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Approaches to neuroprotection in pediatric neurocritical care

Angad Kochar, Kara Hildebrandt, Rebecca Silverstein, Brian Appavu

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Abstract

Acute neurologic injuries represent a common cause of morbidity and mortality in children presenting to the pediatric intensive care unit. After primary neurologic insults, there may be cerebral brain tissue that remains at risk of secondary insults, which can lead to worsening neurologic injury and unfavorable outcomes. A fundamental goal of pediatric neurocritical care is to mitigate the impact of secondary neurologic injury and improve neurologic outcomes for critically ill children. This review describes the physiologic framework by which strategies in pediatric neurocritical care are designed to reduce the impact of secondary brain injury and improve functional outcomes. Here, we present current and emerging strategies for optimizing neuroprotective strategies in critically ill children.

Key Words: Neuroprotection; Pediatric neurocritical care; Cerebral perfusion; Cerebrovascular pressure reactivity

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Core Tip: Acute neurologic injuries are a common cause of morbidity and mortality in critically ill children. A fundamental goal of pediatric neurocritical care is to mitigate the impact of secondary neurologic injury in critically ill children. Here, we discuss strategies for optimizing neuroprotective strategies in critically ill children.

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INTRODUCTION

Neurologic injuries represent a substantial component of pediatric intensive care unit (PICU) utilization in the United States. Analyses of admissions to a large tertiary PICU have demonstrated that neurologic diagnoses are present in approximately one quarter of PICU admissions (25.4%)[1] and acute brain injury is the most common proximate cause of death in children admitted to a PICU accounting for up to 65% of PICU mortality[2]. Additionally, children admitted to the PICU are estimated to acquire new long-term functional disability at a rate of 4.8%[3] by hospital discharge with evidence of further decline in functional status after discharge[4]. The significant contribution of neurologic injury to PICU morbidity and mortality has resulted in an increasing emphasis to develop evidence-based practices to prevent acute brain injury in systemically ill patients and to mitigate the impact of such injuries once they occur. Here, we review current approaches to neuroprotective care in commonly seen pediatric critical care conditions as well as ongoing and future research targets that promise individualized, precision-based care.

MECHANISMS OF SECONDARY NEUROLOGIC INJURY

The evolution of neurologic dysfunction after an acute insult is multiphasic. The primary neurologic injury represents an initial inciting event which results in neuronal cell death, for example acute energy failure in the setting of arterial ischemic stroke or direct mechanical shearing of axons in traumatic brain injury (TBI). Some of the damage caused by the primary injury is typically complete at the time of recognition or presentation to care. However, in many situations there remains at-risk brain tissue that can be acutely rescued if brain homeostasis is optimized with appropriate cerebral blood flow (CBF) to meet metabolic demand. A classic example of such an intervention in adult neurocritical care is thrombolytic and other reperfusion therapy that salvages the ischemic penumbra after acute arterial ischemic stroke. Minimizing ongoing or recurrent mismatch between cerebral perfusion and brain metabolic demand during critical care management represents one of the primary goals of neurocritical care.

Following the primary injury, multiple parallel physiologic pathways emerge that result in further cellular injury if not prevented (Figure 1). A fundamental goal in pediatric neurocritical care is to limit secondary brain injury by optimizing cerebral oxygen delivery and its use[5]. Secondary brain injury is the additive cerebral injury which is created by an imbalance of supply and demand in cerebral metabolism.

TARGETS FOR NEUROPROTECTION IN THE PICU

Neuroprotection generally refers to the preservation of cerebral function by mitigating the above sources of secondary injury[6]. In the PICU, this approach can be broken down into a variety of directives including optimization of cerebral perfusion, limitation of cerebral metabolic demand, and mitigation against cerebral edema.

Optimize cerebral perfusion

The process of optimizing cerebral perfusion for a given patient or pathology requires attention to several physiologic and hemodynamic targets for neuroprotection with consideration of both CBF as well as blood content.

CBF is primarily determined by cerebral perfusion pressure (CPP) and cerebral vascular resistance. CPP is calculated as the difference between mean arterial pressure (MAP) and intracranial pressure (ICP). Importantly, however, measurements of MAP vary significantly by site and methodology[7]. Additionally, adult data has demonstrated that invasive arterial blood pressure measurements levelled at the heart underestimates the MAP at the level of the circle of Willis by approximately 15% when a patient's head of bed is elevated to 30° or 45° suggesting head of bed positioning is an important consideration in critically ill patients[8]. Hypotension in pediatric ICU patients has been associated with increased mortality after cardiac arrest and worse outcomes after stroke and TBI[9-13]. Consensus-based pediatric guidelines have focused on maintaining MAPs above minimum thresholds and CPP thresholds when invasive ICP monitoring is available (Table 1)[14-16]. While specific thresholds have been proposed for both MAPs and ICPs, some evidence suggests optimal values varies by age and are on average higher than current guidelines-based recommendations[17]. Further research is needed to identify appropriate minimum thresholds in pediatric neurocritical care populations.

Cerebral vascular resistance is the other major determinant of CBF. Arterial carbon dioxide tension (PaCO₂) is the primary modifiable physiologic parameter that impacts cerebral vascular resistance in patients with intact cerebrovascular reactivity, though significant hypoxemia can also play a role in cerebrovascular vasodilation[18]. Increased PaCO₂ results in cerebrovascular vasodilation which is often

Table 1 Summary of consensus-based guideline recommendations for pediatric neuroprotection

Pathology	Optimize cerebral perfusion	Limit cerebral metabolic demand	Mitigate cerebral edema
Severe traumatic brain injury[15]	Maintain age appropriate CPP (Minimum ≥ 40 mmHg)	Targeted normothermia: 35 °C–38 °C	Maintain sodium: ≥ 140 mEq/L
	If PbtO ₂ available: ≥ 10 mmHg	Maintain adequate sedation and analgesia	Maintain HOB = 30 °C
	Maintain ICP < 20 mmHg	Benzodiazepine + Opiate as initial therapy	Second tier therapies
	Targeted normoxemia: SpO ₂ 92%–99%	Consider continuous EEG	Surgical intervention
	Maintain PaCo ₂ : 35–40 mmHg	Phenytoin or levetiracetam for seizures	Barbiturate infusion
	Target euglycemia: 100–180 mg/dL		Moderate hypothermia (32 °C–34 °C)
	Target euvoemia: CVP 4–10 mmHg		Hyperventilation (PaCO ₂ 28–34 mmHg)
	Maintain hemoglobin: > 7 g/dL		Increased hyperosmolar therapy
Post-Cardiac arrest[14]	Maintain MAP $\geq 5^{\text{th}}$ percentile for age	Targeted normothermia: 36 °C–37.5 °C	
	Targeted normoxemia: SpO ₂ 94%–99%	Consider 48 h of T 32 °C– 34 °C for OHCA	
	Maintain PaCo ₂ : 35–45 mmHg	Maintain adequate sedation and analgesia	
	Target euglycemia: 80–180 mg/dL	Continuous EEG	
Acute arterial ischemic stroke[80]	Treat hypertension with caution in patients with intracranial vascular stenosis	Treat seizures if identified	Consider decompressive surgery for malignant edema
	Aggressively treat hypotension		For large volume infarcts (> 1/2 MCA territory)
	Treat hyperglycemia to target 140–180 mg/dL		Consider early decompressive hemicraniectomy (< 24 h)
	Treat hypoglycemia: < 60 mg/dL		Serial imaging and frequent assessments for 72 h

CPP: Cerebral perfusion pressure; PbtO₂: Partial pressure of brain tissue oxygenation; ICP: Intracranial Pressure; SpO₂: Peripheral oxygen saturation; PaCo₂: Arterial carbon dioxide tension; CVP: Central venous pressure; EEG: Electroencephalography; HOB: Head of bed; MAP: Mean arterial pressure; OHCA: Out-of-hospital cardiac arrest; MCA: Middle cerebral artery.

desirable when hypoperfusion is the primary insult as seen with permissive hypercapnia in acute stroke care, though is less desirable in cases where cerebral edema and intracranial hypertension are predominant as it results in a net increase in the intracranial blood volume compartment further contributing to increased ICP. Current pediatric literature supports maintaining normocapnia in most pathologies. Impaired carbon dioxide reactivity to brain tissue oxygenation (PbtO₂) can be observed after injuries such as TBI, and recognition of such situations may influence targeting of PaCO₂ levels.

Partial pressure of blood oxygenation (PaO₂), glucose and hemoglobin content are also important in ensuring adequate cerebral perfusion after acute brain injury. Both hyperoxia and hypoxia are common in pediatric patients after cardiac arrest and TBI, however the impact of oxygen exposure on outcomes remains unclear[19–21]. Arterial hypoxemia in the injured brain results in reduced cerebral oxygen delivery, potentiating injury in ischemic tissue and further contributing to neuronal excitotoxicity. Conversely, hyperoxia is thought to increase oxidative stress through increased production of free radical species and has been associated with increased mortality after cardiac arrest in adult populations [22]. Available data from pediatric investigations has been equivocal on the effect of arterial hypoxia or hyperoxia on morbidity or mortality after cardiac arrest or TBI. One large retrospective review demonstrated increased mortality in pediatric post arrest patients with a PaO₂ ≥ 300 mmHg or PaO₂ ≤ 60 mmHg on the first arterial blood gas after PICU admission[23]. Other retrospective cohort studies as well as one prospective multicenter observational study of pediatric post-arrest patients have not redemonstrated this association[19,21,24]. Retrospective analysis of pediatric TBI patients has not demonstrated an association between hypoxia and outcome, though extrapolation of this data is limited as hypoxia is often identified and treated rapidly during resuscitation[20,25,26]. A recently published

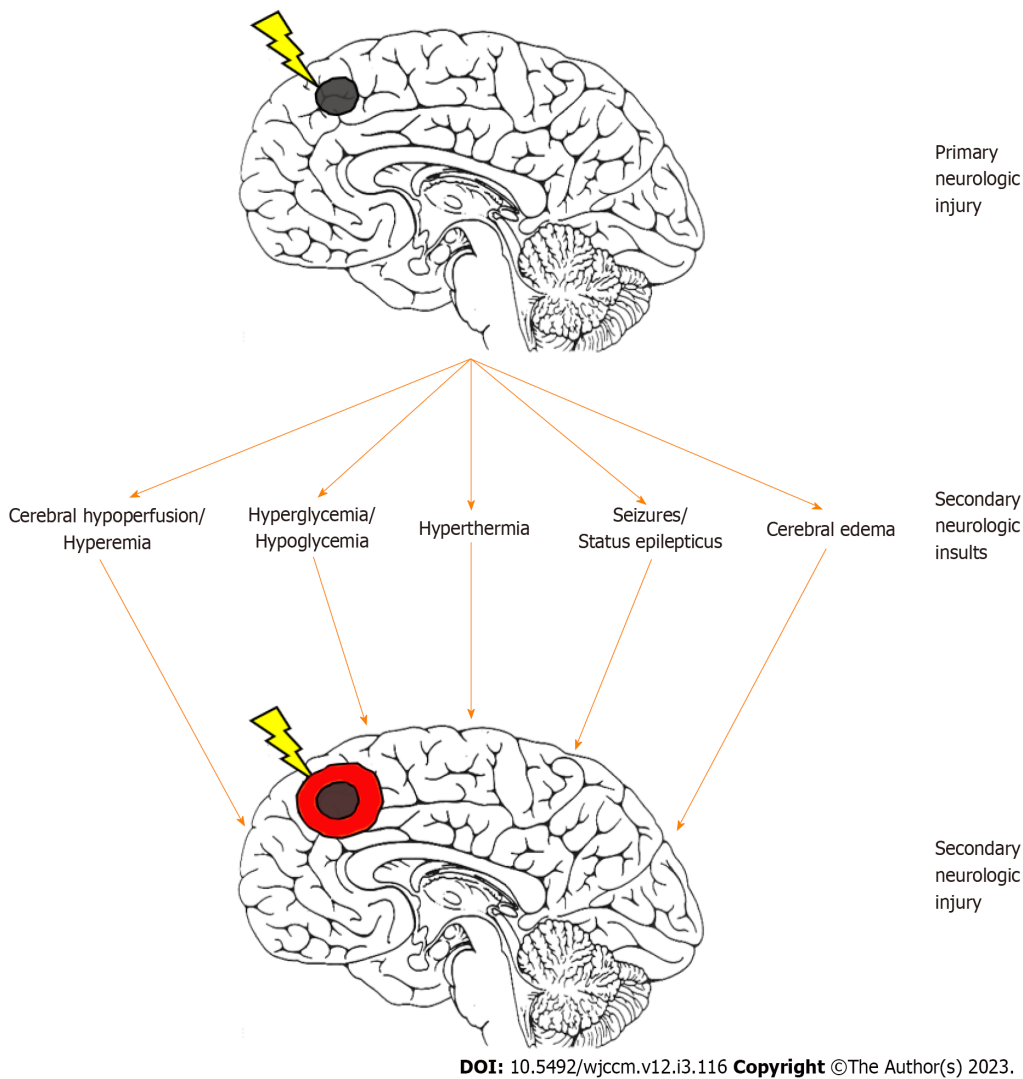


Figure 1 Development of secondary neurologic injury after pediatric acute brain injury. After primary brain injury (black circle), a host of secondary neurologic insults can contribute to worsening of the initial injury, resulting in secondary neurologic injury (red circle). Neuromonitoring for secondary brain insults and optimization of neuroprotection may help mitigate against secondary neurologic injury in children with acute brain injuries.

systematic review and meta-analysis did demonstrate an association between arterial hyperoxia (as defined by $\text{PaO}_2 > 250$ mmHg) and increased mortality pediatric study populations that included post-cardiac arrest, TBI, extracorporeal membrane oxygenation and general pediatric critical care[27]. Neuroprotective strategies in pediatric critical care generally support maintaining normoxemia while avoiding hyperoxia, though specific thresholds vary. Emerging data in pediatric TBI patients where invasive PbtO_2 monitoring is available suggests that episodes of cerebral hypoxia (as measured by $\text{PbtO}_2 < 10$ mmHg or 15 mmHg) is associated with unfavorable clinical outcomes as well as reduced performance on neuropsychiatric testing > 1 year post injury[28-30].

Hyperglycemia (serum glucose > 200 mg/dL) on admission after pediatric TBI has been demonstrated to be a predictor of mortality and ICU length of stay suggesting high serum glucose may be a marker of brain injury severity[31-34]. Similarly, persistent hyperglycemia 12-72 h after admission has also been independently associated with mortality and poor clinical outcomes, though prospective data assessing the impact of narrow glyceimic control on outcomes is limited[35-37].

Retrospective evaluations of anemia in pediatric TBI patients have not demonstrated a significant association between anemia or need for packed red blood cell transfusion with outcomes to support transfusion thresholds that differ from standard pediatric ICU practices[38,39].

Limit cerebral metabolic demand

Decreasing the mismatch between cerebral perfusion and metabolic demand is a critical component to neuroprotection after acute brain injury by reducing the amount of tissue experiencing relative ischemia. Mechanisms that limit cerebral metabolism may also slow the pathological processes that contribute to secondary injury such as the enzymatic pathways that result in cell death and the neuro-inflammatory cascade that potentiates vasogenic edema. Physiologically, there are three primary targets

for intervention that affect cerebral metabolic activity: Temperature, sedation, and antiseizure medications to combat acute symptomatic seizures.

Optimal temperature management for patients with acute brain injuries has been the subject of extensive research in both adult and pediatric populations. Early animal data demonstrated a linear relationship between temperature and CBF and oxygen consumption suggesting a 6% decrease in cerebral metabolic demand for each decrease of 1 °C compared to normothermia[40]. Conversely, animal studies conducted in the 1980-1990s concluded that mild hypothermia of up to 2 °C conferred significant neuroprotective benefits in rat models of focal and global cerebral ischemia[41-43]. Conversely, even brief periods of hyperthermia of 3 h in similar models were associated with increased infarct volume[44-46]. The deleterious effect of fever in neurological injuries has since been redemonstrated in both adult and pediatric populations across multiple neurologic pathologies including stroke, TBI and post cardiac arrest[46-48]. In light of this data, targeted temperature management with the goal of aggressive avoidance of fever has been adopted as standard of care in patients with acute brain injury.

Of greater debate is whether the practice of induced hypothermia (typically within the range of 32-35 °C) improves neurologic outcomes in selected pediatric populations. A recent meta-analysis of eight randomized controlled trials assessing therapeutic hypothermia in pediatric severe TBI found a non-statistically significant trend towards increased mortality in patients who were treated with therapeutic hypothermia compared to normothermic controls[49]. In post-arrest care, two large, multicenter, randomized controlled trials have been conducted to assess the benefit of therapeutic hypothermia after cardiac arrest in children separately evaluating comatose children after in-hospital (THAPCA-IH) and out-of-hospital (THAPCA-OH) arrests. These trials investigated the impact of 48 h of targeted hypothermia (target 33 °C) followed by gradual rewarming and continued targeted temperature management (target 36.8 °C) for a total of 120 h after protocol initiation compared with 120 h of targeted normothermia (target 36.8 °C) on 1-year survival with a good functional outcome (defined as an age corrected standard score of 70 or higher on the Vineland Adaptive Behavior Scales, second edition). The THAPCA-IH trial was terminated during interim analysis for futility as the primary outcome did not differ between groups, though notably the safety analysis did not demonstrate any significant differences in adverse events or 28-d mortality across groups[50]. THAPCA-OH found slightly higher rates of 1-year survival with good functional outcomes in the hypothermia group compared to (20% *vs* 12%) though this difference was not statistically significant. Secondary analysis found significantly increased survival time in the therapeutic hypothermia group when compared to normothermia (149 d *vs* 119 d)[51]. Given these findings, investigation into the potential benefit of therapeutic hypothermia in pediatric out-of-hospital cardiac arrest remains ongoing and there remains provider and center dependent variability in practice. The Pediatric Influence of Cooling Duration on Efficacy in Cardiac Arrest Patients trial (NCT05376267) aims to assess the efficacy of cooling and optimal duration of hypothermia in pediatric survivors of out-of-hospital cardiac arrests and is currently enrolling with estimated completion in 2028.

Effective sedation and analgesia play an important role in limiting cerebral metabolic demand and have also been shown to have independent agent-specific effects on CBF, autoregulation and vasomotor reactivity[52]. As such, the optimal selection of anesthetic agents for pathology dependent neuroprotection is a target for ongoing research. In general, for critically ill children in the ICU the most frequently reported anesthetic agents used are benzodiazepines and opiates with frequently used secondary agents including dexmedetomidine, propofol, barbiturates, ketamine and clonidine[53]. Of these, benzodiazepines, dexmedetomidine, propofol and barbiturates have the effect of decreasing both cerebral oxygen consumption and CBF and are often used in patients where there is concern for increased ICP or significant risk for cerebral edema. Ketamine has historically been avoided in patients with acute brain injury as early data suggested its use resulted in direct cerebrovascular vasodilation leading to increased CBF and potentially increased ICP[54]. A more recent prospective pediatric trial suggested that ketamine administration in ventilated patients with intracranial hypertension refractory to initial therapies may in fact reduce ICP by an average of 30% while increasing CPPs and may therefore be safe and effective in patients with acute brain injury[55]. Neuromuscular blockade has also been shown to decrease global oxygen consumption and energy expenditure in mechanically ventilated children. This is an important consideration in children who are shivering when undergoing targeted temperature management and is used extensively in patients with refractory elevations in ICP[56,57]. The use of barbiturate coma to treat acute, refractory intracranial hypertension for pediatric TBI has been shown to be effective in decreasing ICP and is included as a consideration for second-tier therapies in the most recent consensus-based Brain Trauma Foundation guidelines[15,16,58].

The emergence of continuous electroencephalography (cEEG) has allowed for a greater understanding that seizures and ictal-interictal continuum (IIC) patterns are common after acute brain injury and are associated with physiologic changes that suggest an increase in metabolic demand[59,60]. The IIC represents a pattern on EEG that does not qualify as an electrographic seizure but has a reasonable chance to be contributing toward neuronal injury or pathologic clinical symptoms[61]. Periodic discharges, an IIC pattern, has been observed to be associated with elevated lactate-pyruvate ratios in adult TBI patients undergoing cerebral microdialysis monitoring, indicating metabolic crisis[62]. Higher frequency periodic discharges have been observed to be associated with increases in regional CBF and

CPP, and when reaching frequencies of ≥ 2.0 Hz, are associated with reductions in brain tissue hypoxia [63]. These findings indicate that periodic discharges are associated with increases at metabolic demand which are partially compensated at lower frequencies but are insufficiently compensated at ≥ 2.0 Hz. In a cohort of adult patients with aneurysmal subarachnoid hemorrhage, seizures themselves were associated with tachycardia, tachypnea, hypertension, as well as rise in delayed CBF [64]. Among pediatric TBI patients, specific quantitative electroencephalographic components of seizure activity have been linked to changes in cerebral and systemic physiology, with ictal spectral edge frequency being negatively associated with ICP and peak value frequency being positively associated with heart rate [65]. Seizures and IIC patterns can often be treated effectively with antiseizure medications, indicating that their use may be important as a neuroprotective strategy to mitigate against metabolic crises.

Mitigate against cerebral edema

Cerebral edema represents an increase in brain volume that is contained within cerebral interstitial tissue, and can manifest as vasogenic, cytotoxic, hydrostatic, or osmotic edema [66,67]. Vasogenic edema manifests with blood brain barrier breakdown and increased water permeability within brain interstitia. Cytotoxic edema results due to metabolic crisis, cell death, and an influx of water and ions into intracellular space. Hydrostatic edema can occur in the setting of obstructive hydrocephalus and is the result of a net influx of spinal fluid from the ventricular space into brain parenchyma. Osmotic edema is a very particular form of cerebral edema in which there is a specific isolated osmotic gradient between brain parenchyma and the cerebrovascular system. Optimizing temperature management, ventilation, and sedative therapy, as described above, remain important elements in mitigating secondary brain insults arising from cerebral edema. Hyperosmolar therapy exists to aid in mitigation of cerebral edema, with common utilization of hypertonic saline and mannitol. A recent comparative effectiveness study of pediatric TBI patients demonstrated bolus dosing of hypertonic saline to be superior to mannitol in reduction of intracranial hypertension [68]. Some evidence suggests that hyperosmolar therapy is more likely to be effective in reducing intracranial hypertension when there is evidence of efficient cerebrovascular pressure reactivity (CVPR) [69-71]. Emerging research has demonstrated several biomarkers that target the blood-brain barrier or receptors of aquaporin-4 or vasopressin V1a to mitigate cerebral edema, although these are not yet standard treatment targets in clinical care [72]. When medical efforts to mitigate against malignant cerebral edema have failed in the setting of refractory intracranial hypertension, therapeutic decompressive craniectomy can be considered [15].

STANDARDIZED AND INDIVIDUALIZED APPROACHES TO NEUROPROTECTION

The emergence of neurocritical care as a subspecialty has been strengthened by increasing evidence that clinical care implemented with specialized expertise is associated with improved outcomes for critically ill patients with neurologic injuries. A recent large meta-analysis suggested that adult patients who underwent interventions arising from neurocritical care units, neurointensivists or neurocritical care consulting services had improved survival and functional outcomes as compared to adults with similar conditions who experienced general care in intensive care units [73]. A cohort study of pediatric TBI patients demonstrated that implementation of a pediatric neurocritical care program with a standardized evidence-based approach to neurologic monitoring and clinical care was associated with improved outcomes [74]. Such findings have helped the maturation of several specialized pediatric neurocritical care services across the United States and North America, with an array of diverse models including multidisciplinary consultation services as well as dedicated pediatric neurocritical care units that include involvement from neurologists, pediatric intensivists and neurosurgeons [75-79]. These services work toward providing institutional standardized care pathways for common neurocritical care conditions founded upon the latest evidence-based guidelines, often providing standardized or age-based thresholds for intervention (Figure 2).

Whereas the implementation of standardized institutional pathways for neurocritical care carries an association with improved outcomes at an epidemiological level, there is a severe lack of high-level evidence to demonstrate that specific clinical interventions improve outcomes for commonly seen conditions such as TBI, cardiac arrest, and arterial ischemic and hemorrhagic stroke [14-16,80]. Given the lack of high-level evidence, clinical decisions are often made in context of moderate or low-level evidence alongside fundamental and conceptual knowledge regarding pathophysiological mechanisms of critical care diseases. To this end, there are opportunities to evaluate, at the patient-level, whether individualized targeting of care may aid in optimizing neuroprotection.

Critically ill patients in the ICU often have an abundance of continuous physiologic data collected *via* various monitoring techniques including heart rate, invasive arterial blood pressure, end-tidal CO₂ and respiratory rate or ventilator settings. Patients with acute brain injuries typically warrant additional neurophysiologic monitoring. This includes ICP monitoring using an external ventricular drain or intraparenchymal monitor, intraparenchymal brain tissue oxygenation, regional oxygen saturation *via* near infrared spectroscopy, cEEG, pupillometry, or information on CBF provided by various imaging techniques including transcranial doppler and thermal diffusion flowmetry [81,82]. Until recently, this

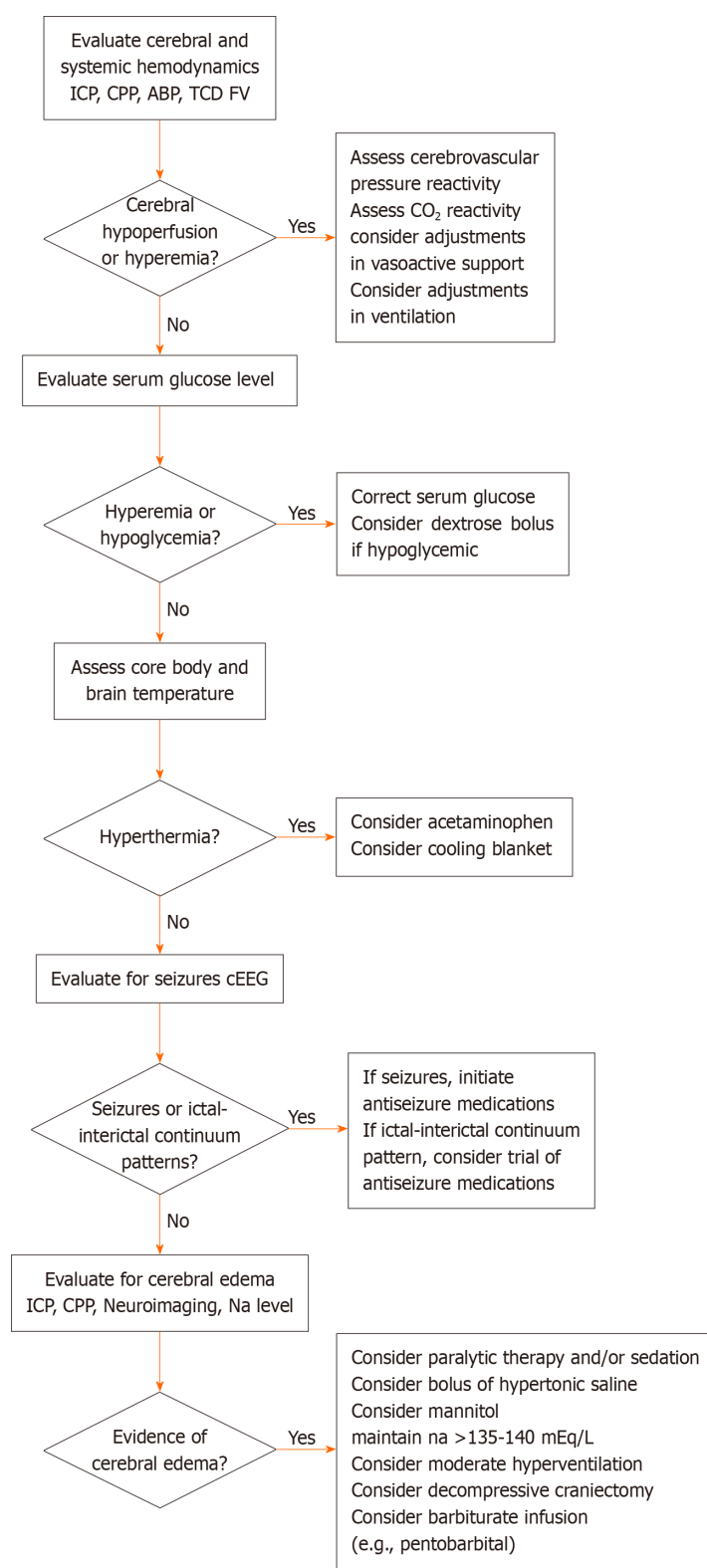


Figure 2 Stepwise algorithm for neuroprotection in pediatric neurocritical care. ICP: Intracranial pressure; CPP: Cerebral perfusion pressure; ABP: Arterial blood pressure; TCD: Transcranial Doppler ultrasound; FV: Flow velocities; CO₂: Carbon reactivity; cEEG: Continuous electroencephalography; NA: Sodium; mEq/L: Milliequivalents per liter.

information was typically evaluated in isolation or in small subsets. Recent advances in technology have facilitated the development of integrated platforms that aggregate and time-synchronize this information, allowing for easier visualization by the clinician. This approach, known as multimodality neurologic monitoring, has also allowed for investigation of how changes in one physiologic parameter potentially affect others. This allows for a greater understanding of real-time, patient-specific physiology to inform clinical decision making[83].

The utilization of neurologic monitoring is aimed towards recognition of biosignatures of secondary brain injury and initiation of treatment based upon such features. The most common and non-invasive form of this is the recognition and treatment of seizures and IIC patterns based on cEEG. Invasive methods allow for detection of intracranial hypertension and brain tissue hypoxia, with a variety of neuroprotective strategies available to use depending on the underlying source of such insults. A recent survey of pediatric neurocritical care centers in 2020 demonstrated that 20 hospitals use transcranial Doppler ultrasound as part of clinical care for management of pediatric intracranial hemorrhage, arterial ischemic stroke, or TBI, with utilization aimed toward determining when to obtain neuroimaging, how to manipulate CPP, and whether to perform surgical interventions[84]. A single-center cohort of TBI patients undergoing standardized multimodality neurologic monitoring reporting demonstrated that such reporting influenced timing of neuroimaging, ICP monitoring discontinuation, use of paralytic, hyperosmolar and pentobarbital therapies, neurosurgical interventions, use of provocative cerebral autoregulation testing, ventilator and CPP adjustments and neurologic prognostication discussions[85]. Future multicenter work describing use of integrated multimodality neurologic monitoring as a means for detecting biosignatures of secondary brain injury may aid in better understanding benign and malignant neurophysiologic patterns, methods of determining therapeutic efficacy of specific interventions, and comparative effectiveness strategies to determine whether such interventions may improve functional outcomes.

The integration of multiple streams of time-synchronized physiologic data has allowed for the development of real-time biomarkers of key neurophysiologic processes. CVPR can be assessed when integrating arterial blood pressure with neuromonitoring features that may act as surrogates of CBF [83]. Using transcranial Doppler ultrasound, the mean velocity index or systolic velocity index describes CVPR utilizing transcranial doppler ultrasound flow velocity characteristics with arterial blood pressure [86,87]. With patients undergoing continuous ICP monitoring, the pressure reactivity index (PRx) and other similar indices can be utilized with an assumption that slow wave fluctuations in ICP are directly related to changes in cerebral arterial blood volume[83]. The PRx, as an example, represents a moving Pearson correlation coefficient relating slow wave fluctuations in arterial blood pressure with ICP. Elevated PRx values (approaching +1) are postulated to represent inefficient CVPR, whereas lower values (approaching -1) are postulated to represent efficient CVPR[88].

When PRx is plotted with error bars across a range of CPP, parabolic curves can often be extrapolated, with the lowest PRx value, or nadir of the parabolic curve, representing the 'optimal CPP' at which CVPR is most efficient. From this, theoretical lower and upper limits of CVPR can be estimated based upon specific thresholds of elevated PRx values[89] (Figure 3). Multiple pediatric TBI studies have linked higher PRx values to worsened outcomes, and there is also evidence that increased time below the lower limit of CVPR is associated with unfavorable outcomes[90-93]. A recent feasibility randomized control trial of adult TBI patients evaluated patients who were treated with CPP targets based upon existing Brain Trauma Foundation guidelines and compared them to patients who were individualized to optimal CPP targets based upon PRx. This trial of 60 patients demonstrated that there were no significant differences in safety endpoints between the two groups, supporting the notion that prospective trials powered for clinical outcomes may be safe and feasible[94]. Other model-based indices of CVPR exist using brain tissue oxygenation, cerebral regional oximetry or other neuromonitoring techniques, with evidence from cardiac arrest, extracorporeal membrane oxygenation and other conditions that suggest that inefficient CVPR or deviations from optimal values of CVPR may be associated with unfavorable outcomes[95-98]. Future prospective work with such techniques may help in determining the efficacy for which they can be used to optimize neuroprotection across a wide range of critical care conditions.

EXISTING KNOWLEDGE GAPS AND FUTURE DIRECTIONS

While emerging evidence demonstrates that specific physiologic biomarkers are linked to functional outcomes after pediatric acute brain injuries, there is a severe lack of evidence toward specific neurotherapeutic strategies that improve functional outcomes. Knowledge gaps remain regarding whether biomarkers can be used to better understand whether specific neuroprotective treatments confer potential to benefit for patients stratified toward specific underlying physiologic profiles. Neuroprotective measures optimal toward care in TBI using invasive neuromonitoring may not necessarily translate to other non-traumatic conditions in which invasive monitoring may not be used. It also remains unclear whether implementation of specific strategies, such as vasoactive support for CPP-guided management, may be appropriate for neonates and very young infants where CBF differs from older children[99]. Future comparative effectiveness studies and clinical trials involving different pediatric acute brain injury conditions will be needed to further address these knowledge gaps.

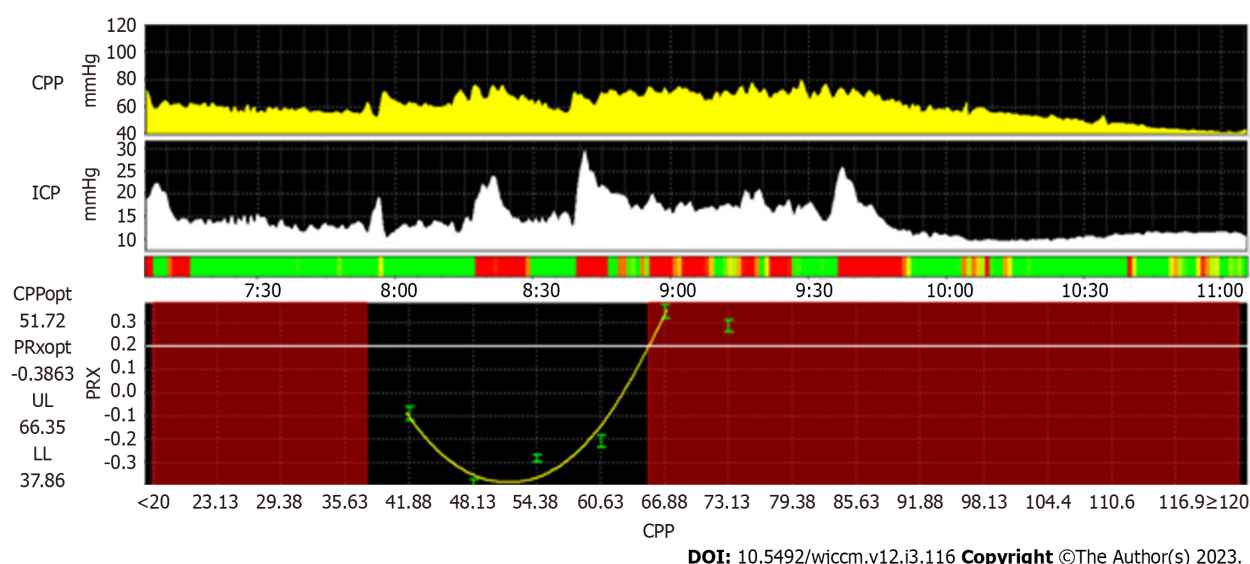


Figure 3 Example of identification of optimal cerebral perfusion in a 2-year-old male with severe traumatic brain injury. Here, the PRx is plotted across a range of CPP values over a four-hour window, demonstrating a parabolic curve which suggests that the lowest point of the curve (51.72 mmHg; CPPopt) represents the CPP at which cerebrovascular pressure reactivity is most efficient. By using cutoffs of greater than 0.2, the lower limit of cerebrovascular pressure reactivity is estimated at 37.86 mmHg and the upper limit of cerebrovascular pressure reactivity is estimated at 66.35 mmHg. PRx: Pressure reactivity index; CPP: Cerebral perfusion pressure; CPPopt: Optimal cerebral perfusion pressure; ICP: Intracranial pressure; PRxopt: Optimal pressure reactivity index; UL: Upper limit of cerebrovascular pressure reactivity; LL: Lower limit of cerebrovascular pressure reactivity.

CONCLUSION

Neuroprotection is a foundational component of pediatric neurocritical care. Standardized clinical approaches that integrate evidence-based guidelines with fundamental and conceptual neurophysiologic knowledge have been associated improved outcomes for patients with acute neurologic injuries. Substantial knowledge gaps remain regarding key clinical interventions that may improve patient outcomes. Multimodality neurologic monitoring demonstrates strong promise toward augmenting a patient-centered approach for optimized neuroprotection.

FOOTNOTES

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