to 46% of children with acute encephalopathy.[5,11] Nonconvulsive seizures are now also increasingly recognized after acute CNS insults, particularly traumatic brain injury and cardiac arrest. A prospective study of 87 children with mild to severe traumatic brain injury identified early posttraumatic seizures in 43%, among which 16% were solely electrographic.[12] Acute seizures (both clinical and nonconvulsive) occurred in 48% of 73 children following spontaneous intracerebral hemorrhage (ICH).[13] After resolution of convulsive status epilepticus in 98 children, electrographic-only seizures were detected in 34%.[14] Electrographic seizures and status epilepticus are particularly common after abusive head trauma, typically without a clinical correlate.[15]

Criteria for Continuous Electroencephalographic Monitoring

Since continuous EEG is a limited resource, some means of selecting patients for monitoring must be identified. Criteria for selection of patients for continuous EEG monitoring in the ICU have been proposed,[16,17] including persistent altered mental status following generalized convulsive status epilepticus or other clinically evident seizures and after supratentorial brain injury with altered mental status. Routine EEG recording fails to detect nonconvulsive seizures in approximately 50% of patients who are critically ill in which nonconvulsive seizures were subsequently detected with continuous EEG monitoring.[18] Accordingly, the recommendations for the use of continuous EEG in the ICU include initiating monitoring as soon as possible and continuing for at least 12 to 24 hours.

Evaluation and Management

Management of seizures in the ICU follows the typical approach of one or two doses of a benzodiazepine for emergent initial therapy. This is followed by a second anticonvulsant such as fosphenytoin, phenobarbital, or levetiracetam. A 2014 review of a protocol for management of refractory status epilepticus is representative of this approach.[19] In the ICU, other important considerations apply. First, in children who are critically ill, seizures may be the first sign of arterial or venous stroke, intracranial hemorrhage, electrolyte disturbances, CNS infection, or adverse drug reaction. Importantly, in parallel with the initiation of or increase in anticonvulsant therapy, appropriate diagnostic studies (imaging, chemistries, drug levels, cultures) and appropriate empiric therapy should begin immediately. Second, treatment should be escalated quickly as seizures may be adding a second insult to a primary neurologic injury. Finally, these patients require meticulous management of temperature, blood pressure, and ventilation, all factors that regulate cerebral metabolic demand and perfusion and may also contribute to secondary neurologic injury. An example of this approach used at the author's institution is shown in FIGURE 14-1.

STROKE IN THE INTENSIVE CARE UNIT

Cardiac disease, infection, and cerebral arteriopathy are three of the most common risk factors for arterial ischemic stroke in children.[20] These risk factors apply to most of the children in a pediatric or cardiac ICU. Therefore, arterial or venous ischemic strokes and ICH must be considered in the differential for a

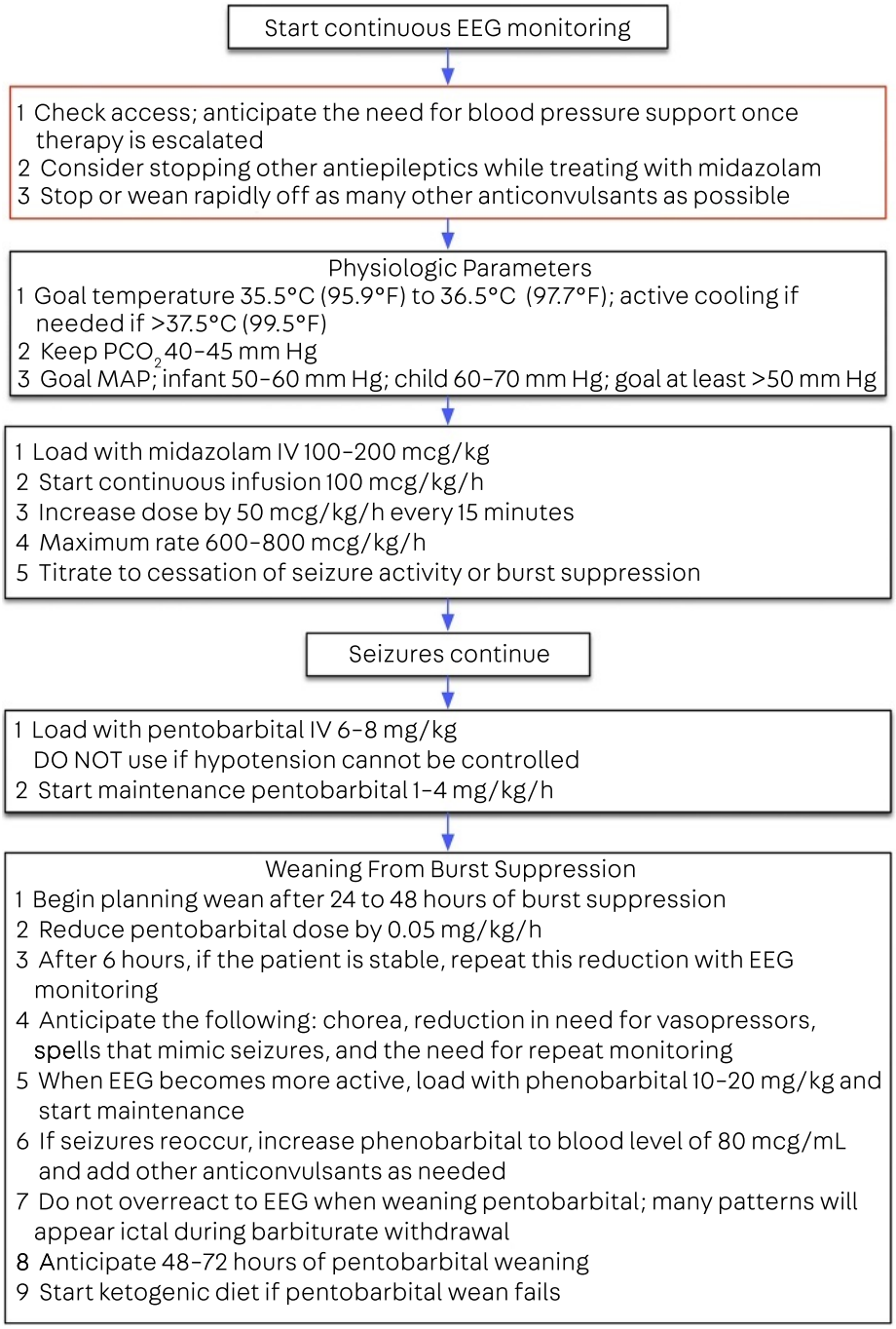

FIGURE 14-1

Approach to the management of refractory status epilepticus in infants and children.

EEG = electroencephalogram; IV = intravenous; MAP = mean arterial blood pressure; Pco_2 = partial pressure of carbon dioxide.

change in the neurologic examination or as the inciting event for seizures in the ICU (CASE 14-1). A high index of suspicion for stroke and rapid access to neuroimaging are essential components of ICU management. The majority of spontaneous hemorrhagic strokes in children are associated with vascular malformations, but they can also occur with transformation of an ischemic stroke, venous thrombosis, or from bleeding into an intracranial tumor.[22]

Acute Management

Guidelines for management of stroke in children are available, but no recommendations exist with Level I evidence.[23] Short-term anticoagulation may be considered for pediatric arterial ischemic stroke pending determination of the cause of the stroke. This is in contrast with the recommended practice in adults, for whom urgent anticoagulation is not recommended.[24] Anticoagulation may be considered for proven cardiac thrombus or extracranial arterial dissection.[23] At present, recombinant tissue plasminogen activator (rtPA) is not recommended as standard care for arterial ischemic stroke in children. However, it has been used following published

CASE 14-1

A previously healthy 4-year-old girl presented to the emergency department with abdominal pain, headache, and clonic movements of the right arm. On initial examination 20 minutes after seizure onset, she was unresponsive to voice, her eyes were deviated to the right, and she had clonic movements of the right arm and leg. Her vital signs were normal. She was treated with 0.1 mg/kg IV lorazepam followed 5 minutes later by fosphenytoin at a loading dose of 20 mg phenytoin equivalents (PE) per kilogram. Her abnormal movements stopped within 10 minutes of administration of fosphenytoin. She was intubated for airway protection. Head CT without contrast was normal. The first set of laboratory results showed normal electrolytes, a white blood cell count of 23,000/μL, hemoglobin of 7.7 g/dL, and platelet count of 1082 $\times$ 10^3/μL. Two hours later, she was still not responsive. Based on the persistent decrease in responsiveness after clinically resolved seizures, continuous EEG monitoring was obtained and showed electrographic seizures with a focus in the left temporal region. To identify the mechanism, an emergent MRI with contrast was obtained and showed a thrombus in the left transverse and sigmoid sinuses. The patient was treated with hydration. Milk-induced anemia, resulting from excess milk intake leading to iron-deficiency anemia, was identified as the primary risk factor for cerebral venous sinus thrombosis.[21] Anticoagulation was considered, but the neurologic examination improved with hydration, and repeat imaging 3 days later showed no progression of the thrombus.

COMMENT

This case illustrates the importance of considering nonconvulsive seizures in patients in the intensive care unit and the need to identify the factors causing seizures in order to initiate timely focused therapy.

consensus-based safety guidelines. For more information on the treatment of ischemic stroke in children, refer to the article "Evaluation and Acute Management of Ischemic Stroke in Infants and Children" by Catherine Amlie-Lefond, MD,[25] in this issue of *Continuum*.

In the ICU, management of arterial or venous ischemic stroke aims to minimize secondary injury through aggressive prevention of fever, maintenance of euglycemia and normotension, and prevention of hypoxia. These recommendations for children are based on limited pediatric data. In practice, these protective measures may include positioning the head of the bed flat, increasing IV fluid rate, reducing antihypertensive dosing, allowing blood pressure at the upper limit of normal for age, and targeted temperature management, with a goal temperature lower than 37°C (98.6°F). These measures augment cerebral blood flow, support cerebral perfusion, and limit excess cerebral metabolic demand. Importantly, all these measures can be undertaken before an ischemic stroke is confirmed or ruled out by neuroimaging, and they should be initiated as soon as a stroke is considered in the differential diagnosis. An approach to the acute management of stroke in children has been published.[26] The fundamental principles of neuroprotection in stroke include restoring cerebral blood flow, either through increasing volume or pressure (giving fluids or pressors); enhancing flow (antiplatelet therapy or anticoagulation); and removing the thrombus while controlling metabolic demand (meticulous temperature management and treatment of seizures).

Hemorrhagic strokes may present with seizures or acute neurologic deficits. Again, the key to management is early recognition. ICH is more likely than arterial ischemic stroke to result in hydrocephalus, cerebral edema, and increased intracranial pressure. Acute management includes elevation of the head of the bed to optimize CSF drainage, hyperosmolar treatment, and prevention of fever. Seizures are common with ICH and may be electrographic only.[13] Prophylactic treatment with an anticonvulsant may be considered in children with elevated intracranial pressure given the increased risk for acute seizures.[13] Blood pressure should be maintained within the normal range for age, but no specific blood pressure range has been associated with a good outcome. Rather, it is essential to identify a target blood pressure range and agree on the steps to maintain pressure in that range. These steps may be accomplished while considering the need for evacuation of the clot.

KEY POINT

- **Empiric neuroprotective measures for suspected ischemic stroke may include positioning the head of the bed flat, increasing IV fluid rate, reducing antihypertensive dosing, allowing blood pressure at the upper limit of normal for age, and targeted temperature management, with a goal temperature lower than 37°C (98.6°F).**

Imaging Studies and Diagnostic Evaluations

Imaging studies should begin with CT or MRI to first establish the diagnosis of stroke to identify the presence of hemorrhage and to delineate the extent of infarct. The author's practice is to use limited MRI with diffusion-weighted and gradient recalled echo (GRE) sequences to confirm the presence of ischemia or hemorrhage.[27] Cerebral venous sinus thrombosis may present with subtle signs, including seizures and subarachnoid hemorrhage or ICH. An echocardiogram is indicated in the evaluation of new stroke to detect a cardiac source of emboli, abnormal cardiac anatomy, or intracardiac shunt and should include bubble contrast. For most children, because of the thin chest wall and good acoustic windows, a transthoracic study is sufficient to confirm the presence or absence of each of these pathologies.[28] Transthoracic studies

also permit performance of the Valsalva maneuver and cough during the procedure to enhance detection of right-to-left shunting. The transesophageal procedure should be reserved for patients for whom the transthoracic study was inconclusive; the risks of sedation and temporary loss of the neurologic examination should be weighed in determining the timing of the study. Initial laboratory studies should, at a minimum, include measures of coagulation and platelet count, with the remainder of the studies determined by the risk factors specific to that patient.

Anticipatory Management

Brain-directed critical care requires a multidisciplinary team and a consensus on best practices for the detection and management of brain insults. The implementation of these practices is best achieved through joint rounds with critical care, neurology, and neurosurgery services.[1] Serial neurologic examinations and close communication between these three services with established goals for temperature, blood pressure, glucose, bed position, and oxygen and P_{CO_2} are essential for the care of children with stroke in the ICU. Criteria for escalation in therapy, including thrombolysis and decompressive hemicraniectomy, should be discussed early in the hospital course and revised at least daily based on the neurologic examination. This approach enables timely recognition of stroke progression and a rapid coordinated escalation of care with additional therapeutic interventions.

IN-HOSPITAL AND OUT-OF-HOSPITAL CARDIAC ARREST

Cardiac arrest in children is most often due to progressive tissue hypoxia and acidosis resulting from respiratory failure and circulatory shock. Approximately 39% of children survive after in-hospital cardiac arrest.[29,30] At present, no pharmacologic therapies are known that target the cellular mechanisms of neurologic injury after cardiac arrest. The Therapeutic Hypothermia After Pediatric Cardiac Arrest (THAPCA) trial first compared outcomes in children with out-of-hospital cardiac arrest who were randomly assigned either to controlled normothermia (36.8°C [98.2°F]) or a moderate therapeutic hypothermia (33.0°C [91.4°F]) treatment protocol.[31] Therapeutic hypothermia did not confer any significant benefit for good neurologic outcome (20% in hypothermia versus 12% in normothermia) or survival (38% in hypothermia versus 29% in normothermia) at 1 year. The in-hospital arm of the study comprised 329 patients and also found no benefit in survival or functional outcome at 1 year.[32] Accordingly, the focus of neuroprotection following acute resuscitation for in- or out-of-hospital cardiac arrest should be on rigorous targeted temperature management with a goal of 36.8°C (98.2°F), maintenance of normoxia, normocarbia, support for blood pressure in a normal range for age, and normal electrolytes.[33] The author's practice is to maintain temperature at 35.5°C (95.9°F) for 48 to 72 hours following cardiac arrest and to use transcranial Doppler (TCD) measurement of cerebral blood flow to adjust blood pressure goals and head-of-bed position to maintain cerebral perfusion. Specifically, the patient is treated with the head of bed flat for the first 24 hours to maintain cerebral perfusion, unless imaging or clinical signs of cerebral edema with increased intracranial pressure exist. In this case, the head of the bed is elevated to 30 degrees. Serial TCDs are obtained daily for at least 3 days. If the TCDs show normal velocities for age (less than 2 standard deviations from

age-dependent normal values over the next 48 hours), the head of the bed is elevated to 30 degrees to offset the development of cerebral edema during reperfusion.

Notably, a new American Academy of Neurology practice guideline for adults based on a review of 50 years of published studies recommends the use of hospital-initiated therapeutic hypothermia (32°C [89.6°F] to 34°C [93.2°F] for 24 hours) for comatose adults following out-of-hospital cardiac arrest and an initial cardiac rhythm of pulseless ventricular tachycardia or ventricular fibrillation.[34] Targeted temperature management (36°C [96.8°F] for 24 hours with rewarming to 37°C [98.6°F] over 8 hours and maintained at less than 37.5°C [99.5°F] for 72 hours) is also effective in patients who are comatose with an initial cardiac rhythm of either ventricular tachycardia or ventricular fibrillation, asystole, or pulseless electrical activity. For pediatrics, these recommendations underscore the critical importance of targeted temperature management within a narrow range of normothermia to ensure optimal neurologic recovery following cardiac arrest.

EXTRACORPOREAL MEMBRANE OXYGENATION AND NEUROLOGIC INJURY

ECMO provides cardiorespiratory support and serves as a rescue therapy for critically ill children. Neurologic complications, including intracranial hemorrhage, stroke, and brain death, have been reported with ECMO.[35] Among 682 patients younger than 18 years of age who underwent ECMO to aid in cardiopulmonary resuscitation, an acute neurologic injury (stroke, intracerebral hemorrhage, or brain death) occurred in 22%. Among these 147 patients, the mortality rate was 89%.[36] The risk for neurologic injury was highest in children with heart disease or who were severely acidotic (pH less than 6.87) before starting ECMO. A study of 2977 patients undergoing carotid artery cannulation for venoarterial ECMO identified neurologic injury, including seizures, stroke, or hemorrhage, in 611 patients (21%).[37] Neonates comprised most of the patients cannulated via the neck vessels (61%) and had the greatest burden of neurologic injury, but no association was shown between age risk for neurologic injury, which was present across all age groups.

Surveillance for Neurologic Injury During Extracorporeal Membrane Oxygenation

The need for sedation and neuromuscular blockade during ECMO impedes the use of a neurologic examination to detect new acute neurologic injury. A retrospective study of 19 children treated with ECMO who underwent continuous EEG monitoring reported seizures in four patients (21%), and they were exclusively nonconvulsive in three.[9] Interictal discharges were associated with seizures, and 24 hours of monitoring were required to detect all seizures. Other approaches to the detection of neurologic injury during ECMO include near-infrared spectroscopy[38] and TCD measurement of cerebral blood flow velocity.[39] None of these approaches have been evaluated in prospective studies. While these noninvasive approaches have promise for detection of vascular CNS injuries, pediatric studies have not shown a reliable association with EEG or TCD abnormalities, and further study is needed.[9,39] At present, the use of continuous EEG for the detection of seizures during the first 24 hours of ECMO is reasonable.

KEY POINTS

- Early recognition of stroke, meticulous control of blood pressure and temperature, and anticipatory planning are the key steps for neuroprotection in patients in the intensive care unit.
- Unlike adults, cardiac arrest in children is most often due to progressive tissue hypoxia and acidosis resulting from respiratory failure and circulatory shock.
- While hypothermia has not been shown to improve outcome after cardiac arrest in children, targeted temperature management to maintain temperature of 36.8°C (98.2°F) for at least 48 hours should be considered standard care.
- Nonconvulsive seizures are common during extracorporeal membrane oxygenation, and continuous EEG may be considered a standard practice.

KEY POINTS

- Young age and fever are risk factors for neurologic deterioration in children with acute liver failure.
- Intensive care unit–acquired weakness occurs in children but the precise impact on morbidity is uncertain because there is no consensus on the criteria for diagnosis in children.
- Before beginning treatment for sympathetic hyperarousal, other treatable medical conditions should be investigated.

ACUTE LIVER FAILURE

Neurologic morbidity is the primary determinant of outcome in pediatric acute liver failure.[40] Young age, fever, and presentation with seizures are risk factors for neurologic deterioration with acute liver failure.[41] Hepatic encephalopathy is graded on a continuum from no or minimal evidence of neurologic dysfunction (stages 0 to 2) to stupor (stage 3) and coma (stage 4). Stage 1 is characterized by subtle changes in affect (anxiety or euphoria) and shortened attention span. In stage 2, the patient may be disinhibited, have a disruption of the sleep-wake cycle, or be less active. The clinical assessment of stage 1 and stage 2 hepatic encephalopathy in infants and children with subtle impairments of higher cognitive function depends on the experience and skill of the examiner. The objective of the neurologist in the care of these patients is to detect early signs of neurologic deterioration and cerebral edema (CASE 14-2). Changes in the EEG background may be an early sign of hepatic encephalopathy in children.[42] The optimal duration of such monitoring has not been studied. The author's practice is to obtain continuous EEG monitoring on admission to the ICU for a minimum of 1 to 2 hours for all patients with acute liver failure, independent of the presence of clinical signs of hepatic encephalopathy. If the EEG is abnormal, EEG monitoring is continued for 24 hours. Thereafter, the frequency of monitoring depends on the progression of any EEG abnormalities. Management is aimed at limiting neurologic injury until the patient has a recovery of liver function or receives a liver transplant. An approach to neuroprotection in acute liver failure has been published.[42] The key principles involve the prevention of fever, aggressive treatment of infection, and the early use of continuous renal replacement therapy or hemodialysis for treatment of rising ammonia not responsive to lactulose. Hyperosmolar therapy or therapeutic hypothermia may be considered for the patient who progresses to stage 3 hepatic encephalopathy, although a randomized trial of therapeutic hypothermia in adults with acute liver failure showed no survival benefit.[43]

INTENSIVE CARE UNIT–ACQUIRED WEAKNESS

ICU-acquired weakness is a significant cause of morbidity in critically ill adults. For children, no consensus exists on the criteria for ICU-acquired weakness. Among 830 children admitted to an ICU, 1.7% had generalized weakness, which persisted for up to 1 year.[44] A study using *International Classification of Diseases* (*ICD*) codes to identify ICU-acquired weakness using the Virtual Pediatric Intensive Care Unit's database reported an incidence of 0.02%.[45] In adults, the risk factors for ICU-acquired weakness include difficulty in weaning from the ventilator, severe sepsis, and prolonged mechanical ventilation. Until a standardized approach to confirming the diagnosis in children is established, the incidence and impact of this disorder on morbidity following critical illness in children cannot be determined.

SYMPATHETIC HYPERAROUSAL

Autonomic dysfunction is common after acquired brain injury and has been called autonomic, diencephalic, or sympathetic storms. The current nomenclature is *paroxysmal sympathetic hyperactivity*, which is characterized by episodic changes in vital signs, including hyperthermia, tachycardia, hypertension, or tachypnea. Paroxysmal sympathetic hyperactivity occurs

in approximately 15% of children following acute brain injury, particularly traumatic brain injury or cardiac arrest.[46] The most important first step is to evaluate for other treatable medical problems that can trigger increased sympathetic tone in brain-injured patients, including dystonia storm, urinary retention, ileus or constipation, hip or other dislocation or fractures, gastroesophageal reflux, corneal abrasion, dental issues, or infection. Once these conditions have been ruled out, the author of this article begins treatment with gabapentin, followed by a scheduled benzodiazepine, then clonidine or propranolol.[47] No prospective studies have shown that any one therapy is better than another.

CASE 14-2

A previously healthy 3-year-old boy presented with 1 week of vomiting and 2 days of jaundice. His physical examination showed an enlarged liver. He was irritable but could be soothed by his mother, and this was considered appropriate, as he had not slept well in 2 days. On neurologic examination, he was able to follow commands and had fluent speech. Routine EEG was normal. International normalized ratio (INR) was 1.6, ammonia 75 µmol/L, aspartate aminotransferase (AST) 1200 IU/L, and alanine aminotransferase (ALT) 900 IU/L. He was treated with medical management for acute liver failure. The next day he developed a fever and antibiotics were started. On the morning of the second hospital day, his INR increased to 4.5, he was more irritable, and his responses to commands were slow. EEG showed new generalized slowing. He was transferred to the pediatric intensive care unit for targeted temperature management using an external cooling device. The case was discussed with nephrology (in case plasma exchange or continuous renal replacement therapy was needed) and with neurosurgery (for placement of an intracranial pressure monitor). A noncontrast head CT was obtained and showed no evidence of cerebral edema or increased intracranial pressure. Over the next 12 hours, he progressed to stupor with extensor posturing. During this progression, continuous renal replacement therapy and hyperosmolar therapy with 3% normal saline were initiated. An intracranial pressure monitor could not be safely placed because of the coagulopathy. To prevent shivering while he was maintained at low normothermia (35.5°C [95.9°F]), the patient was pharmacologically paralyzed. EEG was used for surveillance for nonconvulsive seizures and transcranial Doppler was obtained daily to monitor cerebral perfusion and detect increased intracranial pressure. After 2 days of medical management, liver synthetic function began to recover and neuroprotective measures were relaxed.

COMMENT

This case illustrates the need for serial neurologic examinations in the intensive care unit and anticipatory planning for neurologic deterioration at the earliest sign of new neurologic findings. Early treatment with targeted temperature management to prevent fever, even if this means loss of the neurologic examination, in this high-risk patient population is essential.

CONCLUSION

Recognition of neurologic complications of critical illness requires serial neurologic examinations and an appreciation for the multiple risk factors for neurologic injury present in most patients in the pediatric or cardiac ICU. Through attention to the fundamentals of neuroprotection, including maintaining cerebral perfusion and regulating cerebral metabolic demand, combined with multidisciplinary care and anticipatory planning, these complications can be prevented or the neurologic injury mitigated.

REFERENCES

1 Wainwright MS, Grimason M, Goldstein J, et al. Building a pediatric neurocritical care program: a multidisciplinary approach to clinical practice and education from the intensive care unit to the outpatient clinic. Semin Pediatr Neurol 2014;21(4): 248–254. doi:10.1016/j.spen.2014.10.006.

2 LaRovere KL, Graham RJ, Tasker RC. Pediatric neurocritical care: a neurology consultation model and implication for education and training. Pediatr Neurol 2013;48(3):206–211. doi:10.1016/j.pediatrneurol.2012.12.006.

3 Wainwright MS. Neurologic assessment and monitoring. In: Fuhrman B, Zimmerman J, eds. Pediatric critical care. 5th ed, Philadelphia, PA: Elsevier, 2017:842–856.

4 Abend NS, Arndt DH, Carpenter JL, et al. Electrographic seizures in pediatric ICU patients: cohort study of risk factors and mortality. Neurology 2013;81(4):383–391. doi:10.1212/WNL.0b013e31829c5cfe.

5 Payne ET, Zhao XY, Frndova H, et al. Seizure burden is independently associated with short term outcome in critically ill children. Brain 2014;137(pt 5):1429–1438. doi:10.1093/brain/awu042.

6 Abend NS, Wagenman KL, Blake TP, et al. Electrographic status epilepticus and neurobehavioral outcomes in critically ill children. Epilepsy Behav 2015;49:238–244. doi:10.1016/j.yebeh.2015.03.013.

7 Jafarpour S, Loddenkemper T. Outcomes in pediatric patients with nonconvulsive status epilepticus. Epilepsy Behav 2015;49:98–103. doi:10.1016/j.yebeh.2015.06.015.

8 McCoy B, Sharma R, Ochi A, et al. Predictors of nonconvulsive seizures among critically ill children. Epilepsia 2011;52(11):1973–1978. doi:10.1111/j.1528-1167.2011.03291.x.

9 Piantino J, Wainwright M, Grimason M, et al. Nonconvulsive seizures are common in children treated with extracorporeal cardiac life support. Pediatr Crit Care Med 2013;14(6):601–609. doi:10.1097/PCC.0b013e318291755a.

10 Naim MY, Gaynor JW, Chen J, et al. Subclinical seizures identified by postoperative electroencephalographic monitoring are common after neonatal cardiac surgery. J Thor Cardiovasc Surg 2015;150(1):169–178; discussion 178–180. doi:10.1016/j.jtcvs.2015.03.045.

11 Abend NS, Gutierrez-Colina A, Topjian AA, et al. Nonconvulsive seizures are common in critically ill children. Neurology 2011;76(12):1071–1077. doi:10.1212/WNL.0b013e318211c19e.

12 Arndt D, Lerner J, Matsumoto J, et al. Subclinical early posttraumatic seizures detected by continuous EEG monitoring in a consecutive pediatric cohort. Epilepsia 2013;54(10):1780–1788. doi:10.1111/epi.12369.

13 Beslow LA, Abend NS, Gindville MC, et al. Pediatric intracerebral hemorrhage: acute symptomatic seizures and epilepsy. JAMA Neurol 2013;70(4): 448–454. doi:10.1001/jamaneurol.2013.1033.

14 Sánchez Fernández I, Abend NS, Arndt DH, et al. Electrographic seizures after convulsive status epilepticus in children and young adults: a retrospective multicenter study. J Pediatr 2014;164(2):339–46.e1-2. doi:10.1016/j.jpeds.2013.09.032.

15 Goldstein JL, Leonhardt D, Kmytyuk N, et al. Abnormal neuroimaging is associated with early in-hospital seizures in pediatric abusive head trauma. Neurocrit Care 2011;15(1):63–69. doi:10.1007/s12028-010-9468-5.

16 Herman ST, Abend NS, Bleck TP, et al. Consensus statement on continuous EEG in critically ill adults and children, part I: indications. J Clin Neurophysiol 2015;32(2):87–95. doi:10.1097/WNP.0000000000000166.

17 Herman ST, Abend NS, Bleck TP, et al. Consensus statement on continuous EEG in critically ill adults and children, part II: personnel, technical specifications and clinical practice. J Clin Neurophysiol 2015;32(2):96–108. doi:10.1097/WNP.0000000000000165.

18 Claassen J, Mayer SA, Kowalski RG, et al. Detection of electrographic seizures with continuous EEG monitoring in critically ill patients. Neurology 2004; 62(10):1743–1748. doi:10.1212/01.WNL.0000125184.88797.62.

19 Abend NS, Loddenkemper T. Pediatric status epilepticus management. Curr Opin Pediatr 2014;26 (6): 668–674. doi:10.1097/MOP.0000000000000154.

20 Mallick AA, Ganesan V, Kirkham FJ, et al. Childhood arterial ischaemic stroke incidence, presenting features, and risk factors: a prospective population-based study. Lancet Neurol 2014;13(1): 35–43. doi:10.1016/S1474-4422(13)70290-4.

21 Kwiatkowski JL, West TB, Heidary N, et al. Severe iron deficiency anemia in young children. J Pediatr 1999;135(4):514–516. doi:10.1016/S0022-3476(99)70177-0.

22 Beslow LA, Licht DJ, Smith SE, et al. Predictors of outcome in childhood intracerebral hemorrhage: a prospective consecutive cohort study. Stroke 2010; 41(2):313–318. doi:10.1161/STROKEAHA.109.568071.

23 Roach ES, Golomb MR, Adams R, et al. Management of stroke in infants and children: a scientific statement from a Special Writing Group of the American Heart Association Stroke Council and the Council on Cardiovascular Disease in the Young. Stroke 2008;39(9):2644–2691. doi:10.1161/STROKEAHA.108.189696.

24 Adams HP Jr, del Zoppo G, Alberts MJ, et al. Guidelines for the management of adults with ischemic stroke: a guideline from the American Heart Association/American Stroke Association Stroke Council, Clinical Cardiology Council, Cardiovascular Radiology and Intervention Council, and the Atherosclerotic Peripheral Vascular Disease and Quality of Care Outcomes in Research Interdisciplinary Working Groups: the American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists. Stroke 2007;38(5):1655–1711. doi:10.1161/STROKEAHA.107.181486.

25 Amlie-Lefond C. Evaluation and acute management of ischemic stroke in infants and children. Continuum (Minneap Minn) 2018;24(1 Child Neurology):150–170.

26 Elbers J, Wainwright MS, Amlie-Lefond C. The pediatric stroke code: early management of the child with stroke. J Pediatr 2015;167(1): 19–24.e1-4. doi:10.1016/j.jpeds.2015.03.051.

27 Mallick AA, Ganesan V, Kirkham FJ, et al. Diagnostic delays in paediatric stroke. J Neurol Neurosurg Psychiatry 2015;86(8):917–921. doi:10.1136/jnnp-2014-309188.

28 Dowling MM, Ikemba CM. Intracardiac shunting and stroke in children: a systematic review. J Child Neurol 2011;26(1):72–82. doi:10.1177/0883073810383913.

29 Phillips RS, Scott B, Carter SJ, et al. Systematic review and meta-analysis of outcomes after cardiopulmonary arrest in childhood. PLoS One 2015;10(6):e0130327. doi:10.1371/journal.pone.0130327.

30 Del Castillo J, López-Herce J, Matamoros M, et al. Long-term evolution after in-hospital cardiac arrest in children: prospective multicenter multinational study. Resuscitation 2015;96:126–134. doi:10.1016/j.resuscitation.2015.07.037.

31 Moler FW, Silverstein FS, Holubkov R, et al. Therapeutic hypothermia after out-of-hospital cardiac arrest in children. N Engl J Med 2015;372(20):1898–1908. doi:10.1056/NEJMoa1411480.

32 Moler FW, Silverstein FS, Holubkov R, et al. Therapeutic hypothermia after in-hospital cardiac arrest in children. N Engl J Med 2017;376(4):318–329. doi:10.1056/NEJMoa1610493.

33 Topjian AA, Berg RA, Taccone FS. Haemodynamic and ventilator management in patients following cardiac arrest. Curr Opin Crit Care 2015;21(3):195–201. doi:10.1097/MCC.0000000000000205.

34 Geocadin RG, Wijdicks E, Armstrong MJ, et al. Practice guideline summary: reducing brain injury following cardiopulmonary resuscitation: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. Neurology 2017;88(22):2141–2149. doi:10.1212/WNL.0000000000003966.

35 Cengiz P, Seidel K, Rycus PT, et al. Central nervous system complications during pediatric extracorporeal life support: incidence and risk factors. Crit Care Med 2005;33(12):2817–2824. doi:10.1097/01.CCM.0000189940.70617.C3.

36 Barrett CS, Bratton SL, Salvin JW, et al. Neurological injury after extracorporeal membrane oxygenation use to aid pediatric cardiopulmonary resuscitation. Pediatr Crit Care Med 2009;10(4):445–451. doi:10.1097/PCC.0b013e318198bd85.

37 Teele SA, Salvin JW, Barrett CS, et al. The association of carotid artery cannulation and neurologic injury in pediatric patients supported with venoarterial extracorporeal membrane oxygenation*. Pediatr Crit Care Med 2014;15(4):355–361. doi:10.1097/PCC.0000000000000103.

38 Wong JK, Smith TN, Pitcher HT, Hirose H, Cavarocchi NC. Cerebral and lower limb near-infrared spectroscopy in adults on extracorporeal membrane oxygenation. Artif Organs 2012;36(8):659–667. doi:10.1111/j.1525-1594.2012.01496.x.

39 O'Brien NF, Hall MW. Extracorporeal membrane oxygenation and cerebral blood flow velocity in children. Pediatr Crit Care Med 2013;14(3):e126–e134. doi:10.1097/PCC.0b013e3182712d62.

40 Sundaram SS, Alonso EM, Narkewicz MR, et al. Characterization and outcomes of young infants with acute liver failure. J Pediatr 2011;159(5):813–8.e1. doi:10.1016/j.jpeds.2011.04.016.

41 Ng VL, Li R, Loomes KM, et al. Outcomes of children with and without hepatic encephalopathy from the pediatric acute liver failure study group. J Pediatr Gastroenterol Nutr 2016;63(3):357–364. doi:10.1097/MPG.0000000000001178.

42 Hussain E, Grimason M, Goldstein J, et al. EEG abnormalities are associated with increased risk of transplant or poor outcome in children with acute liver failure. J Pediatr Gastroenterol Nutr 2014;58(4):449–456. doi:10.1097/MPG.0000000000000271.

43 Bernal W, Murphy N, Brown S, et al. A multicentre randomized controlled trial of moderate hypothermia to prevent intracranial hypertension in acute liver failure. J Hepatol 2016;65(2):273–279. doi:10.1016/j.jhep.2016.03.003.

44 Banwell BL, Mildner RJ, Hassall AC, et al. Muscle weakness in critically ill children. Neurology 2003;61(12):1779–1782. doi:10.1212/01.WNL.0000098886.90030.67.

45 Field-Ridley A, Dharmar M, Steinhorn D, et al. ICU-acquired weakness is associated with differences in clinical outcomes in critically ill children. Pediatr Crit Care Med 2016;17(1):53–57. doi:10.1097/PCC.0000000000000538.

46 Kirk KA, Shoykhet M, Jeong JH, et al. Dysautonomia after pediatric brain injury. Dev Med Child Neurol 2012;54(8):759–764. doi:10.1111/j.1469-8749.2012.04322.x.

47 Meyfroidt G, Baguley IJ, Menon DK. Paroxysmal sympathetic hyperactivity: the storm after acute brain injury. Lancet Neurol 2017;16(9):721–729. doi:10.1016/S1474-4422(17)30259-4.