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Topical Review

Multimodal Neurologic Monitoring in Children With Acute Brain Injury

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ABSTRACT

Children with acute neurologic illness are at high risk of mortality and long-term neurologic disability. Severe traumatic brain injury, cardiac arrest, stroke, and central nervous system infection are often complicated by cerebral hypoxia, hypoperfusion, and edema, leading to secondary neurologic injury and worse outcome. Owing to the paucity of targeted neuroprotective therapies for these conditions, management emphasizes close physiologic monitoring and supportive care. In this review, we will discuss advanced neurologic monitoring strategies in pediatric acute neurologic illness, emphasizing the physiologic concepts underlying each tool. We will also highlight recent innovations including novel monitoring modalities, and the application of neurologic monitoring in critically ill patients at risk of developing neurologic sequelae.

Introduction

Acute neurologic illness in children is associated with high mortality and morbidity. Unfavorable neurologic outcomes are seen in over half of children with normal baseline neurological function who become critically ill due to an acute neurologic insult.[1]

Because few targeted therapies exist, neuroprotective strategies address causes of "secondary" brain injury (e.g., cerebral edema, ischemia). Critical care for children with acute neurological injuries emphasizes maintaining cerebral perfusion and oxygenation, while anticipating and addressing pathologic increases in intracranial pressure (ICP). These children require intensive monitoring based on physiologic principles including intracranial compliance and cerebral autoregulation.

Prognostication of outcome represents an important challenge in pediatric critical care, as the neurologic examination may be limited. For example, following cardiac arrest, examination can be confounded by pharmacologic agents (e.g., sedatives, neuromuscular blockade), metabolic abnormalities, and the child's developmental stage. In small pediatric studies, absent motor response, Glasgow Coma Scale (GCS) score <5, absent spontaneous respiratory effort, and nonreactive pupils at 24 hours following return of circulation are associated with poor outcome.[2,3] Given the limitations of physical examination, neurologic monitoring technologies have emerged to provide multimodal assessment of pathophysiology, guide intervention, and improve prognostication.[2]

In this review, we will discuss current indications, modalities, and strategies for neurologic monitoring in critically ill children (Table). This discussion will focus on traumatic brain injury (TBI), cardiac arrest, stroke, and central nervous system (CNS) infection, as well as critical illness conferring risk of brain dysfunction. We

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will highlight current research describing innovative approaches, including multimodal monitoring, computed physiologic indices, and noninvasive techniques.

Intracranial pressure and cerebral perfusion pressure monitoring

Elevated ICP is a life-threatening consequence of many acute neurological illnesses. In severe TBI (GCS score ≤8), elevated ICP leads to secondary neurologic injury.[36] Because the neurological examination is often limited, ICP and cerebral perfusion pressure (CPP, the difference between mean arterial pressure and ICP) represent targets to guide treatment. Current guidelines for pediatric severe TBI emphasize maintaining ICP <20 mmHg and CPP above age-based targets.[36,37] In a single-center observational study of children with ICP monitors placed for a variety of conditions (TBI, brain tumor with hydrocephalus, headache and craniosynostosis, spontaneous intracranial hemorrhage, shunt malfunction or infection), mean ICP, age-based mean CPP, and diagnosis were predictive of in-hospital mortality.[38] Notably, the cutoff ICP value predictive of survival to hospital discharge was lower in non-TBI patients (15 mmHg) than for patients with TBI (18 mmHg). In all patients, mean CPP less than 67 mmHg was independently predictive of mortality, with threshold CPP values increasing with age. In patients with TBI, mean CPP values predictive of in-hospital mortality exceeded age-based targets in current TBI guidelines (less than two years, 45 mmHg; two to less than eight years, 57 mmHg; eight years or greater, 68 mmHg). A more thorough understanding of subtle differences in pathophysiology between patients could lead to improved precision in physiologic targets (e.g., CPP); this may facilitate utilizing neurological monitoring modalities and designing interventions to address individual needs and potentially optimize outcomes.

ICP can be elevated following cardiac arrest or anoxic brain injury. However, ICP monitors are rarely placed, as post-anoxic cerebral edema is understood to be a consequence rather than a cause of neuronal death.[39] In two small pediatric studies of anoxic brain injury from drowning, elevated ICP predicted mortality, but not neurologic outcome in survivors.[40,41] A study of adults with ICP measured via lumbar puncture before undergoing therapeutic hypothermia postcardiac arrest did show a correlation between ICP and neurologic outcome at six months.[42] Neither has any pediatric study identified consistent ICP thresholds associated with neurologic outcome nor has ICP-directed therapy been shown to improve outcome postcardiac arrest.[43] The absence of a meaningful ICP target to guide neuroprotective therapy has informed the development of noninvasive modalities, discussed later in this review.

Ischemic stroke management in children is informed by consensus guidelines[44] and includes frequent neurologic examination to monitor for complications such as seizure and neurologic deterioration, which may signify worsening cerebral edema or hemorrhagic transformation. Severe ischemic and hemorrhagic stroke can be complicated by intracranial hypertension, necessitating ICP monitor placement and consideration of hemicraniectomy.[44]

Children with CNS infections are at risk for poor outcome, often related to increased ICP.[8,9] Bacterial meningitis can lead to cerebral edema, microthrombi, cerebritis, abscesses, infarction, and obstructive hydrocephalus.[10] In viral meningitis, cerebral edema can lead to elevated ICP.[8] ICP monitors are sometimes used to guide therapy in children with meningitis or encephalitis and a GCS score < 8.[45] A small randomized trial compared ICP-directed versus CPP-directed therapy in children with meningitis, finding that the latter led to higher GCS and improved outcomes at 90 days.[46] Future studies may identify ICP and CPP thresholds warranting intervention, guiding therapy and prognostication in children with CNS infections.

$P_{BT}O_2$

Because the brain requires constant oxygen delivery to prevent secondary injury, treatment protocols have incorporated brain tissue partial pressure of oxygen ($P_{BT}O_2$) measurement for a variety of conditions, with the majority of published data derived from studies of severe TBI. $P_{BT}O_2$ is measured by an intracranial sensor either placed near the site of injury or on the less injured hemisphere to reflect global oxygenation. Independent of ICP and CPP, brain tissue hypoxia develops in widespread areas of the brain after TBI, often far from the primary injury site.[47] When $P_{BT}O_2$ is low, treatment addresses oxygen delivery to the brain by supporting systemic oxygenation and raising CPP.[36] $P_{BT}O_2$ monitoring is associated with decreased mortality and favorable outcomes in adult patients, and a clinical trial is underway to assess the effectiveness of $P_{BT}O_2$-targeted therapy.[4] In pediatric TBI, $P_{BT}O_2$ inversely correlates with ICP,[5] and prolonged brain tissue hypoxia ($P_{BT}O_2$ < 5 mmHg for more than one hour) is associated with poor outcome.[6] Although $P_{BT}O_2$ monitoring is not explicitly recommended, current TBI guidelines recommend maintaining $P_{BT}O_2$ > 10 mmHg.[36,37] Interestingly, $P_{BT}O_2$ thresholds higher (>30 mmHg) than those used in adults may be associated with favorable outcome in children[48]; this may reflect the relationship between cerebral perfusion and oxygenation, as cerebral blood flow (CBF) decreases from childhood to adulthood.[49] If $P_{BT}O_2$-guided therapy leads to improved functional outcome in adults, delineating optimal application of this technique in pediatric TBI will be crucial. It will be important to consider the correct intervention (e.g., augmenting systemic oxygen delivery versus CPP) when ICP is normal but $P_{BT}O_2$ is low.

Following stroke, cerebral ischemia due to reduced blood flow and secondary hypoxia leads to neuronal death in regions of low blood flow. Two small case series present examples of concurrent $P_{BT}O_2$ and ICP monitoring after carotid dissection, intraparenchymal hemorrhage, and venous sinus thrombosis.[50] Remarkably, two patients had decreased ICP and increased $P_{BT}O_2$ following mechanical thrombectomy.[51] In select populations of children with meningitis or encephalitis, $P_{BT}O_2$ monitoring may be useful. A report of two patients highlighted use of $P_{BT}O_2$ monitors in tuberculosis meningitis.[52] These highly preliminary reports highlight novel potential applications of $P_{BT}O_2$ monitoring. To evaluate the role of this technique beyond TBI, subsequent studies should define indications for monitor placement and pediatric-specific thresholds for intervention.

Near-infrared spectroscopy (NIRS)

Numerous noninvasive modalities have been incorporated into the practice of neuromonitoring. Although diverse in technological basis and application, these tools rely on similar physiologic principles to provide additional insight. Near-infrared spectroscopy (NIRS) is a noninvasive real-time technology used to measure cerebral oxygenation. Using similar principles to pulse oximetry, NIRS devices emit near-infrared light, which changes wavelength upon contact with oxygenated hemoglobin, and is reflected back to a detector.[53] This technology has the potential to identify intracranial hematoma formation by detecting intravascular versus extravascular blood. NIRS has a high sensitivity but variable specificity in hematoma detection in adult patients with TBI.[54,55] A small prospective case-control study demonstrated that NIRS had a sensitivity of 100% and specificity of 80% in detecting intracranial hemorrhage in pediatric TBI.[56] Given limited subsequent larger studies confirming these findings, and perhaps due to the comparative inability of NIRS to identify lesions, computed tomography remains the gold standard. Nevertheless, these studies

TABLE.
Neurologic Monitoring Modalities

Modality	Technique	Advantages	Limitations	Indications & Evidence
Invasive				
$P_{BT}O_2$[4-6,7]	Surgically-placed oxygen-sensing electrochemical or fluorescent probe monitors ***regional cerebral oxygen tension***	Detects brain tissue hypoxia, a therapeutic target not available with ICP monitoring alone	Additional invasive monitor, brain-region-specific	*TBI, SAH* • Lower $P_{BT}O_2$ independently associated with outcome • Multimodal strategy using ICP and $P_{BT}O_2$ is safe and might reduce mortality in adult TBI
PRx[8-10,5,11-13]	Continuous slow-wave ABP, ICP correlated over time to quantify ***cerebral autoregulation***. PRx <0 indicates intact pressure reactivity; PRx >0 indicates impaired pressure reactivity	• No additional invasive probe (uses existing ICP monitor) • May detect derangement when ICP not pathologically elevated • Personalized target: "optimal CPP" (CPP at which PRx is minimal) • Potential prognostic value	• Assumes constant cerebral metabolic demand • Global, not reflective of regional differences	*TBI, stroke, intracranial hemorrhage* • Time burden of impaired PRx associated with adverse outcome in pediatric severe TBI
Intracranial Compliance Indices (RAP, PCI)[14-19]	Calculated indices to evaluate **intracranial compliance**. • PCI: correlation between ICP, $ETCO_2$ • RAP: correlation between mean ICP, pulse amplitude of ICP waveform	• No additional invasive probe (uses existing ICP monitor) • May detect derangement when ICP not pathologically elevated • May inform proactive rather than reactive strategy	• Indices do not account for other possible contributions to ICP fluctuations • Require additional validation	*TBI, SAH, hydrocephalus* • Feasibility of measurement established
Noninvasive				
NIRS[20-23]	**RSO_2** measured by detecting changes in oxyhemoglobin and deoxyhemoglobin in the brain tissue	• Widely used in pediatric, neonatal, and cardiac critical care	• Unclear role in acute brain injury • Current devices have limited spatial resolution	*TBI, hydrocephalus* • Improved RSO_2 following CSF diversion • Investigation underway to noninvasively infer ICP, autoregulation
TCD[24,25]	Measures cerebral blood flow velocity in cerebral arteries to estimate and **cerebral autoregulation.** PI reflects vascular resistance, possibly indicative of **ICP**	• "Gold standard" for noninvasive cerebral autoregulation assessment	• Technique- and operator-dependent	*TBI, DKA, ECMO monitoring, screening for stroke risk in sickle cell disease* • PI 100% sensitive, 83% specific for ICP >20 mmHg in pediatric severe TBI
QEEG[22,26-30]	Fourier analysis of EEG waveforms quantifies power by waveform frequency to infer **brain injury severity**	• Continuous, real-time • Objective • Novel application of established clinical tool • Prognostic value	• Requires validation in larger pediatric studies	*TBI, ECMO monitoring, postcardiac arrest, HIE, ischemic stroke* • High specificity and sensitivity in predicting neurologic outcomes after cardiac arrest • May allow regional identification of stroke, targeted physiologic management of penumbra
ONSD[29,31]	Ultrasound measurement of optic nerve sheath widening to detect **increased ICP**	• Noninvasive • Rapid point-of-care assessment	• Technique- and operator-dependent	*TBI, DKA* • Correlation between ONSD and increases in ICP • May predict cerebral edema in DKA

Pupillometry[30,32-34]	Handheld device measures **pupil, diameter, reactivity**, composite score (NPi). Can detect **increased ICP**	• Noninvasive, portable device • Rapid, simple, point-of-care assessment • Quantitative, objective • Assess trends over time	• Limited by periorbital edema, ocular injury, movement • Requires additional validation in pediatrics	*TBI* • NPi inversely correlates with ICP, improves with osmotic therapy • Constriction velocity detects ICP ≥20 in ICP-monitored children (AUROC 0.71) *Cardiac arrest* • Bilateral absence is associated with poor neurological outcome
SSEPs[35]	Noninvasive measurement of **somatosensory cortex** after tactile stimulation. Absence indicates **severe neurological injury**	• Noninvasive • Objective • Prognostic value	• May be confounded by sedation	

Abbreviations:
ABP = Arterial blood pressure
AUROC = Area under receiver-operator characteristic curve
CPP = Cerebral perfusion pressure
CSF = Cerebrospinal fluid
DKA = Diabetic ketoacidosis
ECMO = Extracorporeal membrane oxygenation
EEG = Electroencephalography
$ETCO_2$ = End-tidal carbon dioxide
HIE = Hypoxic-ischemic encephalopathy
ICP = Intracranial pressure
NIRS = Near-infrared spectroscopy
NPi = Neurologic pupil index
ONSD = Optic nerve sheath diameter
$P_{BT}O_2$ = Brain tissue partial pressure of oxygen
PCI = ICP-PCO_2 compliance index
PI = Pulsatility index
PRx = Pressure reactivity index
QEEG = Quantitative electroencephalography
RAP = Compensatory reserve index
RSO_2 = Regional cerebral oxygen saturation
SAH = Subarachnoid hemorrhage
SSEP = Somatosensory evoked potentials
TBI = Traumatic brain injury
TCD = Transcranial Doppler

demonstrate a potential use of NIRS for screening, especially in settings where computed tomography is not rapidly available or patient transport for neuroimaging is high risk.[57]

Because cerebral NIRS noninvasively assesses the cortical microvasculature, it may offer improved neurologic evaluation following cardiac arrest. In a small pediatric study, cerebral NIRS was used to guide blood pressure management to optimize cerebral oxygenation using the hemoglobin volume index (HVx). This index estimates cerebral autoregulation as the correlation between arterial blood pressure and NIRS-measured relative tissue hemoglobin (a surrogate marker of cerebral blood volume). Greater deviation from HVx-based targets correlated with poor outcome.[58]

There exists no broad consensus regarding the role of NIRS after cardiac arrest, and association with outcome remains unclear.[59] Shortcomings in spatial resolution and brain tissue specificity of clinical NIRS devices partially explain these limitations. Advanced NIRS devices are an area of active development and may eventually facilitate innovative uses including improved noninvasive assessment of cerebral autoregulation[14] and real-time monitoring of CBF during cardiopulmonary resuscitation.[15]

Cerebral autoregulation may be impaired in patients at risk for cerebral ischemia due to moyamoya disease, and NIRS-based estimates of autoregulation may help determine patient-specific hemodynamic goals. In a small study of children who underwent surgical revascularization for moyamoya disease, optimal blood pressure was determined using the HVx and cerebral oximetry index. In patients with unilateral disease, HVx values were higher (indicating impaired autoregulation) on the side with vasculopathy.[16]

NIRS may also provide prognostic information in patients supported with extracorporeal membrane oxygenation (ECMO). Although ECMO survival has greatly improved in children, neurologic complications are seen in up to 35% of patients.[26] Depth and duration of low NIRS-measured cerebral oximetry values may be associated with increased mortality.[60] Unfortunately, manipulating ECMO flow rates does not necessarily improve cerebral oxygenation.[61] Recently, NIRS was used to characterize cerebral autoregulation in pediatric patients on ECMO support. In this small prospective study, ischemic injury was associated with impaired cerebral autoregulation, suggesting impaired cerebral perfusion with blood pressure below the lower limit of autoregulation. Such patients could conceivably benefit from higher blood pressure targets, although validation of these findings in larger study is warranted.[26] These studies suggest that NIRS shows promise as a neurologic monitoring tool but requires thoughtful delineation of optimal use in selecting targeted interventions.

Transcranial Doppler (TCD)

First introduced for the detection of vasospasm following subarachnoid hemorrhage,[62] transcranial Doppler (TCD) has been applied in other forms of acute neurologic illness. Adult stroke management employs TCD to identify proximal arterial stenosis to guide treatment and detect middle cerebral artery recanalization after thrombolysis.[63] In children, TCD is the gold standard for the prediction of first stroke in children with sickle cell disease.[64] TCD is routinely used in adult aneurysmal subarachnoid hemorrhage[65] to detect vasospasm[66] and direct therapy, although this practice varies widely among pediatric centers.[24]

The ability to detect subtle derangements in CBF may translate to future use in critically ill patients at risk of cerebrovascular derangement. Abnormal TCD measurements may detect elevated ICP following TBI. In a small pediatric study, the middle cerebral artery pulsatility index (the difference between the peak-systolic and end-diastolic flow velocity divided by the mean flow velocity) on postinjury day 1 had 100% sensitivity and 82% specificity in predicting ICP >20 mmHg; this suggests that TCD might detect early intracranial hypertension, possibly useful in informing the decisions to place invasive ICP monitors.[25] Although promising, TCD is resource intensive and operator dependent, thus limiting application. In a recent survey of pediatric neurocritical care centers, 10 of 27 reported TCD use in patients with TBI. Data from TCD were used to inform decisions to obtain imaging, modify CPP goals, and perform surgical intervention.[24]

TCD may provide useful prognostic information after cardiac arrest. In a small retrospective cohort of children who underwent therapeutic hypothermia after cardiac arrest, TCD measurements were obtained. Diastolic reversal or undetectable flow through the middle cerebral artery were associated poor prognosis, whereas normal mean flow velocity and normal pulsatility index were associated with favorable outcome.[67] In a retrospective cohort study of children after cardiac arrest, drowning, and asphyxia, TCD-measured blood flow velocities on days 1 and 2 were more severely elevated in those who had unfavorable outcomes.[68]

TCD may also have prognostic utility in children with CNS infections. In children with bacterial meningitis, abnormalities of flow and pulsatility index are predictive of poor outcome.[69] In children with cerebral malaria, TCD may help distinguish vasospasm, associated with survival, from low-flow states associated with mortality.[70]

Children with diabetic ketoacidosis are at risk of mortality related to cerebral edema,[71-73] with associated detectable alterations in CBF. Innovative application of neurologic monitoring modalities might facilitate earlier detection of cerebral edema, and therefore quicker intervention. In studies combining TCD and NIRS, children with altered mental status due to diabetic ketoacidosis have increased cerebral blood volume and cerebral oxygenation.[74,75]

Noninvasive neurologic monitoring in patients receiving ECMO support is an area of active inquiry. TCD flow velocities may facilitate detection of acute neurologic sequelae. Two studies[76,77] have observed lower flow velocities in children on ECMO than age-matched controls, even in the absence of detectable neurologic injury. Abnormal TCD findings may also lead to early detection of hemorrhagic complications of ECMO,[27] with elevated flow velocities two to six days before clinical recognition of cerebral hemorrhage. Application of TCD to detect subtle derangements in CBF could lead to targeted intervention (i.e., manipulation of arterial blood pressure and ECMO flow) and improved recognition and management of neurological complications of ECMO.

Neurologic dysfunction occurs in one of five children with sepsis[78,79] and is associated with a fivefold increased risk of mortality in children with sepsis.[80,81] TCD may identify those at increased risk of brain injury who may benefit from targeted intervention. A prospective observational study found that elevated pulsatility index was associated with sepsis-associated encephalopathy and mortality in children.[82] This novel application of TCD could lead to earlier recognition of patients at risk of severe neurologic complications, potentially leading to more prompt and effective intervention.

These studies highlight growing use of TCD beyond its established role as a screening test that allows for primary stroke prevention in sickle cell disease. Innovative applications require large-scale validation to inform optimal, standardized use.

Electroencephalography

Electroencephalography (EEG) is a mainstay of neuromonitoring in critical care. Seizures are common after moderate and severe TBI, detected in up to one-third of EEG-monitored children, 40% of whom have only nonmotor, electrographic seizures.[83] One in five

critically ill children with TBI will develop posttraumatic symptomatic epilepsy, which can lead to long-term cognitive dysfunction.[84] Seizures represent disrupted balance between neuronal metabolic demands and blood flow (neurovascular coupling), associated with metabolic crisis in brain tissue,[85] potentially leading to increased secondary brain injury. Current TBI guidelines emphasize seizure prophylaxis with phenytoin or levetiracetam for seven days.[36] EEG is useful in monitoring burst suppression during barbiturate therapy for refractory intracranial hypertension.

Intracranial EEG has also been used in a small number of pediatric patients with severe TBI requiring other invasive neuromonitoring.[86] If further validated, this technique could improve the detection of secondary neurologic insults.

Quantitative EEG (QEEG) refers to a variety of computationally derived electrographic features obtained from EEG, including quantification of waveform frequencies using Fourier and wavelet analysis, peak-envelope calculation, and amplitude-integrated EEG, as well as suppression ratio determination. In adult TBI, QEEG has shown utility in prognostication. Vespa et al. found reduced alpha variability to be predictive of poor outcome or death (75% specificity and sensitivity for poor outcome during the initial three days of monitoring).[87,88]

Given the limitations of clinical examination, EEG has been used as an adjunct for monitoring and prognostication after cardiac arrest. Electrographic seizures occur in nearly half of children following cardiac arrest[89] and are associated with worse outcomes.[90] Emerging evidence also supports the use of EEG in prognostication.[91] Normal EEG background activity is associated with favorable neurologic outcomes.[92,93] Abnormal findings such as burst suppression are associated with worse outcome.[94] Models incorporating multiple EEG features have been predictive of outcome in children after cardiac arrest.[28,92,95] Emerging use of QEEG may enrich objective neuromonitoring and outcome prediction. In a prospective observational study of 87 children after cardiac arrest, a model incorporating QEEG features was highly predictive of outcome after cardiac arrest with an area under receiver-operator characteristic curve of 0.88.[96] Asymmetric QEEG findings may also precede clinically apparent severe neurologic decompensation, as illustrated in a recent case series.[97] Amplitude-integrated EEG uses a semilogarithmic display of peak-to-peak amplitude and is used in neonatal hypoxic-ischemic encephalopathy.[98] Recently, amplitude-integrated EEG was used to detect seizures and predict outcome following pediatric cardiac arrest.[99,100] A model incorporating amplitude-integrated EEG was highly predictive of neurologic outcome in a small prospective study of children with nontraumatic disturbance of consciousness.[101] This technique may be especially useful in resource-limited settings where standard continuous EEG is infeasible.

Seizures occur in one in five children with acute stroke. Thus, EEG is routinely performed in children with stroke and seizure or altered mental status. QEEG may provide added utility. In a recent study in 11 children with ischemic or hemorrhagic anterior circulation stroke, characteristic QEEG patterns were seen in injured versus uninjured brain regions. In those with hemorrhagic stroke, spectral power varied with arterial blood pressure. If validated in larger studies, these interesting preliminary observations could lead to improved physiologic monitoring of the stroke penumbra.[102]

Because seizures are associated with increased mortality, current guidelines recommend EEG monitoring patients receiving ECMO support,[103] as well as patients requiring pharmacologic neuromuscular blockade while at risk of seizures.[104] In two single-center retrospective studies, roughly half of pediatric patients on ECMO were monitored with EEG. About 16% to 22% had electrographic seizures, with observed associations with intracranial hemorrhage and death.[105,106] Critically ill patients with encephalitis are also at an increased risk of seizures and often require continuous EEG monitoring.[107]

Optic nerve sheath diameter (ONSD)

Elevated ICP is transmitted to the optic nerve sheath and can be assessed noninvasively. Ultrasound-measured optic nerve sheath diameter (ONSD) represents a promising noninvasive tool, potentially useful for screening and monitoring patients following TBI. In a small pediatric TBI study ONSD greater than 4 mm was 98% sensitive and 75% specific in detecting raised ICP.[108] In addition, Young et al. found significant correlation between mean and maximum ONSD with ICP, with findings suggesting that ONSD over 6.1 mm are associated with need for invasive monitoring.[109] These promising preliminary studies should be interpreted with caution. ONSD may represent a tool to identify elevated ICP, but changes over time do not clearly correlate with changes in ICP.[110]

The rarity of invasive ICP monitoring following cardiac arrest has led to innovation in noninvasive monitoring. A recent prospective study found that TCD and ONSD measurements predicted elevations in invasively monitored ICP in 18 adults after hypoxic-ischemic brain injury.[111] In a retrospective study of 37 adults with ICP monitoring via a lumbar catheter after cardiac arrest, ONSD correlated well with ICP. Consistent with earlier studies of ICP in similar patients, neither ICP nor ONSD predicted neurologic outcome.[112] These findings suggest that ONSD measurement may detect severe disease when neurologic examination is confounded during postcardiac arrest management. Further validation of ONSD in children may lead to more accurate prognostication following cardiac arrest, without invasive monitoring.

ONSD may be useful to noninvasively detect cerebral edema in diabetic ketoacidosis. ONSD was recently evaluated serially in 31 children with diabetic ketoacidosis. During treatment, ONSD was observed to increase, peaking at hours 12 to 16, with the highest values observed in children with greater disease severity.[113] If these findings are replicated, ONSD measurement could enhance clinical examination to identify patients in need of treatment of cerebral edema. In general, broad application of ONSD in pediatric critical care would require normative values and efforts to ensure inter-observer reliability.

Pupillometry

Pupillary size, symmetry, and reactivity are monitored closely, because acute changes can indicate brainstem injury and herniation. To supplement subjective assessment, pupillometers provide objective, reproducible measurements. One such device combines pupillary size and reactivity into the neurologic pupil index (NPi). In adult TBI, decreased NPi is associated with increased ICP.[114] NPi has also been shown to have potential prognostic value, with depressed readings associated with unfavorable 6-month outcomes.[114] NPi has been studied as a triage tool to predict the need for intervention in adults.[115] In a prospective study of ICP-monitored children, NPi readings predicted ICP greater than 20 mmHg.[32] Use of the NPi in pediatric critical care may be limited, as its proprietary computation algorithm has only been extensively validated in adults. Although normative pupillometry values have been established in children,[116] care should be taken in applying this technology in pediatrics.

Somatosensory evoked potentials (SSEPs)

Somatosensory evoked potentials (SSEPs) noninvasively measure electrical activity over the somatosensory cortex after tactile stimulation. The N20 wave is measured after median nerve

stimulation. In adults, bilaterally absent N20 waves at 24 and 72 hours predict poor outcome and may be less confounded by sedative drugs.[31,43] McDevitt et al. recently performed a small prospective cohort study evaluating SSEPs in children postarrest. Bilaterally absent N20 waves predicted poor neurological outcome with 88% specificity. All five patients with intact SSEPs had a good neurological outcome.[35] Notably, one patient with unfavorable SSEPs had a good outcome. Given the small preliminary nature of this study and imperfect interrater reliability,[117] SSEPs should be interpreted with caution, especially in young children. Larger pediatric studies are needed to evaluate this technique in children.

Computed indices using ICP

Innovative bedside tools enrich the utility of ICP monitoring and may personalize the approach to managing intracranial pathophysiology. Computed indices of intracranial physiology leverage data already monitored for patient care. Although no single approach has been widely accepted, most rely on principles of intracranial compliance, cerebrovascular autoregulation, and brain oxygenation. Intracranial compliance is the ratio of changes in intracranial volume to ICP. When compliance is low, increasing volume (i.e., hematoma, cerebral edema) results in increased ICP. Cerebral autoregulation refers to changes in vascular tone to maintain CBF with varying CPP. In severe injury, autoregulation may be impaired, and CBF can become “pressure-passive,” varying linearly with blood pressure.

Pressure reactivity index (PRx)

The pressure reactivity index (PRx) estimates cerebral autoregulation as the correlation over time between ICP and arterial blood pressure. If the PRx is high, autoregulation is said to be impaired. In children with severe TBI, higher PRx is associated with mortality and lower CPP.[118] A U-shaped relationship has been observed between PRx and CPP, such that PRx is minimal within a range of CPP values, termed “optimal CPP.” In two small prospective observational studies, pediatric TBI survivors' CPP fell within this optimal range for a higher proportion of time than for those who died.[119,120] If these findings are corroborated in larger studies, PRx-derived optimal CPP ranges versus age-based goals might offer high precision in predicting outcomes and guiding management strategies in TBI.

Knowledge of cerebral autoregulation may aid in management of children after stroke. A recent study of children with ICP monitors placed after hemorrhagic stroke due to arteriovenous malformation rupture found an association between abnormal PRx and poor outcome. Notably, increased time with CPP below the PRx-derived optimal range was associated with poor outcome. These preliminary findings suggest a possible future role of the PRx in personalizing physiologic targets.[11] Because the PRx assumes constant cerebral metabolic rate, it may not distinguish physiologic increases in CBF due to metabolic demand from pathologic increases due to impaired autoregulation.[12] The PRx calculation also requires prolonged monitoring epochs and specialized software. Despite these limitations, the PRx might aid in personalizing CPP goals. Additional validation, determination of appropriate targets, and analysis of clinical impact of PRx-guided therapy on outcome are warranted.

Estimates of intracranial compliance

Historically, attempts to estimate intracranial compliance required injection of fluid into the ventricles, or insertion of a separate intracranial monitor.[13,121] Recently, computed indices have utilized available data to generate similar insight. The cerebrospinal compensatory reserve index (RAP) estimates intracranial compliance as the correlation (R) between ICP pulse amplitude (A) and mean ICP (P). The RAP correlates with ICP in adult TBI and can track changes in compliance during treatment of refractory ICP elevations in pediatric TBI.[122-124] The ICP-PCO_2 compliance index (PCI) estimates compliance using the principle of CO_2 reactivity. Because cerebral blood volume varies exponentially with CO_2-induced vasodilatation, the correlation between end-tidal CO_2 and ICP may inversely reflect intracranial compliance. In a small cohort of pediatric patients with TBI, the PCI increased over the first 12 hours after admission and remained elevated, whereas ICP remained below the treatment threshold. The PCI may detect more subtle decreases in intracranial compliance than ICP monitoring alone.[125] These findings should be interpreted with caution, as the PCI has only been described in a single study in which a majority of patients underwent surgical decompression. Like the PRx, the PCI and RAP rely on running correlations and require time to generate potentially meaningful data. Validation efforts may identify trends or threshold values warranting intervention.

Taken together, computed indices might inform a proactive rather than reactive approach to detecting and treating physiologic derangement. The ideal tool would provide an accurate, real-time assessment of intracranial pathology, perhaps to the point of predicting elevated ICP to facilitate prevention.

Conclusion

Many children with acute neurologic pathology warrant intensive monitoring using a multimodal approach. Critically ill children are at risk of developing neurologic sequelae. Consideration of the underlying pathophysiology, local monitoring capabilities, and national guidelines compared with emerging evidence are important. Monitoring techniques informed by principles of CBF, oxygenation, autoregulation, and intracranial compliance may lead to personalized care and improved outcomes. Efforts are underway to further validate these modalities, with the goal of refining strategies for multimodal physiologic monitoring. Established guidelines for neuromonitoring exist in pediatric TBI, whereas advanced monitoring in other neurological conditions varies by institution. As innovative monitoring methods are further investigated in the pediatric population, they may become incorporated into more widely accepted standardized approaches.

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