

New Concepts in Treatment of Pediatric Traumatic Brain Injury

Jimmy W. Huh, MD^{a,*}, Ramesh Raghupathi, PhD^b

KEYWORDS

- Traumatic brain injury • Pediatric • Child • Guidelines
- Treatment • Anesthetics

Since the publication in 2003 of the first version of the guidelines for the medical management of severe traumatic brain injury (TBI) in infants, children, and adolescents,¹ there has been increasing clinical and basic science research to better understand the pathophysiologic responses associated with pediatric TBI. Evidence is beginning to accumulate that the traumatized pediatric brain may have unique responses that are distinct from the traumatized adult brain. Even within the immature brain, there seem to be age-dependent responses following trauma. As anesthesiologists play an important role in resuscitating infants and children with severe TBI in the emergency room and operating room, it is integral that they understand the injury patterns, pathophysiology, recent advances in diagnostic modalities, and different therapeutic options. In this article a review of the recent studies relevant to these important issues in pediatric TBI is presented. Areas for future investigation, such as neuromonitoring and the effects of anesthetics on the developing brain, are also discussed.

INJURY PATTERNS

Age-dependent injury patterns occur following pediatric TBI.² In infants and young children, inflicted or nonaccidental TBI is a major cause of brain injury and often is associated with repetitive injury.^{3,4} Accidental TBIs in this age group are mainly due

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^a Critical Care and Pediatrics, Department of Anesthesiology and Critical Care Medicine, Children's Hospital of Philadelphia, University of Pennsylvania School of Medicine, Critical Care Office, 7 South Tower, Room 7C26, 34th Street & Civic Center Boulevard, Philadelphia, PA 19104-4399, USA

^b Department of Neurobiology and Anatomy, Drexel University College of Medicine, 2900 Queen Lane, Philadelphia, PA 19129, USA

* Corresponding author.

E-mail address: huh@email.chop.edu (J. W. Huh).

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to motor vehicle accidents and falls. By toddler age, falls are the predominant injury mechanism, but abuse must also be considered if the history is not consistent with the injury pattern. Among motor vehicle-related injuries in toddlers, pedestrian versus vehicle crashes are more common than motor vehicle occupant injuries.^{5,6} In school-aged children, falls requiring hospitalization decrease with age, whereas there is an increase in injuries associated with bicycle crashes. In adolescents, there is a dramatic increase in TBI due to motor vehicle accidents and sports-related repetitive injury, with violence being an unfortunate common cause.⁷

Age-dependent pathology following pediatric TBI is also common. In infants and young children, diffuse injury, such as diffuse cerebral swelling, and subdural hematomas are more common than focal injury, such as contusions.^{8,9} Hypoxia-ischemia seems to be more common in infants and young children sustaining nonaccidental than accidental TBI.^{10,11}

PATHOPHYSIOLOGY: IMMEDIATE (PRIMARY) AND DELAYED (SECONDARY) INJURY

Immediate or primary brain injury results from the initial forces generated following trauma. Focal injuries such as contusions and hematomas are generated by contact, linear forces when the head is struck by a moving object. Inertial, angular forces produced by acceleration-deceleration can lead to immediate physical shearing or tearing of axons termed “primary” axotomy. Following primary brain injury, two forms of secondary brain injury can occur. The first form of secondary brain injury, such as hypoxemia, hypotension, intracranial hypertension, hypercarbia, hyper- or hypoglycemia, electrolyte abnormalities, enlarging hematomas, coagulopathy, seizures, and hyperthermia are potentially avoidable or treatable.¹ The primary goal in the acute management of the severely head-injured pediatric patient is to prevent or ameliorate these factors that promote secondary brain injury.

The other form of secondary brain injury involves an endogenous cascade of cellular and biochemical events in the brain that occurs within minutes and continues for months after the primary brain injury, leading to ongoing or “secondary” traumatic axonal injury (TAI) and neuronal cell damage (delayed brain injury), and ultimately, neuronal cell death.¹² Intense research continues in the ultimate hope of discovering novel therapies to halt the progression or to inhibit these mechanisms for which there is no current therapy. Some of these important mechanisms associated with secondary brain injury are discussed later in this article. For a more detailed review of these and other mechanisms associated with secondary brain injury the reader is referred to an excellent article by Kochanek and colleagues.¹³

NECROSIS AND APOPTOSIS

Following head trauma, the release of excessive amounts of the excitatory amino acid glutamate, termed “excitotoxicity,” is believed to occur, which can lead to neuronal injury in two phases. The first phase is characterized by sodium-dependent neuronal swelling, followed by delayed, calcium-dependent neuronal degeneration.¹⁴ These effects are mediated through ionophore-linked receptors such as *N*-methyl-D-aspartate (NMDA), kainite, and α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) (glutamate receptors), and metabotropic receptors, which are receptors linked to second-messenger systems. Activation of these receptors allows calcium influx through receptor-gated or voltage-gated channels, or through the release of intracellular calcium stores. This increase in intracellular calcium is then associated with activation of proteases, lipases, and endonucleases, that can lead to neuronal degeneration and necrotic cell death. Consistent with excitotoxic-mediated neuronal

cell death, recent research has shown that calcium-activated proteases, calpains, may participate in neuronal cell loss in the injured cortex following TBI in the immature rat.¹⁵ In addition, experimental pediatric TBI has been shown to alter NMDA receptor subunit composition.¹⁶

In contrast to necrotic cell death that is marked by neuronal cell swelling, apoptotic cell death is marked by DNA fragmentation and the formation of apoptotic cell bodies associated with neuronal cell shrinkage. Apoptosis requires a cascade of intracellular events for completion of “programmed cell death,” and is initiated by intracellular or extracellular signals. Intracellular signals are initiated in the mitochondria as a result of depletion of ATP (dATP), oxidative stress, or calcium flux.¹⁷ Mitochondrial dysfunction leads to cytochrome *c* release in the cytosol, which in the presence of apoptotic-protease activating factor (APAF-1) and dATP activates the initiator protease caspase-9.¹⁸ Caspase-9 then activates the effector protease caspase-3, which ultimately causes apoptosis.¹⁹ Extracellular signaling occurs by way of the tumor necrosis factor (TNF) superfamily of cell surface death receptors, which include TNFR-1 and Fas/Apo1/CD95.²⁰ Receptor ligand binding of TNFR-1-TNF- α or Fas-Fas L promotes “death domains” which activate caspase-8, ultimately leading to caspase-3 activation and apoptotic cell death.²¹ Because differentiating necrotic versus apoptotic cell death is sometimes difficult in TBI, cells that die can be characterized as a morphologic continuum ranging from necrosis to apoptosis.²²

There seems to be an age-dependent response in relation to excitotoxicity and apoptosis. Animal studies have shown that the developing neuron is more susceptible to excitotoxic injury than the mature neuron, probably because more calcium is transmitted through the NMDA-mediated calcium channel in the immature brain.²³ However, following TBI, calcium accumulation in the injured brain was more extensive and appeared for a longer duration in the mature animal than in the immature animal.²⁴ This difference may have been because the immature animals were less severely injured as no neuronal cell death was observed, whereas delayed cell death was present in the traumatized mature animals. This result suggests that in addition to age, injury severity may play an important role in the extent of excitotoxicity. Additional studies are needed to look at the effects of injury severity in the developing brain. Other animal studies have shown that the administration of NMDA or excitotoxic antagonists following TBI in immature and mature rats decreased excitotoxic-mediated neuronal death; however, apoptotic cell death increased in immature rats.^{25,26} The increased propensity of the developing brain for posttraumatic apoptotic cell death is a key area for further research.

To date, no novel antiexcitotoxic agents have been shown to be successful in clinical trials of TBI. However, this failure may be due to many causes including incorrect dosing, delayed treatment, and failure to administer injury-specific and mechanism-specific treatments. Many investigators believe that further research is still needed to better understand the role of excitotoxicity and apoptosis following TBI at different developmental stages of the brain.

CEREBRAL SWELLING

Diffuse cerebral swelling following pediatric TBI is an important contributor to intracranial hypertension, which can result in ischemia and herniation. Some studies suggest that diffuse cerebral swelling is more common in children than in adults.⁸ Cerebral swelling is believed to result from osmolar shifts, edema at the cellular level (cytotoxic or cellular edema), and blood-brain barrier breakdown (vasogenic edema). Furthermore, cerebral swelling is believed to be worsened with hypoxia and hypoperfusion.

Osmolar shifts occur primarily in areas of necrosis whereby osmolar load increases with the degradation of neurons. As reperfusion occurs, water is drawn into the area secondary to the high osmolar load and the surrounding neurons become edematous. Cellular swelling independent of osmolar load primarily occurs in astrocyte foot processes and is believed to be brought on by excitotoxicity and uptake of glutamate. Glutamate uptake is coupled to sodium-potassium adenosine triphosphatase (AT-Pase), with sodium and water being accumulated in astrocytes.²⁷ Recent experimental data also suggest the role of endogenous water channels, called aquaporins, present in the astrocyte that may participate in brain edema.²⁸ Clinical studies suggest that cellular edema, and not hyperemia or vasogenic edema, may be the major component of cerebral swelling.^{29,30} Further studies to better understand the mechanisms associated with diffuse cerebral swelling are strongly warranted.

CEREBRAL BLOOD FLOW AND AUTOREGULATION

Early important studies in cerebral blood flow (CBF) suggested that hyperemia was the mechanism underlying secondary diffuse cerebral swelling in pediatric TBI.^{31,32} However, the values of "hyperemia" were based on referencing the head-injured children's CBF to that of normal young adults, whose CBF values are lower than that of normal children.³³ Reanalysis of the published pediatric TBI CBF studies compared with the age-dependent changes of CBF in normal children have suggested that hyperemia does not play a large role following severe pediatric TBI.³⁰ Other data suggest that posttraumatic hypoperfusion was more common and a global decreased CBF (<20 mL/100 g/min) in the initial first day following TBI in infants and children was associated with poor outcome.³⁴

Recent studies have demonstrated impaired cerebral autoregulation in infants and children following TBI. Using transcranial Doppler imaging, impaired cerebral autoregulation early after severe pediatric TBI was associated with poor outcome.³⁵ In a subsequent study, all of the children with nonaccidental TBI had impaired cerebral autoregulation in both hemispheres and poor outcome.³⁶ Furthermore, age younger than 4 years old was a risk factor for impaired autoregulation, independent of TBI severity.³⁷

Following experimental pediatric TBI, age-dependent changes in CBF have been described. Younger age was associated with more prolonged decreases in CBF and sustained hypotension compared with older animals following diffuse pediatric TBI.^{38,39} In contrast, following focal (contusive) injury, the older animals exhibited the most pronounced decrease in CBF.⁴⁰ This suggests that besides age, the pathologic type of TBI may also contribute to CBF alterations. Mechanisms that may underlie posttraumatic hypoperfusion include direct damage to cerebral blood vessels and reduced levels of vasodilators, including nitric oxide, cyclic guanosine 3',5'-monophosphate (cGMP), cyclic adenosine 3',5'-monophosphate (cAMP), and prostaglandins, which are believed to contribute to decreased CBF.⁴¹⁻⁴³ In a similar way increased levels of vasoconstrictors, such as endothelin-1, are also implicated in cerebral blood flow alterations.⁴⁴ NMDA and endogenous opioids (NOC/OFQ) recently were also found to participate in age-dependent impairment of cerebrovascular reactivity in the youngest animals following diffuse TBI.⁴⁵

TRAUMATIC AXONAL INJURY

A common pathologic condition observed in infants and young children in accidental and nonaccidental TBI is diffuse or TAI. TAI involves widespread damage to axons in the white matter of the brain, most commonly in the corpus callosum, basal ganglia,

and periventricular white matter.⁴⁶ Hypoxic-ischemic injury, calcium and ionic flux dysregulation, and mitochondrial and cytoskeletal dysfunction are believed to play important roles in axonal injury.⁴⁷ TAI is believed to be a major cause of morbidity in pediatric TBI.^{48–50} Using recent advances in MRI to detect axonal injury, such as susceptibility-weighted and diffusion tensor imaging, more extensive TAI in pediatric TBI patients was associated with worse outcomes.⁵¹

Whereas immediate or “primary” axotomy or immediate physical tearing of the axon can occur following TBI, TAI is believed to primarily occur by a delayed process called “secondary” axotomy.⁵² This suggests an extended window of opportunity for therapeutic intervention to stop this delayed and ongoing axonal degeneration, in the ultimate hope of improving outcome. Animal data suggest that the younger brain may be more vulnerable to widespread TAI with equivalent injury severity than the adult brain.⁵³ A clinically relevant animal model of pediatric TBI has recently been developed that exhibits diffuse TAI and ongoing axonal degeneration associated with chronic cognitive dysfunction.⁵⁴ Ongoing research on better understanding the mechanisms associated with TAI and chronic cognitive dysfunction in the traumatized developing brain may lead to novel therapies in the future.

EMERGENCY DEPARTMENT EVALUATION

On arrival of a head-injured pediatric patient in the emergency department (ED), information on the timing and mechanism of injury and resuscitative efforts from emergency medical personnel and witnesses at the scene are vital. The use of the “AMPLE” mnemonic (Allergies, Medications currently used, Past illnesses, Last meal, and Events/environment related to the injury) may be useful to quickly acquire the necessary information to improve understanding the pediatric patient’s current physiologic state.⁵⁵ Initial symptoms on presentation have been found to have little or no correlation with injury severity following pediatric TBI, and the anesthesiologist must rely on repeated physical examinations and vital signs.⁵⁶

Physical Examination

The anesthesiologist is an expert in quickly assessing the “ABCs” (Airway, Breathing, Circulation). He or she must also be adept at quickly assessing and reassessing the patient’s neurologic status, while simultaneously evaluating for life-threatening signs and symptoms of intracranial hypertension or impending herniation, such as altered level of consciousness, pupillary dysfunction, lateralizing extremity weakness, Cushing’s triad (hypertension, bradycardia, and irregular respirations), or other herniation syndromes (**Table 1**). The patient should have rapid assessment and reassessments of vital signs including heart rate, respiratory rate, blood pressure, pulse oximetry, and temperature. The head and spine should be examined for any external evidence of injury such as scalp lacerations and skull depressions, which warrants concern for an underlying skull fracture and severe intracranial injury. In the infant, a bulging fontanelle may be a sign of increased intracranial pressure (ICP).⁵⁷ Mastoid (“Battle’s sign”) and peri-orbital (“raccoon eyes”) bruising due to dissection of blood, hemotympanum, and clear rhinorrhea are all signs of possible basilar skull fracture.

A quick, but detailed and easily reproducible neurologic assessment should be performed and documented. Whereas the Glasgow Coma Scale (GCS) for older children and adults is the most widely used method to quantify initial neurologic assessment,⁵⁸ the Children’s Coma Scale is most often used in infants and younger children (**Table 2**).⁵⁹ With regard to TBI, a GCS score of 13 to 15 is mild, 9 to 12 is moderate, and 3 to 8 is severe. It is critical that the GCS be recorded on the initial medical record and

Table 1			
Herniation syndromes			
	Eye Findings	Gross Motor	Respiration
Uncal (lateral transtentorial)	Ipsilateral fixed pupillary dilatation and ptosis	Contralateral hemiparesis	Irregular
Diencephalic	Small midpoint pupils, but reactive to light	Decorticate posturing, hypertonia	Cheyne-Stokes (episodes of apnea and tachypnea)
Midbrain	Midpoint fixed pupils	Decerebrate posturing	Hyperventilation
Medullary	Dilated and fixed pupils	No response to pain	Irregular or gasping

reassessed regularly to detect changes in GCS over time. For example, a child suffering a head injury may arrive in the ED with an initial GCS of 14 but it then can rapidly decrease over time, secondary to an expanding epidural hematoma and impending herniation.

The pupillary examination is of paramount importance when assessing the neurologic status of the head-injured child. The size, shape, and reactivity to light provide vital insight into the balance of sympathetic and parasympathetic influences. An enlarged unreactive pupil (mydriasis) can be secondary to dysfunction or injury to the oculomotor nerve (cranial nerve III) and can be associated with disorders of oculomotor muscle and ptosis.⁵⁷ Uncal (lateral transtentorial) herniation or a lesion along the course of the oculomotor nerve may cause unilateral mydriasis and ptosis. Direct trauma to the eye may cause injury to the iris and result in mydriasis without

Table 2	
Modified children's coma scale	
Eye opening	
Spontaneous	4
To speech	3
To pain	2
None	1
Verbal	
Coos, babbles	5
Irritable	4
Cries to pain	3
Moans to pain	2
None	1
Motor	
Normal spontaneous movements	6
Withdraws to touch	5
Withdraws to pain	4
Abnormal flexion	3
Abnormal extension	2
Flaccid	1

oculomotor dysfunction. Bilateral mydriasis can be the result of ingestions (anticholinergics) or administration of atropine or adrenergic agonists such as epinephrine during resuscitation. A small pupil (miosis) is usually secondary to dysfunction of sympathetic innervation. Because the efferent sympathetic fibers travel along the carotid artery, injury to the neck or skull base must also be considered in the pediatric TBI patient.

Evaluation of eye movements and brain stem reflexes can help localize the intracranial lesion. Dysfunction of all the three cranial nerves in eye movement (oculomotor, trochlear, and abducens nerves) can be the result of injury to the ipsilateral cavernous sinus. Cough and gag reflexes detect glossopharyngeal and vagus nerve function. Abnormalities in respiratory pattern may also assist in localizing brain injury and herniation syndromes (**Table 1**). Deep tendon reflexes (DTR) are typically exaggerated in head-injured patients due to the lack of cortical inhibition. However, decreased DTR may suggest a spinal cord injury. Babinski response, characterized by extension of the great toe and abduction of the remaining toes, is an abnormal finding in children older than 6 months of age when the plantar reflex is tested.

Diagnostic Studies

The mainstay of the initial radiologic evaluation of the severely head-injured pediatric patient is CT imaging; but before transport to the CT scanner “the ABCs must always be addressed,” and appropriate monitoring must be instituted and blood samples sent. For intubated patients, continuous capnometry is vital for titrating treatment of intracranial hypertension.

A chemistry panel should be sent to assess electrolyte abnormalities and renal function, especially if hyperosmolar therapy may be instituted.⁶⁰ Liver enzymes and pancreatic function should also be evaluated for possible blunt trauma, especially if nonaccidental trauma is suspected. Complete blood count (CBC) to evaluate for anemia and especially thrombocytopenia in the presence of intracranial bleeding is imperative. Tests for coagulopathy and a type and screen should be sent. In one prospective observational study, 22% of children with severe head injury had laboratory evidence of disseminated intravascular coagulation.⁶¹ Furthermore, a normal coagulation profile and platelet count on presentation does not rule out the possibility of coagulopathy or thrombocytopenia developing over time.⁶² In the adolescent population, a toxicology screen should also be considered.

Cervical spine films should be obtained, as well as chest radiographs for intubated patients to evaluate for right main stem intubations or pneumothorax. Other radiographs should be performed based on the results of the secondary survey. If there is no clear history or mechanism of accidental trauma, especially in infants and young children, further investigation for other occult injuries such as abdominal injuries, skeletal injuries, and retinal hemorrhages (which are commonly associated with nonaccidental TBI or shaken-baby or shaken-impact syndrome) should be sought.³ However, this workup should not take precedence over life-threatening issues such as hypoxemia, hypotension, and intracranial hypertension.

CT scan is the imaging modality of choice and can rapidly detect intracranial hematoma, intraparenchymal contusion, skull fracture, and cerebral edema, as well as transependymal flow and obliteration of the basal cisterns, which are concerns for elevated ICP. Certain findings on early CT scan have been associated with outcome.^{63,64} The basal cisterns are evaluated at the level of the mid brain; compressed or absent cisterns increase the risk of intracranial hypertension and are associated with poor outcome.⁶⁵ The presence of midline shift at the foramen of Monroe is also inversely related to prognosis.^{63,65} The presence of traumatic subarachnoid hemorrhage increases mortality and its presence in the basal cisterns is also

a predictor of poor outcome.^{63,65} MRI, especially susceptibility-weighted and diffusion tensor imaging, has demonstrated superiority on detecting traumatic axonal injury and its correlation with long-term outcome.^{51,66} Due to the length of time required for image acquisition and limited physiologic monitoring in the MRI suite, this imaging modality is of limited value in the initial evaluation of the critically ill pediatric TBI patient. However, an ongoing study is evaluating a quick-brain MRI to enhance image quality in areas such as the posterior fossa without the potential risk of radiation associated with CT.⁶⁷

THERAPEUTIC OPTIONS: THE "INITIAL GOLDEN MINUTES" OF PEDIATRIC TRAUMATIC BRAIN INJURY

Airway, Breathing, and Circulation

Hypoxemia and hypotension are to be avoided or treated to prevent or minimize secondary brain injury from hypoxic-ischemic brain damage, which may promote diffuse cerebral swelling and intracranial hypertension. Criteria for tracheal intubation include hypoxemia not resolved with supplemental oxygen, apnea, hypercarbia ($\text{PaCO}_2 >45$ mm Hg), GCS of 8 or less, a decrease in GCS of greater than three independent of the initial GCS, anisocoria greater than 1 mm, cervical spine injury compromising ventilation, loss of pharyngeal reflex, and any clinical evidence of a herniation syndrome or Cushing's triad.⁵⁷

All patients should be assumed to have a full stomach and cervical spine injury, so the intubation should be carried out using a cerebroprotective, rapid-sequence induction whenever possible. Bag-valve-mask (BVM) ventilation should not be done unless the patient has signs and symptoms of impending herniation, apnea, or hypoxemia.⁵⁷ Vigilant care of the cervical spine is especially advised during BVM ventilation due to an increased risk for cervical spine injury.⁶⁸ A second person's sole responsibility is to maintain the child's neck in the neutral position by mild axial traction during airway maneuvers. Cricoid pressure should be applied by a third individual. Orotracheal intubation by direct laryngoscopy is the preferred method; nasotracheal intubation should be avoided, due to the possibility of direct intracranial damage in a patient with a basilar skull fracture and also because nasotracheal intubation may require excessive movement of the cervical spine. After successful tracheal intubation, oxygen saturation of 100%, normocarbica (35–39 mm Hg) and no hyperventilation, confirmed by arterial blood gas and trended with an end-tidal CO_2 , and a chest radiograph showing the tracheal tube in good position above the carina (as right main stem tracheal intubation is common) should be confirmed.

Unless the patient has signs or symptoms of herniation, prophylactic hyperventilation ($\text{PaCO}_2 <35$ mm Hg) should be avoided. Hyperventilation causes cerebral vasoconstriction, which decreases CBF and subsequent cerebral blood volume that will lower ICP, but ischemia can also occur.⁶⁹ Furthermore, respiratory alkalosis caused by hyperventilation makes it more difficult to release oxygen to the brain, by shifting the hemoglobin-oxygen curve to the left.

Because endotracheal intubation is a noxious stimulus and can increase ICP, appropriate medications should be used during rapid-sequence induction. The hemodynamic and neurologic status of the patient dictates the choice of drugs used. For the patient in cardiopulmonary arrest, no medications are needed for tracheal intubation. All other patients should usually receive lidocaine (1–1.5 mg/kg) intravenously (IV) before intubation to help blunt the increase in ICP that occurs during direct laryngoscopy.⁷⁰ For the hemodynamically unstable patient, the combination of lidocaine, etomidate (0.2–0.6 mg/kg), and neuromuscular blockade with rocuronium (1 mg/kg) or

vecuronium (0.3 mg/kg) intravenously is a popular choice. An alternative is the combination of lidocaine, fentanyl (2–4 µg/kg), and rocuronium or vecuronium. In the hemodynamically stable patient, either of the above combinations with the fast-acting benzodiazepine, midazolam (0.1–0.2 mg/kg) can be added. Another alternative in the hemodynamically stable patient is the combination of thiopental (3–5 mg/kg), lidocaine, and rocuronium or vecuronium. Thiopental and etomidate are ultrafast-acting and quickly reduce cerebral metabolism, which ameliorates the increased ICP associated with direct laryngoscopy. In addition the short-acting narcotic fentanyl, when used with lidocaine, can decrease the catecholamine release associated with direct laryngoscopy.⁵⁷ The endotracheal tube should be secured with tape, but this adhesive tape should not pass around the neck as venous return from the brain can be obstructed and potentially elevate ICP. The neck should be immobilized in an appropriately pediatric-sized collar.

Assessment and reassessment of the patient's circulatory status (central and peripheral pulse quality, capillary refill, heart rate, blood pressure) is critical as hypotension after pediatric TBI is associated with increases in morbidity and mortality.^{1,71,72} The most common cause for compensated or early shock (tachycardia with normal blood pressure) and uncompensated or late shock (low blood pressure) in the trauma patient is hypovolemic (ie, hemorrhagic) shock. In severe TBI, rapid intravenous fluid resuscitation is the goal for hypovolemic shock. Isotonic solutions, such as 0.9% NaCl solution or packed red blood cells (for hemorrhagic shock) can be administered, but hypotonic fluids should not be used in the initial resuscitation of these patients. Although not yet studied in a clinical trial, resuscitation with hypertonic saline (3% saline) in a severe pediatric TBI patient with initial signs and symptoms of hypovolemic shock and intracranial hypertension may be considered (further discussed in the "Intracranial hypertension management: first-tier therapies" section).

Special consideration must be given to spinal (neurogenic) shock, especially with suspected cervical-thoracic spine injuries, in addition to hypovolemic or hemorrhagic shock as the cause of hypotension. These patients may be bradycardic with shock. Bradycardia and shock must be treated accordingly with isotonic fluid/blood resuscitation to ensure adequate circulation and prevent further ischemia. In spinal shock, α -adrenergic agonists, such as intravenous phenylephrine, are also needed to treat the vasodilatation that results from injury to the sympathetic outflow tract.

Prophylactic brain-specific interventions (such as hyperventilation and hyperosmolar therapy with mannitol or 3% saline) in the absence of signs and symptoms of herniation or other neurologic deterioration currently are not recommended. However, in the presence of signs and symptoms of herniation, such as Cushing's triad (irregular respirations, bradycardia, and systemic hypertension), pupillary dysfunction, lateralizing extremity weakness, or extensor posturing, emergency treatment is needed.

Herniation

While the ABCs are being addressed, signs and symptoms of impending herniation, such as Cushing's triad or one of the herniation syndromes, must also be immediately treated. Early consultation with a neurosurgeon is important. Hyperventilation with 100% oxygen can be life-saving in the setting of impending herniation, such as in a child who has a rapidly expanding epidural hematoma with pupillary dilatation, bradycardia, systemic hypertension, and extensor posturing. Elevating the head to 30° increases venous drainage and lowers ICP.⁷³ Furthermore, the head should be midline to prevent obstruction of venous return from the brain. If these maneuvers do not relieve the signs and symptoms of herniation, such as by improvement in

pupillary response or resolution of Cushing's triad, hyperosmolar therapy (mannitol, 3% saline) should be instituted (further discussed in the "Intracranial hypertension management: first-tier therapies" section). In addition, short-acting medications such as thiopental (3–5 mg/kg) can be administered emergently in this setting.⁵⁷ During this time the patient usually goes to the CT scanner or directly to the operating room with the neurosurgeon, as the definitive therapy for a rapidly expanding epidural hematoma with herniation symptoms is surgery. Besides expanding mass lesions, diffuse cerebral swelling may also lead to herniation. As a result, secondary causes of brain injury such as hypoxemia, hypercarbia, hypotension, excessive fluid administration, or seizures can precipitate herniation and therefore must be avoided or immediately treated.

PEDIATRIC TRAUMATIC BRAIN INJURY GUIDELINES AND BEYOND

The "Guidelines for the acute medical management of severe TBI in infants, children, and adolescents" are summarized in **Figs. 1** and **2**.¹ Although they are informative and helpful, most of the recommendations are at the "Option" level or are "Class III" evidence. As the number of evidence-based pediatric studies were lacking, the authors of these guidelines made many recommendations after reaching a consensus based on published adult guidelines. Still, this seminal publication has been an important step toward a better understanding of pediatric TBI and is helping to increase the number of clinical and experimental pediatric TBI studies.

INTRACRANIAL HYPERTENSION MANAGEMENT: FIRST-TIER THERAPIES

Once the initial resuscitation with the ABCs, herniation, and expanding intracranial masses have been medically and surgically addressed, further management is aimed at preventing or treating causes of secondary brain injury (such as hypoxemia, hypotension, intracranial hypertension, hypercarbia, hyper- or hypoglycemia, electrolyte abnormalities, enlarging hematomas, coagulopathy, seizures, and hyperthermia).

One of the most important consequences of secondary brain injury is the development of intracranial hypertension. First described in the Monroe-Kellie doctrine, the intracranial vault is a fixed volume of brain, cerebrospinal fluid (CSF), and blood.⁵⁷ An enlarging space-occupying lesion, such as an expanding epidural hematoma or worsening cerebral edema, will not initially cause intracranial hypertension, as the initial compensatory mechanisms of displacement of CSF to the spinal canal and venous blood to the jugular veins prevent elevated ICP. However, once these compensatory mechanisms are exhausted, even a small increase in the size of the hematoma or cerebral edema will lead to increased ICP, which will compromise cerebral perfusion. This increase will then lead to brain ischemia and further edema, and ultimately lead to brain herniation.

Cerebral autoregulation and cerebral perfusion pressure is another important concept. Under normal conditions, cerebral autoregulation provides constant CBF over a wide range of cerebral perfusion pressures and is "coupled" to the metabolic demands of the brain. Cerebral perfusion pressure (CPP) is defined as the difference between mean systemic arterial blood pressure (MAP) minus the greater of the ICP or central venous pressure (CVP) (or $CPP = MAP - ICP$ or CVP).⁵⁷ After TBI, cerebral autoregulation can become "uncoupled" from the metabolic demands of the brain and alterations in CPP (due to either rising ICP or changing MAP) may result in fluctuations of CBF, which can lead to cerebral ischemia or hyperemia. For example, a study using xenon CBF-CT studies in children after TBI demonstrated marked reductions in CBF

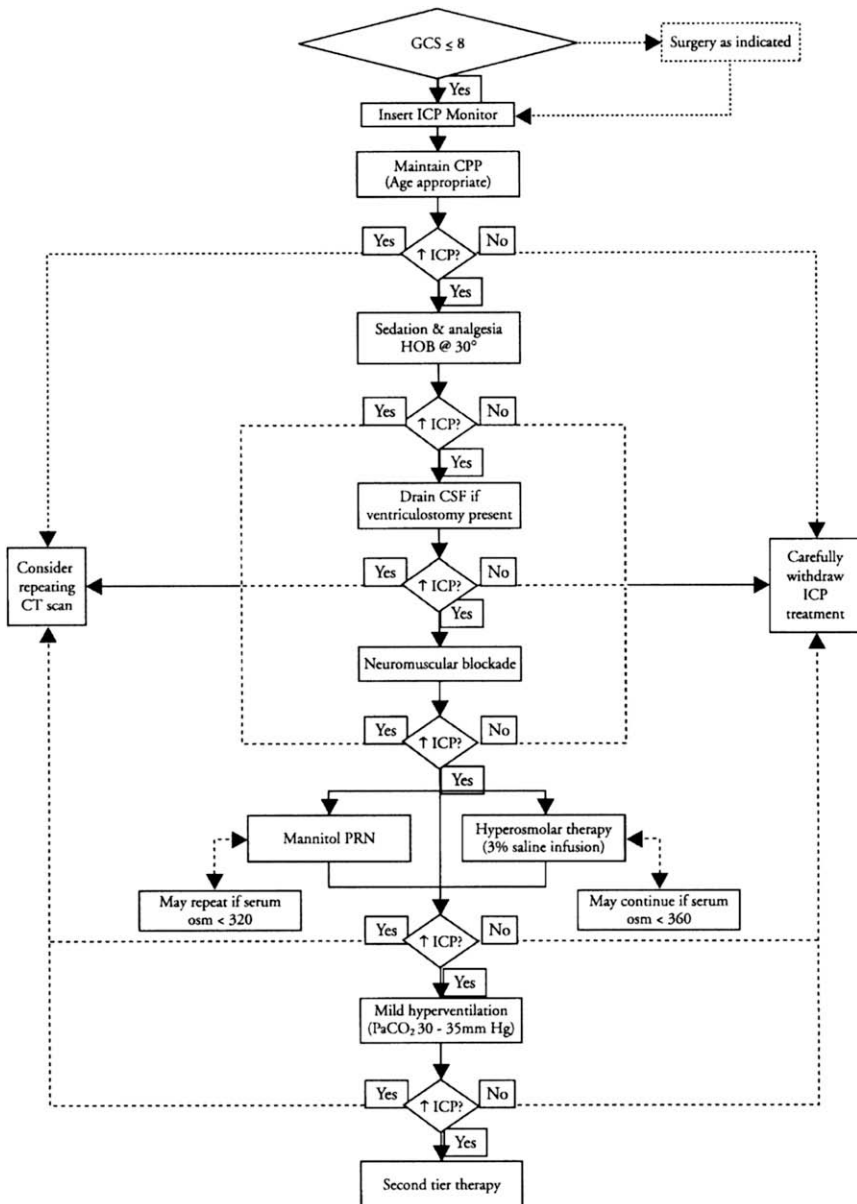


Fig. 1. First tier. CPP, cerebral perfusion pressure; CSF, cerebrospinal fluid; CT, computed tomography; GCS, Glasgow coma scale; HOB, head of bed; ICP, intracranial pressure; PRN, as needed. (Reprinted from Adelson PD, Bratton SL, Carney NA, et al. Critical pathway for the treatment of established intracranial hypertension in pediatric traumatic brain injury. *Pediatr Crit Care Med* 2003;4(3 suppl):S66; with permission.)

within the first 24 hours after injury, which was associated with poor outcome, whereas the children with high CBF 24 hours after the injury exhibited improved outcome.³⁴ However, because this type of study cannot measure minute-to-minute assessment of CBF changes, and due to the potential risk of transporting and of performing

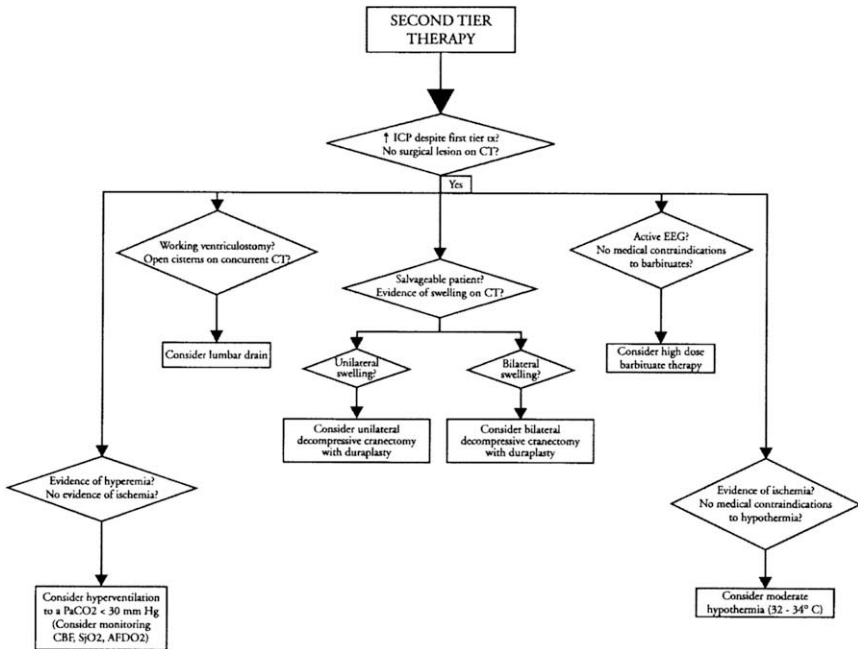


Fig. 2. Second tier. AJDO₂, arterial-jugular venous difference in oxygen content; CBF, cerebral blood flow; CT, computed tomography; EEG, electroencephalogram; ICP, intracranial pressure; SjO₂, jugular venous oxygen saturation. (Reprinted from Adelson PD, Bratton SL, Carney NA, et al. Critical pathway for the treatment of established intracranial hypertension in pediatric traumatic brain injury. *Pediatr Crit Care Med* 2003;4(3 suppl):S67; with permission.)

prolonged studies in critically ill patients, most institutions continuously measure CPP to “estimate CBF.”

A flow diagram showing a general approach to first-tier treatments for established intracranial hypertension in pediatric TBI was provided in the 2003 Guidelines (Fig. 1).¹ As discussed fully later, first-tier therapies include maintaining age-appropriate CPP, head position, sedation, analgesia, neuromuscular blockade, ventricular CSF drainage, hyperosmolar therapy, and mild hyperventilation. In general, an ICP monitor is placed by the neurosurgeon in children with an initial GCS of eight or less, after initial stabilization and resuscitation for treatment of potential intracranial hypertension. If the ventricles are not compressed due to severe cerebral swelling, ICP monitoring by a ventricular catheter allows a potential therapeutic option of CSF drainage. Because clinical signs and symptoms of herniation are late signs of intracranial hypertension, the use of ICP monitors allows early detection of intracranial hypertension before signs and symptoms of herniation are observed.⁷⁴ However, ICP monitors can cause hemorrhage and infection. Coagulopathy needs to be corrected before ICP monitor placement, and some centers use prophylactic antibiotics.

Intracranial Pressure and Cerebral Perfusion Pressure

Treatment of intracranial hypertension should begin at an ICP of 20 mm Hg or less, as most pediatric TBI studies show poor outcome with ICP 20 mm Hg or more, and aggressive treatment of intracranial hypertension is associated with improved

outcomes in some studies.⁷⁵⁻⁷⁸ However, further studies need to be done to determine an age-appropriate treatment for intracranial hypertension. In infants and young children, the threshold for “intracranial hypertension” treatment may be an ICP less than 20 mm Hg (because the MAP is lower) to optimize CPP (MAP minus ICP).

The optimal or “age-appropriate” CPP for pediatric TBI is currently unknown and there is no evidence that targeting a specific CPP for a specific age of the pediatric patient improves outcome. However, there are pediatric TBI studies showing that CPP ranging from 40 to 65 mm Hg are associated with favorable outcome and a CPP less than 40 mm Hg is associated with poor outcome.⁷⁹⁻⁸¹ As a result, the 2003 pediatric recommendations are that a CPP greater than 40 mm Hg and an “age-related continuum” of CPP from 40 to 65 mm Hg in infants to adolescents be maintained.¹ In a recent study, CPP values of 53 mm Hg for 2 to 6 years old, 63 mm Hg for 7 to 10 years old, and 66 mm Hg for 11 to 16 years old were suggested to represent minimum values for favorable outcome.⁸² However, this study was limited by the following: only the initial 6 hours of CPP data were analyzed, the specificity of the study was only 50%, and no infants and children younger than 2 years old were included. Further studies are paramount to determine the “age-appropriate” CPP.

According to the formula for CPP, lowering the ICP or raising the MAP will increase CPP. Most treatments are aimed at lowering ICP, maintaining normal MAP, and euvolemia. If the treatments fail to lower ICP, vasopressors are commonly added to increase the CPP by augmenting the MAP; this mechanism works if autoregulation is intact. Otherwise, as the MAP is increased the ICP will also increase and there is no net augmentation in CPP. If the child is hypotensive, isotonic fluid boluses or vasopressors can be administered to augment the MAP in the hope of improving CPP. In a recent pilot study comparing “CPP-targeted therapy” (CPP >60 mm Hg for children less than 2 years old; CPP >70 mm Hg for children at least 2 years old) to “ICP-targeted therapy” (ICP <20 mm Hg; CPP >50 mm Hg) in children with severe TBI, the “CPP-targeted” group revealed a trend toward improved outcome ($P=.08$).⁸³ However, this study was limited by a small number of patients: 12 patients in the “CPP” group and 5 patients in the “ICP” group. Furthermore, the “ICP” group was also a “CPP” group as they had to maintain a minimum CPP of greater than 50 mm Hg. In another study, aggressive treatment to lower ICP to 20 mm Hg or less using systemic antihypertensive agents and aggressive maintenance of normovolemia (the “Lund concept”) revealed favorable outcomes.⁸⁴ One major concern of the “Lund concept” is the potential for hypotension, which can promote secondary brain injury and worsen outcome.^{1,71,72}

Head Position

In adults after severe TBI, the head elevated at 30° reduced ICP without decreasing CPP.⁷³ Whereas no pediatric studies are known, the same degree of head elevation with midline position to promote venous drainage is currently recommended in the pediatric guidelines. In some centers, practitioners avoid placing a central venous catheter in the internal jugular vein to maximize venous drainage from the brain. In addition, minimal mean airway pressure from positive pressure ventilation is used to adequately ventilate and oxygenate the tracheally intubated patient to prevent impedance of venous return and to maximize venous drainage from the brain.

Sedation, Analgesia, and Neuromuscular Blockade

If there is continued ICP elevation, sedation, analgesia, and neuromuscular blockade can be administered.

It is well known that anxiety, stress, and pain can increase cerebral metabolic demands, which can pathologically increase cerebral blood volume and increase ICP. Narcotics, benzodiazepines, or barbiturates are commonly used. There are virtually no randomized, controlled studies on varying the use of sedatives in pediatric patients with severe TBI. As a result, the choice of sedatives is left up to the "treating physician," according to the guidelines.¹ However, the goal should be to use the minimum amount to lower ICP without causing side effects such as hypotension. In addition, potentially noxious stimulus such as endotracheal tube suctioning should be pretreated with sedation or analgesics, and lidocaine (1 mg/kg IV) should be considered to blunt increases in ICP.

Two drugs that are worth mentioning are ketamine and propofol. Ketamine is a potent cerebrovasodilator and increases CBF.⁸⁵ Ketamine markedly increases ICP, which can be reduced, but not prevented, by hyperventilation.^{86,87} Whereas some recent clinical adult TBI studies have argued that ketamine may be safe,⁸⁸⁻⁹⁰ there are no data on ketamine in clinical pediatric TBI. Though controversial, ketamine is believed to be contraindicated in patients with increased ICP.⁹¹ In our institution, ketamine is NOT administered to pediatric TBI patients. Several non-TBI and one TBI case report have reported metabolic acidosis and death in pediatric patients on prolonged (24 h) continuous infusion of propofol.⁹²⁻⁹⁴ Based on recommendations of the Food and Drug Administration, "continuous infusion of propofol is not recommended in the treatment of pediatric traumatic brain injury" in the pediatric guidelines.¹

Neuromuscular blocking agents are believed to reduce ICP by reducing airway and intrathoracic pressure with improved cerebral venous outflow and by preventing shivering, posturing, or ventilator-patient asynchrony.⁹⁵ Risks of neuromuscular blockade include hypoxemia and hypercarbia due to inadvertent extubation, masking of seizures, nosocomial pneumonia (shown in adults with severe TBI), immobilization stress due to inadequate sedation and analgesia, increased length of stay in the intensive care unit, and critical illness myopathy.⁹⁵ The loss of clinical examination should be of less concern if ICP monitoring is used, as increases in ICP usually occur before changes in clinical examination.

Overall, it is clear that a paucity of data exists on the use of sedatives, analgesics, and neuromuscular blocking agents in pediatric TBI patients. This is an area of research that has tremendous potential.

Ventricular Cerebrospinal Fluid Drainage

The intracranial volume decreases by removing CSF, which may decrease ICP in a patient with intracranial hypertension. If a child with severe TBI requires ICP monitoring in our center, the neurosurgeon is encouraged to place a ventricular ICP monitor, unless contraindications such as coagulopathy or small ventricles due to diffuse cerebral edema make catheter placement difficult. In a recent study, continuous CSF drainage was associated with lower mean ICP, lower concentrations of CSF markers of neuronal and glial injury, and increased CSF volume drained compared with intermittent CSF drainage.⁹⁶ Further study is warranted to find out if prolonged continuous CSF drainage may affect electrolyte balance or intravascular volume status. One potential concern of continuous CSF drainage is that ICP can only be monitored intermittently, not continuously. Whether either mode of CSF drainage improves outcome would be an important subject of future study.

Hyperosmolar Therapy

The blood-brain barrier is nearly impermeable to mannitol and sodium. Whereas mannitol has been traditionally administered, hypertonic saline (3% saline) is also

gaining favor. There is no literature to support the superiority of one over the other in severe pediatric TBI. Mannitol reduces ICP by two mechanisms. Mannitol rapidly reduces blood viscosity, which promotes reflex vasoconstriction of the arterioles by autoregulation, and decreases cerebral blood volume and ICP. This mechanism is rapid but transient, lasting about 75 minutes and requiring an intact autoregulation.^{97,98} The second mechanism by which mannitol reduces ICP is through an osmotic effect: it increases serum osmolality, causing the shift of water from the brain cell to the intravascular space, and decreases cellular or cytotoxic edema. Whereas this effect is slower in onset (more than 15–30 minutes), the osmotic effect lasts up to 6 hours. This effect also requires an intact blood-brain barrier, and there are concerns that if the blood-brain barrier is not intact, mannitol may accumulate in injured brain regions and cause a shift from the intravascular space to the brain parenchyma and worsen ICP. However, this side effect is reported to be more likely when mannitol is present in the circulation for extended periods of time, supporting the use of intermittent boluses.^{99,100} Furthermore, mannitol is a potent osmotic diuretic and may precipitate hypotension and renal failure if the patient becomes hypovolemic and the serum osmolality is greater than 320 mOsm/L.^{1,101} Mannitol is administered in intravenous bolus doses of 0.25 g/kg to 1 g/kg.¹

Hypertonic saline has been gaining favor recently as hyperosmolar therapy in pediatric head-injured patients with signs and symptoms of herniation. The main mechanism of action is the osmotic effect, similar to mannitol. The main theoretical advantage over mannitol is that hypertonic saline can be administered in a hemodynamically unstable patient with impending herniation, as hypertonic saline is believed to preserve intravascular volume status.^{102–104} Hypertonic saline exhibits several other theoretical benefits such as restoration of normal cellular resting membrane potential and cell volume, inhibition of inflammation, stimulation of atrial natriuretic peptide release, and enhancement of cardiac output.^{104–106} Hypertonic saline, as 3% saline, has recently become the most popular concentration used in the setting of TBI. It can be administered as a bolus intravenous dose; though not well studied, 1 to 6 mL/kg IV has become a popular bolus dose (unpublished observations). Doses as high as 10 mL/kg IV bolus have been reported in the literature.¹⁰⁷ In our pediatric institution, 2 to 6 mL/kg as an initial bolus dose is commonly used. Continuous infusions of 0.1 to 1 mL/kg/h titrated to maintain ICP at less than 20 mm Hg have also been reported.^{108,109} Whereas the guidelines state that 3% saline will not precipitate renal failure as long as serum osmolality is less than 360 mOsm/L,¹ caution should be exercised if the serum osmolality approaches 320 mOsm/L as there may be an increased risk of renal insufficiency.⁶⁰ Another potential concern with the use of hypertonic saline is central pontine (demyelination of the pons) or extrapontine myelinolysis (demyelination of the thalamus, basal ganglia, and cerebellum) that occurs with hypernatremia or rapid increase in serum Na,¹¹⁰ although this has not been clinically reported. A further theoretical concern with the use of hypertonic saline is subarachnoid hemorrhage due to rapid shrinking of the brain associated with mechanical tearing of the bridging vessels; this too has not been clinically reported. Rebound intracranial hypertension has been described clinically with the use of hypertonic saline bolus administration or after stopping continuous infusion.^{108,111}

Future studies are needed to compare mannitol administration with hypertonic saline, particularly studies evaluating optimal dosing and evaluating long-term outcome.

Hyperventilation

Hyperventilation is one of the fastest methods to lower ICP and is the best initial medical therapy with a child in impending herniation. However, without signs of

herniation, mild or prophylactic hyperventilation ($\text{PaCO}_2 < 35$ mm Hg) in children should be avoided. Mild hyperventilation (PaCO_2 30–35 mm Hg) may be considered as a first-tier option for longer periods of intracranial hypertension refractory to all the above measures (sedation, analgesia, neuromuscular blockade, CSF drainage, and hyperosmolar therapy).¹ This rationale is based on studies that CBF may be decreased early following pediatric TBI and may be associated with poor outcome, and that prophylactic hyperventilation may cause further ischemia.⁶⁹ However, no studies on the use of hyperventilation and long-term outcomes exist in the pediatric population following TBI.

INTRACRANIAL HYPERTENSION MANAGEMENT: SECOND-TIER THERAPIES

Refractory intracranial hypertension occurs in as much as 42% of cases of severe pediatric TBI and is associated with mortality rates of between 29% and 100%.^{112–115} At this point, a repeat CT scan should be performed to rule out a surgical cause for persistent, refractory intracranial hypertension. If there is no surgical lesion, the 2003 guideline recommends second-tier therapies (**Fig. 2**), which include aggressive hyperventilation, barbiturates, hypothermia, decompressive craniectomy, and lumbar CSF drainage.¹

Hyperventilation

Aggressive hyperventilation ($\text{PaCO}_2 < 30$ mm Hg) may be considered as a “second-tier” option in the setting of refractory intracranial hypertension. Cerebral blood flow, jugular venous oxygen saturation, or brain tissue oxygen monitoring to help identify cerebral ischemia is suggested.^{116,117}

Barbiturates

As the use of aggressive hyperventilation for treatment of refractory intracranial hypertension has become less popular, other therapies such as barbiturates are being used. Barbiturates reduce ICP by decreasing the cerebral metabolic rate.^{118–120} An electroencephalogram (EEG) should be used to assess the cerebral metabolic response to barbiturate treatment. Either a continuous infusion or frequent dosing is used. Pentobarbital or thiopental is often administered to achieve burst suppression on the EEG. However, the minimum dose should be administered as smaller doses that are associated with EEG activity may still decrease ICP and higher doses can lead to decreased cardiac output, decreased systemic vascular resistance, and hypotension.¹¹³ If high-dose barbiturate therapy is used to treat refractory intracranial hypertension, then appropriate hemodynamic monitoring and cardiovascular support must be provided.

Further studies need to address optimal dosing to prevent unwanted side effects such as hypotension and the long-term effects of barbiturate therapy.

Decompressive Craniectomy

The main goal of decompressive craniectomy is to control ICP and maintain CPP, and prevent herniation in the face of refractory cerebral swelling. This surgical option may be particularly appropriate in patients who have a potentially recoverable brain injury. These patients have no episodes of sustained ICP of more than 40 mm Hg before surgery and exhibit a GCS greater than three at some point subsequent to injury. Other indications for decompressive craniectomy include secondary clinical deterioration or evolving cerebral herniation syndrome within 48 hours of injury.¹ A randomized trial of early decompressive craniectomy in children with TBI and sustained intracranial

hypertension revealed that 54% of the surgically treated patients versus only 14% of the medically treated group had favorable outcome.¹²¹ Other small case series and retrospective reviews have also reported benefits.^{122–125} Furthermore, decompressive craniectomy may be considered in the treatment of severe TBI and refractory intracranial hypertension in infants and young children with nonaccidental head trauma or shaken-impact syndrome, as these patients had improved survival and neurologic outcomes compared with those undergoing medical management alone.¹²⁶

However, there are concerns that this procedure may exacerbate hemorrhage and cerebral edema formation. In a recent study, decompressive craniectomy was associated with an increased incidence of posttraumatic hydrocephalus, wound complications, and epilepsy in children with severe TBI.¹²⁷ Further studies are warranted on the timing, efficacy, safety, and the type of decompressive craniectomy (unilateral vs bilateral), and the effects on long-term outcome.

Hypothermia

Posttraumatic hyperthermia is defined as a core body temperature greater than 38.5°C. Whereas hypothermia is defined as a temperature of less than 35°C. In animal studies of experimental TBI, hyperthermia has been shown to exacerbate neuronal cell death. However, therapeutic hypothermia was found to be neuroprotective by ameliorating mechanisms of secondary brain injury, such as decreasing cerebral metabolism, inflammation, lipid peroxidation, and excitotoxicity.¹²⁸ In one recent study early hyperthermia (within 24 hours of admission) occurred in 29.9% of pediatric TBI patients and was associated with poor outcome.¹²⁹ Whereas most agree that hyperthermia should be avoided in children with severe TBI, the role of hypothermia is unclear. A phase II clinical trial showed that 48 hours of moderate hypothermia (32–34°C) initiated within 6 to 24 hours of acute TBI in pediatric patients reduces ICP and was “safe,” although there was a higher incidence of arrhythmias (reversed with fluid administration or rewarming) and rebound ICP elevation after rewarming.¹³⁰ This rebound ICP elevation after rewarming was also observed in another study.¹³¹ A multicenter, international (Canada, UK, and New Zealand) study of children with severe TBI randomized to hypothermia therapy (32.5°C for 24 hours) initiated within 8 hours after injury or to normothermia (37°C) was conducted recently.¹³² The study reported a worsening trend with hypothermia therapy: 31% of the patients in the hypothermia group had an unfavorable outcome, compared with 22% in the normothermia group. Another multicenter, clinical trial is currently ongoing in the United States with earlier randomization to hypothermia (within 6 hours) after injury and longer duration of hypothermia (48 hours).

Until further clinical studies are completed, avoidance of hyperthermia is prudent. However, before hypothermia can become a standard of care for pediatric TBI patients, further issues need to be addressed, such as: (1) the degree of hypothermia: is mild (35°C) hypothermia just as effective as moderate hypothermia?, (2) the onset of hypothermia, (3) the duration of hypothermia, (4) the rate of rewarming after hypothermia, (5) the effect of hypothermia on drug metabolism, and (6) potential complications associated with hypothermia, such as increased bleeding risk, arrhythmias, and increased susceptibility to infection.

Seizure

Seizures should be aggressively treated as they can cause hyperthermia and intracranial hypertension. Whereas prophylactic anticonvulsants may be considered a treatment option to prevent early posttraumatic seizures (occurring within 7 days following injury) in infants and young children, prophylactic anticonvulsants are not

recommended for preventing late posttraumatic seizures (occurring after 7 days) as this has not been shown to improve outcome.^{133,134} Future studies with newer anti-convulsants, such as levetiracetam and topiramate, are warranted.¹³⁵

Lumbar CSF Drainage

Although not commonly used, lumbar CSF drainage has been shown to be successful in treating refractory intracranial hypertension following pediatric TBI.¹³⁶ However, to avoid the risk of herniation the child must already have a functional ventriculostomy drain and open basal cisterns, and no mass effect or shift on concurrent CT.

FUTURE DIRECTIONS

Neuromonitoring

An area of considerable clinical interest since publication of the guidelines is the use of protein biomarkers in the diagnosis and prognosis of pediatric TBI. One study revealed that in children with accidental TBI, early (within 12 hours) elevated serum levels of S100 β , a marker of astrocyte injury or death, were associated with poor outcome.¹³⁷ A recent study also revealed that S100 β was elevated early after children sustained accidental TBI but also in children who sustained nonaccidental (inflicted) TBI or hypoxic-ischemic encephalopathy (HIE).¹³⁸ In addition, peak levels of serum neuron-specific enolase (NSE), a marker of neuronal injury or death, occurred early (within 12 hours) after accidental pediatric TBI whereas peak levels of NSE were delayed (as much as 3–5 days) in children with nonaccidental TBI or HIE. Furthermore, serum levels of myelin basic protein (MBP), a marker of white matter injury, revealed a delayed increase after accidental and nonaccidental TBI, but not in the HIE group. These data suggest that the biochemical response of the developing brain to nonaccidental TBI is distinct from the response to accidental TBI and shares similarities with hypoxic-ischemic brain injury. Studies have also shown CSF biomarkers to be valuable in assessing pathologic mechanisms associated with pediatric TBI, such as excitotoxicity, apoptosis, and oxidative stress.^{139–141} The potential use of urine biomarkers in pediatric TBI has recently been evaluated. Because serum S100 β has a short half-life that may limit its usefulness in detecting injury, a recent study revealed that urine S100 β levels were elevated in children with TBI.¹⁴² Whereas further studies need to address the sensitivity and specificity of serum and urine biomarkers, including the possibility of a nonneuronal origin for some of these biomarkers, the sampling error of hemolyzed specimens as NSE is present in red blood cells,¹⁴³ how the CSF biomarkers are obtained (continuous vs intermittent drainage) which can affect the protein biomarker levels,⁹⁶ and whether the CSF values truly correlate with the brain tissue or interstitial concentration, the use of biomarkers may potentially become an invaluable asset for monitoring the pediatric TBI patient.

In recent years intraparenchymal ICP devices have been modified to also measure the partial pressure of oxygen within the brain interstitial space (PbO₂) to monitor for cerebral hypoxia (<15 mm Hg).¹⁴⁴ In a recent prospective study in adult TBI patients, the use of ICP- and PbO₂-guided monitoring and therapy (ICP <20 mm Hg, CPP >60 mm Hg, and PbO₂ >25 mm Hg) significantly decreased the mortality rate from 44% to 25% compared with historical controls in using ICP monitoring and therapy alone.¹⁴⁴ Whereas the major limitation of this study was of the use of “historical controls,” the potential advantage of PbO₂ monitoring and therapy mandates further evaluation. Whereas there is less published literature on the use of PbO₂ in children with TBI, one study revealed that PbO₂ was decreased when ICP was increased or CPP was decreased; surprisingly, there were episodes of low PbO₂ despite normal ICP and

CPP.¹¹⁷ Another pediatric TBI study revealed that PbO_2 was increased in survivors.¹⁴⁵ One major limitation of the PbO_2 monitor is that it may represent only local, but not global assessment of brain oxygenation. Further studies clearly need to be conducted to answer questions such as: (1) where should the location of this monitor be placed: in the “uninjured” area versus “the injured” or “peri-injured” area?; (2) does optimizing PbO_2 improve outcome in a head-injured pediatric patient?

Other neuromonitoring modalities, such as magnetic resonance spectroscopy (MRS) and cerebral microdialysis, may become an important area of investigation to better understand the metabolic demands of the head-injured child. The major disadvantage of MRS is that it provides information only at a particular point in time; there is also a potential risk in transporting a critically ill patient to and from the MRS scanner. Limitations of cerebral microdialysis are the invasiveness needed to monitor the brain metabolism and, similar to the PbO_2 monitor, the question of where to place the microdialysis catheter in the brain.

Effects of Anesthetics on the Developing Brain

It is arguable that nothing has garnered more investigation and discussion among anesthesiologists than the effects of anesthetics on the developing brain. There is increasing animal data demonstrating that the administration of NMDA-antagonist or γ -aminobutyrate (GABA)-agonist anesthetics (isoflurane, nitrous oxide, ketamine, benzodiazepines, barbiturates) in the neonatal brain lead to a marked increase in apoptotic cell death, with some studies also demonstrating cognitive dysfunction.^{146–151} Following TBI in neonatal rats, the administration of NMDA antagonists also increased apoptotic cell death.²⁵ Because the neonatal brain requires excitatory-mediated neurotransmission for normal development and activity, it is not surprising that the indiscriminate inhibition of the normal excitotoxicity-mediated events during a critical period may interfere with normal brain maturation. However, other animal data suggest beneficial effects of antiexcitotoxic agents. Following hypoxia-ischemia in neonatal rodents, administration of isoflurane was found to be neuroprotective.^{152–154} Following deep hypothermic circulatory arrest or low-flow cardiopulmonary bypass in newborn pigs, administration of desflurane also improved neurologic outcome.^{155,156}

It is obvious that further research is of paramount importance regarding the role of anesthetics and apoptosis in the developing brain. For example, there may be an age-dependent response to anesthetics: the vulnerability to anesthesia-induced apoptosis quickly diminishes with increasing age in the developing rodent brain.^{157,158} Following experimental TBI, whereas NMDA antagonists promoted apoptosis in the neonatal rodent brain,²⁵ the administration of isoflurane (an NMDA antagonist) provided neuroprotection in the adult rodent brain.¹⁵⁹ Furthermore, whereas animal data suggest that anesthetics clearly promote apoptosis, it is unknown whether this is beneficial or harmful; are anesthetics promoting cell death in healthy neurons or are anesthetics accelerating cell death in neurons that were supposed to die anyway? Another area of research is looking at different combinations of medications and their effects on apoptosis and long-term neurologic outcome: is administration of an NMDA-antagonist medication with a GABA-agonist agent worse or better than administering 2 NMDA-antagonist or 2 GABA-agonist agents to induce anesthesia?

Most importantly, caution should be advised when extrapolating animal data to human data. Whereas there are anecdotal cases of temporary neurologic dysfunction after early exposure to anesthetics, most pediatric patients are safely anesthetized and there are no published data on anesthetics causing long-term neurologic problems or structural brain abnormalities in infants and children.¹⁵⁸ That said, further

investigation is a must on the role of anesthetics on the developing brain in the laboratory and in the pediatric population.

SUMMARY

The publication of the 2003 pediatric TBI guidelines have served as an impetus for new studies that have led to an improved understanding of the unique age-dependent responses following pediatric TBI. Whereas ongoing research to better understand the unique injury patterns, pathophysiology, therapeutic options, neuromonitoring, and the effects of anesthetics on different developmental stages of the head-injured pediatric TBI is important, it is clear that management in the “initial golden minutes” is critical to improving outcomes. Avoiding or rapidly correcting hypotension and hypoxemia, and other causes of secondary brain injury such as intracranial hypertension, cannot be overemphasized. Anesthesiologists must recognize the signs and symptoms of severe pediatric TBI and initiate appropriate therapeutic interventions.

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