

Pediatric Neurocritical Care



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KEYWORDS

- Pediatric traumatic brain injury • Pediatric neurocritical care • Pediatric stroke
- Neuroimaging • Neurologic monitoring

KEY POINTS

- Pediatric brain injury can occur from a primary neurologic cause or as a sequela of multi-system illness.
- Pediatric neurocritical care (PNCC) is an expanding multidisciplinary field incorporating brain-specific imaging, monitoring, and treatment modalities along with focused efforts in education, quality improvement, and collaboration.
- Although PNCC is emerging as a specialty, services are not universally available. Thus, all pediatric practitioners should develop an approach to diagnosis, monitoring, and management for children with brain injuries.

INTRODUCTION

Whether the disease process originates from the neurologic system or manifests as a neurologic complication of a systemic critical illness, pediatric brain injury is a major health problem, accounting for 20% to 25% of all admissions and 65% of all deaths in pediatric intensive care units (PICUs).¹ Au and colleagues² reported that more than half of all patients in a large tertiary care PICU who died had an acute neurologic injury, and in 90% of those, brain injury was the proximate cause of death. There are numerous causes of primary pediatric brain injury. Traumatic brain injury (TBI) is the leading cause of death and disability related to trauma in children. In the United States, pediatric TBI caused 7440 deaths, 60,000 inpatient stays, and 600,000 visits to the emergency department.³ Although the Brain Trauma Foundation has released guidelines for the management of severe pediatric TBI,^{4,5} significant variability exists in management among practitioners.⁶ Status epilepticus is another common neurologic emergency, with an annual incidence of approximately 20 cases per 100,000 children, with a 3% mortality.⁷ Stroke in children carries an annual incidence of 1–2 cases per 100,000.⁸ In contrast to adult stroke, which is primarily caused by atherosclerotic disease, the causes of stroke in children range widely and include sickle cell disease, inherited or acquired hypercoagulability, congenital heart disease, and arterial

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dissection. The field of pediatric neurocritical care (PNCC) has been ushered in recent years by the recognition of this vast heterogeneity in causes, natural history, pathophysiology, and treatment. Several large pediatric centers have instituted neurocritical care services, consisting of specialists from several disciplines including critical care, neurosurgery, and neurology. Because these services are not universal, all pediatric practitioners should develop an approach to diagnosis, monitoring, and management for pediatric brain injuries. The purpose of this review is to discuss the emerging subspecialty of PNCC, to review the pathophysiology of primary and secondary brain injuries, and to highlight contemporary imaging and monitoring modalities.

DISCUSSION

PNCC Subspecialty Service

Pediatric critical care as a subspecialty is only several decades old.⁹ Unlike ICUs for adults, most PICUs are general and not designated based on a specific organ system. However, this has changed in pediatric cardiac critical care, which has been increasingly recognized as a field requiring specific resources and teams with a highly specialized skill set.¹⁰ PNCC is an expanding field directed toward the mitigation of secondary brain injury caused by systemic illness, stroke, cardiac arrest, trauma, infection/inflammation, postneurosurgical conditions, and seizures. Although the development of guidelines in adult neurocritical care may be several years ahead than that of its pediatric counterpart, developmental differences between adults and children prevent drawing undue parallels between the natural history of neurologic disease and treatments across the age groups. A comprehensive, multidisciplinary approach to care, including current techniques of imaging, neuromonitoring, and neuroprotective strategies, augmented by focus on patient safety, quality, and education can improve outcomes in children with brain injury.¹¹ Recent data indicate that the development of a PNCC service within an institution that includes experts from neurosurgery, neurology, and critical care medicine may improve patient outcomes.^{12,13} Potential benefits of neurocritical care services include facilitation of communication among the numerous services involved in the care of patients who often have complicated needs, focused efforts on patient safety, quality improvement and education among diverse groups of practitioners, as well as coordination of limited resources in imaging and monitoring. In addition, the involvement of neurology and neurosurgery services facilitates long-term follow-up after ICU and hospital discharge. A recent survey of PICU medical directors and program directors of pediatric neurosurgery and child neurology fellowships reported the existence of 45 neurocritical care services in the United States, 80% of which were consultant services to the PICU/CICU.¹⁴ Respondents had an overall positive opinion on the value of PNCC as a specialty service. The few negative opinions pointed out that developing a PNCC service would be “redundant.” Recent studies have shown that a PNCC service can add diagnostic considerations,¹⁵ and that it can be associated with a reduction in mortality and an improvement in the favorable outcome.¹² However, an important limitation in studies exploring outcomes in specialized services in any discipline is uncertainty regarding generalizability across different institutions, and whether it is the service itself conferring benefit, or if it is due to increased resources and attention. Overall, the impact on outcome of dedicated PNCC services warrants more study.

Pathophysiology of Brain Injury

Brain injury can be classified as either primary or secondary. Primary injury results from the inciting event. In TBI, this consists of direct disruption of neurons and

vascular structures that occurs at the moment of impact or acceleration/deceleration force. Practitioners are relatively powerless against primary TBI, outside of physical prevention measures and anticipatory guidance. In hypoxia/ischemia, stroke, infection, and seizures, the primary event leading to brain injury can often be treated or prevented. If possible, every measure should be considered to reverse the primary cause of brain injury. Secondary brain injury begins the instant following the inciting event and is therefore the target of therapeutic interventions from the prehospital stage through the entire hospitalization and rehabilitation phases. There are many ways a brain cell can die from secondary injury, including inadequate supply of oxygen and substrates to meet the metabolic demands of the vulnerable brain, inflammation, apoptosis, and excitotoxicity. Mitigating imbalances in the supply and demand of oxygen and nutrients following brain injury begins with supportive care of other organ systems. Establishing and maintaining adequate airway, breathing, and circulation is essential in ensuring cerebral oxygen delivery. This can be achieved using pediatric critical care principles of airway management, ventilator strategies, fluid resuscitation, and inotropic or vasopressor therapies.

Cerebral oxygen delivery = cerebral blood flow \times arterial oxygen content.

Arterial oxygen content (mL/dL) = $1.36 \times S_aO_2/100 \times Hb$ (g/dL) + $0.003 \times P_aO_2$ (mm Hg).

Considering the determinants of cerebral oxygen delivery, it is important to ensure adequate cardiac output, hemoglobin concentration, hemoglobin oxygen saturation, and partial pressure of arterial oxygen. In children, there exist age-related differences in cerebral blood flow, which range from 60 mL/100 g/min at 3 years, to 70 mL/100 g/min at age 6 years, to 50 mL/100 g/min in adulthood.¹⁶ In addition, prevention of hypoglycemia is also essential in maintaining adequate cellular respiration.

Local oxygen delivery in the injured brain also depends on cerebral perfusion. Cerebral perfusion pressure is equal to the difference between the mean arterial pressure (MAP) and the intracranial pressure (ICP).

CPP = MAP-ICP.

Ensuring an adequate MAP and limiting ICP are important in maintaining cerebral perfusion. Strategies to increase MAP include optimizing intravascular volume, use of inotropes, and vasopressors if needed. ICP is influenced by the Monro-Kellie principle, which states that the volume of the contents of the intracranial vault, that is, the brain, cerebrospinal fluid, and blood, is constant. Therefore, if the volume of one of the components increases, the volume of the other components must decrease to compensate. When the compensatory mechanisms are exhausted, ICP rapidly increases. Brain volume can increase with cytotoxic, vasogenic, osmotic, and interstitial cerebral edema. An increase in the blood component can occur with cerebral hyperemia or hemorrhage. Finally, the CSF volume can be increased due to disorders of CSF drainage or resorption. Relative to the magnitude of increase in the volume of intracranial contents, ICP can be lower in children with an open fontanelle or in those who have undergone decompressive craniectomy. However, it is important to note that ICP can still be high in such circumstances, and that injury can still be severe in the absence of ICP elevation. Given the developmental differences in norms of systemic blood pressure and cerebral blood flow, there is likely an age-related continuum for optimal cerebral perfusion pressure. In a recent report, Allen and colleagues¹⁷ studied 317 adults and children with severe TBI using specific CPP targets more than 50–60 mm Hg in adults, more than 50 mm Hg in the 6–17-year age group, and more than 40 mm Hg in the 0–5-year age group. Regardless of the likely existence of a similar age-related continuum, the 2019 Brain Trauma Foundation guidelines for severe pediatric TBI support a CPP threshold of greater than 40 mm Hg irrespective of age.¹⁸

In addition to ensuring an adequate supply of blood and energy substrate, limiting cerebral oxygen demand is also important to prevent secondary brain injury. Studies on the effects of different classes of sedatives and anesthetics on cerebrovascular response and compensatory reserve in TBI are conflicting,^{19,20} and studies in children are even more limited. However, sedatives can reduce the cerebral metabolic rate of oxygen, an effect that is possibly coupled with a global reduction in cerebral blood flow. Thus, in the brain-injured child requiring mechanical ventilation, analgesia and sedation are mainstays of treatment to prevent pain, agitation, and ventilator desynchrony, all of which can increase cerebral blood volume and ICP.^{21–23} Preventing fever through targeted temperature management and management of seizures with the antiepileptic therapy with electroencephalography (EEG) monitoring can also reduce the cerebral metabolic demand.

Neurologic Examination

Evaluation of neurologic injury in a child begins with the pupillary examination and measurement of vital signs. Any combination of bradycardia, systemic hypertension, disordered regulation of respiration, and abnormal pupillary reflex could indicate an acute herniation syndrome, requiring immediate medical or surgical treatment. Another early step in assessment is the Glasgow Coma Score (GCS). The GCS was initially developed in 1974 to assess the altered consciousness after TBI.²⁴ The GCS ranges from 3 to 15, with a score between 1 and 6 assigned for motor function, between 1 and 5 for verbal function, and between 1 and 4 for eye opening. The initial 1974 scale did not include children younger than 5 but modified scales are available and can be applied to children,²⁵ although they have not been widely validated for the younger age groups.²⁶ Initial GCS in children correlates with outcome,^{27,28} and it is often used to stratify severity of TBI among mild (GCS 13–15), moderate (GCS 9–12), and severe (GCS 3–8) both in clinical practice and in research. A recent study showed that further stratifying the group of children with severe TBI with GCS between 3 and 8 is associated with mortality.²⁹ Although the GCS has not been rigorously validated outside of trauma, its ease, reproducibility, and quantitative nature have resulted in wide acceptance to represent the degree of impairment across various neurologic conditions. Indeed, it is often used by practitioners to communicate the severity of injury to each other for several different disease states causing encephalopathy.²⁶ It can also be applied serially to determine improvement or deterioration. Limitations of the GCS in the assessment of severe brain injury includes lack of inclusion of other important neurologic examination parameters such as pupillary and brainstem reflexes, focality/laterality, and airway protective reflexes.³⁰ Therefore, a more comprehensive neurologic examination assessing consciousness, airway protection, cranial nerves, motor function, reflexes, and sensory function should be performed along with the GCS.

Imaging

Indications for imaging of a child with brain injury are based on the mechanism of injury, findings from the clinical neurologic examination and GCS, likelihood of imaging findings to affect management decisions, and the stability of the patient for transport. Computed tomography (CT) continues to be widely used to detect and stage various neurologic injuries because it is usually readily available, expeditious, and does not always require sedation of the patient. Noncontrast head CT is a good first-line test to detect bony abnormalities in the skull and upper cervical spine, acute intracranial hemorrhage, hydrocephalus, mass effect, cerebral edema, and extraaxial fluid collections. Because the detection of these abnormalities can change the medical or

surgical management following head trauma, CT is the preferred modality for the initial evaluation and staging of adults and children with severe TBI.^{31–33} One drawback of CT is the risk of acquired malignancy due to radiation.³⁴ A study of CT scans in the US children from 1996 to 2011 projected that 4 million pediatric CT scans per year would cause about 5000 future cancers, and reducing the highest radiation doses given might prevent cancers.³⁵ Other important limitations of noncontrast head CT include failure to detect important neurologic abnormalities such as ischemia, inflammation, subacute hemorrhage, axonal injury, ligamentous high cervical spine injury, subtle cerebral edema, thrombosis, vascular abnormalities, and abnormalities of posterior fossa contents. If any of these conditions are suspected, magnetic resonance imaging (MRI) should be performed. Limitations of MRI include availability, duration, requirement of sedation in young children, and challenges of monitoring during the procedure. It is therefore not routinely performed in children during the acute stage of TBI because patients are often unstable in the first several days following injury, and most of the information necessary to guide therapy can be obtained from CT. However, it is superior to CT in the evaluation of ischemic stroke, and rapid sequence MRI protocols confer the added benefits of shorter duration, more widespread availability, and the dispensing with the need for sedation. A recent study showed that the rapid sequence MRI can be used in the evaluation of both ischemic and nonischemic brain attacks in children.³⁶ In that study, diffusion-weighted imaging was shown to be more sensitive and specific in detecting ischemic strokes compared with fluid-attenuated inversion recovery techniques, as the latter was useful in the identification of inflammatory and metabolic disorders.

Other Monitoring Modalities

Nonconvulsive seizures (NCS) and nonconvulsive status epilepticus (NCSE) are increasingly recognized conditions in pediatrics. The gold standard for diagnosis of NCS, and for monitoring of children with neurologic injuries at risk for NCS, is continuous EEG (cEEG). In the past, limitations of cEEG included inadequate equipment, lack of technologists and personnel to interpret the study at regular intervals, and lack of data on its benefit on outcome. In adults, studies have shown that the mental status changes out of proportion to the degree of the primary neurologic illnesses of TBI, stroke, or intracerebral hemorrhages can be due to NCS.³⁷ A growing body of pediatric literature recognizes NCS as a common primary diagnosis or a common harmful sequela of other neurologic conditions.^{1,38,39} Prompt recognition and treatment of seizures is essential, as NCSE has been shown to be an independent predictor of mortality in children.^{40,41} Various studies have shown that delayed initiation of treatment of seizures is associated with refractoriness of status epilepticus.⁴² In addition, failure to treat seizures according to a protocol is associated with the development of status epilepticus,⁴³ and a proportion of seizure-related deaths are preventable.⁴⁴ Specific disease states in pediatrics warrant heightened index of suspicion for NCS, as it can occur frequently in children on extracorporeal membrane oxygenation,⁴⁵ following neonatal cardiac surgery on bypass,⁴⁶ and following TBI.⁴⁷ cEEG monitoring should be considered for children at high risk for NCS in whom a neurologic examination cannot be used for sequential evaluation, such as children on sedation or neuromuscular blockade. cEEG should also be used to monitor response to intensive therapies for known status epilepticus, for example, high-dose benzodiazepines or barbiturates.

Cerebral oximetry is an additional modality useful for monitoring a child with brain injury. It can be used to assess imbalances between the supply and demand of oxygen delivery to titrate therapies intended to mitigate secondary brain injury. Analogous to the use of central venous oxygen saturation to monitor oxygen delivery, cardiac

output, and oxygen extraction in shock, jugular bulb oximetry ($S_{jv}O_2$) can be used to assess the cerebral blood flow, oxygen delivery, and extraction. Although it has been used in pediatric neurosurgery,^{48,49} and there are reports of correlation between $S_{jv}O_2$ and outcome after brain injury in adults and children,^{50–52} it is not currently widely used in pediatric critical care. Another tool used to monitor cerebral oxygenation is the brain tissue oxygen monitoring ($P_{br}O_2$), where a catheter is inserted directly into the brain tissue. Therapeutic measures to improve $P_{br}O_2$ include pulmonary and hemodynamic strategies to increase the cerebral oxygen delivery and arterial PO_2 to facilitate oxygen diffusion to brain tissue, and neuroprotective measures such as limiting cerebral metabolic demand and raised ICP. Studies in both adult and pediatric neurotrauma showed an association between unfavorable outcome and $P_{br}O_2$ less than 10 mm Hg.^{53–56} An important limitation of the goal-directed $P_{br}O_2$ therapy is related to the placement of the $P_{br}O_2$ catheters. In one of the largest pediatric studies, the monitors were placed either in normal appearing right frontal white matter if there were no focal lesions or in the hemisphere with the greater swelling or more localized lesions.^{53,54} If the monitor is placed in healthy brain tissue, the impact of therapy may not reflect effects on at-risk brain tissue. Conversely, if the monitor is placed in dead brain tissue with minimal local cerebral blood flow, therapy may not change measured $P_{br}O_2$. Because there was variability and subjectivity even in a single center series which is considered a landmark study in this area, this modality may have limited generalizability. The 2019 Brain Trauma Foundation Guidelines for Management of Severe TBI state that while there is insufficient data to make a recommendation regarding $P_{br}O_2$ monitoring, therapy should aim for a threshold of greater than 10 mm Hg if it is used.¹⁸ Transcranial near-infrared spectroscopy (NIRS) is a noninvasive modality of cerebral oximetry, which uses a probe attached to the skin of the forehead to measure the absorption of light in the near-infrared spectrum. Because oxyhemoglobin and deoxyhemoglobin absorb light at different wavelengths, the proportion of absorption can represent the oxygenation of brain tissue deep to the probe. Using the goal-directed therapy for cerebral hypoxia monitored by NIRS to decrease the risk of death or improved survival with severe brain injury in preterm infants has shown promise in a phase II study.^{57,58} Cerebral NIRS has been extensively used intraoperatively in cardiac surgery in children and adults⁵⁹ and has been used as a marker of hemodynamics in pediatric critical care.⁶⁰ Specifics of the NIRS signal and the duration of desaturation have been shown in the pediatric cardiac ICU setting to be associated with longer time on mechanical ventilation, and longer duration of PICU and hospital stay.⁶¹ One important limitation of NIRS, similar to that of $P_{br}O_2$ monitoring, is the uncertainty of using a local problem as a representation of global cerebral oxygenation, and whether the probe placement limits the assessment of oxygenation locally where brain is at risk. Overall, studies evaluating the use of NIRS to provide the goal-directed therapy in PNCC are lacking.

SUMMARY

The greatest advances in medicine are generalizable across institutions regardless of resources and are based on universal fundamentals of assessment, pathophysiology, and natural history of disease, and applied through continuous processes of education, safety, and quality improvement. Recently, there have been tremendous improvements in the field of PNCC, including the development and implementation of monitoring and imaging techniques, evidence-based practice guidelines for stroke and TBI, and the organization of multidisciplinary PNCC programs. Because the cause of pediatric brain injury is at once diverse and relatively infrequent, a specialized model

similar to adult neurocritical care and high-volume pediatric areas such as cardiac critical care may not be feasible. To further advance the field, the PNCC community must continue to foster a culture of brain-oriented critical care through a focus on education, quality improvement, and multidisciplinary collaboration within and across institutions.

CLINICS CARE POINTS

- A comprehensive, multidisciplinary approach to care, including current techniques of imaging, neuromonitoring, and neuroprotective strategies augmented by a focus on patient safety, quality, and education can improve outcomes in children with brain injury.
- The overarching goal of PNCC in mitigating secondary brain injury can be achieved by balancing the supply and demand of blood, oxygen, and nutrients of vulnerable brain tissue. Ensuring adequate cerebral oxygen delivery begins with applying pediatric critical care principles of airway management, ventilator strategies, fluid resuscitation, and inotropic or vasopressor therapies, and continues with brain-specific therapies of ICP control, improvement of CPP, and limiting cerebral metabolic demand.
- Evaluating and assessing illness severity in a child with brain injury begins with the interpretation of vital signs and pupillary examination, as well as determining the GCS. Indications for CT or MRI to evaluate injury depend on the mechanism of injury, initial clinical examination, and patient stability.
- cEEG can be used to evaluate for NCS or NCSE, monitor intensive therapies for seizures such as barbiturates or high-dose benzodiazepines, or if neurologic examination is limited, such as in the setting of neuromuscular blockade or ECMO. Cerebral oximetry via NIRS, jugular venous oximetry, or brain tissue oximetry can be used to assess imbalances between the supply and demand of oxygen delivery to guide therapy intended to mitigate secondary brain injury.

DISCLOSURE

Author has nothing to disclose.

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