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New Concepts in Treatment of Pediatric Traumatic Brain Injury

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Synopsis

Emerging evidence suggests unique age-dependent responses following pediatric traumatic brain injury. As the anesthesiologist plays a pivotal role in the acute treatment of the head-injured pediatric patient, this review will provide important updates on the pathophysiology, diagnosis, and age-appropriate acute management of infants and children with severe traumatic brain injury. In addition, areas of important clinical and basic science investigations germane to the anesthesiologist, such as the role of anesthetics and apoptosis in the developing brain, will be discussed.

Keywords

Traumatic brain injury; Pediatric; Child; Guidelines; Treatment; Anesthetics

Introduction

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 appears 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 in the operating room, it is integral that they understand the injury patterns, pathophysiology, recent advances in diagnostic modalities, and different therapeutic options. In this issue of *Pediatric Anesthesiology*, 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, will also be discussed.

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Injury Patterns

Age-dependent injury patterns following pediatric TBI occurs ². In infants and young children, inflicted or non-accidental TBI is a major cause of brain injury and often is associated with repetitive injury ^{3,4}. Accidental TBI in this age are mainly due 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, while there is a rise in injuries associated with bicycle crashes. In adolescents, there is a dramatic rise in TBI due to motor vehicle accidents, sports-related repetitive injury, and 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 appear to be more common in infants and young children sustaining non-accidental 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. Importantly, 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 hypo-glycemia, 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 that lead 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 hopes of discovering novel therapies to halt the progression or inhibit these mechanisms for which **there is no current therapy**. Some of these important mechanisms associated with secondary brain injury are discussed below. For a more detailed review of these and other mechanisms associated with secondary brain injury, the reader is referred to an excellent chapter, “Molecular biology of brain injury”, by Kochanek and colleagues ¹³.

Necrosis and apoptosis

Following head trauma, the release of excessive amounts of the excitatory amino acid glutamate is thought to occur termed “excitotoxicity”, which can lead to neuronal injury in two phases. The first phase is characterized by sodium-dependent neuronal swelling, which is then followed by delayed, calcium-dependent neuronal degeneration ¹⁴. These effects are mediated through both 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 protease, calpains, may participate in neuronal cell loss in the injured cortex following TBI in the immature rat¹⁵. In addition, experimental pediatric TBI has also been shown to alter NMDA receptor subunit composition¹⁶.

In contrast to necrotic cell death which 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 flux¹⁷. 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-9¹⁸. Caspase-9 then activates the effector protease caspase-3, which ultimately causes apoptosis¹⁹. Extracellular signaling occurs via tumor necrosis factor (TNF) superfamily of cell surface death receptors, which include TNFR-1 and Fas/Apo1/CD95²⁰. Receptor–ligand binding of TNFR-1-TNF- α or Fas-Fas L promotes “death domains” which activates caspase-8, which ultimately lead to caspase-3 activation and apoptotic cell death²¹. 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 apoptosis²².

There appears 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 via the NMDA-mediated calcium channel in the immature brain²³. However, following TBI, calcium accumulation in the injured brain was more extensive and appeared for a longer duration in the mature animal than the immature animal²⁴. This difference may have been due to the fact that 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 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 the immature rats^{25,26}. The increased propensity of the developing brain for post-traumatic apoptotic cell death is a key area for further research.

To date, no novel anti-excitotoxic 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 feel 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 adults⁸. Cerebral swelling is thought 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 thought to be worsened with hypoxia and hypoperfusion. Osmolar shifts occur primarily in areas of necrosis where 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 thought to be brought on by excitotoxicity and uptake of glutamate. Glutamate uptake is coupled to sodium-potassium adenosine triphosphatase (ATPase), with sodium and water being accumulated in astrocytes²⁷. Recent experimental data also suggest the role of endogenous water channels called aquaporins present in the astrocyte that may participate in brain edema²⁸. Clinical studies suggests that cellular edema, and not hyperemia, nor 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 children³³. Re-analysis of the published pediatric TBI CBF studies compared to the age-dependent changes of CBF in normal children have suggested that hyperemia does not play a large role following severe pediatric TBI³⁰. Other data suggests that posttraumatic hypoperfusion was more common and a global decreased CBF (<20 mL/100 g/min) in the initial 1st day following TBI in infants and children was associated with poor outcome³⁴.

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 outcome³⁵. In a subsequent study, all of the children with non-accidental TBI had impaired cerebral autoregulation in both hemispheres and poor outcome³⁶. Furthermore, age less than 4 years old was a risk factor for impaired autoregulation, independent of TBI severity³⁷.

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 than older animals following diffuse pediatric TBI^{38,39}. In contrast, following focal (contusive) injury, the older animals exhibited the most pronounced decrease in CBF⁴⁰. This suggests that besides age, the pathologic type of TBI may also contribute to CBF alterations. Mechanisms that may underlie post-traumatic 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 thought to contribute to decreased cerebral blood flow⁴¹⁻⁴³. Similarly, increased levels of vasoconstrictors, such as endothelin-1, are also implicated in cerebral blood flow alterations⁴⁴. Recently, NMDA and endogenous opioids (NOC/OFQ) were also found to participate in age-dependent impairment of cerebrovascular reactivity in the youngest animals following diffuse TBI⁴⁵.

Traumatic axonal injury

A common pathology observed in infants and young children, in both accidental and in non-accidental TBI is diffuse or traumatic axonal injury (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 matter⁴⁶. Hypoxic-ischemic injury, calcium and ionic flux dysregulation, and mitochondrial and cytoskeletal dysfunction are thought to play important roles in axonal injury⁴⁷. TAI is thought to be a major cause of morbidity in pediatric TBI^{48,49,50}. 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 outcomes⁵¹.

Pathologically, while immediate or “primary” axotomy or immediate physical tearing of the axon can occur following TBI, TAI is thought to primarily occur by a delayed process called “secondary” axotomy⁵². This suggests an extended window of opportunity for therapeutic intervention to stop this delayed and ongoing axonal degeneration, in the ultimate hopes of improving outcome. Animal data suggest that the younger brain may be more vulnerable to widespread TAI with equivalent injury severity than the adult brain⁵³. Recently, a clinically-relevant animal model of pediatric TBI has been developed that exhibits diffuse TAI and ongoing axonal degeneration associated with chronic cognitive dysfunction⁵⁴. Ongoing research on better understanding mechanisms associated with TAI and chronic cognitive dysfunction in the traumatized developing brain may lead to novel therapies in the future.

ED evaluation

Upon arrival of a head-injured pediatric patient to the 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 state⁵⁵. 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 signs⁵⁶.

Physical Examination

The anesthesiologist is an expert in quickly assessing the “ABC's” (Airway, Breathing, Circulation). He/she must also be adept at quickly assessing and re-assessing the patient's neurological 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 re-assessments 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 neurological assessment should be performed and documented. While the Glasgow Coma Scale (GCS) for older children and adults is the most widely used method to quantify initial neurological assessment⁵⁸, the Children's Coma Scale is most often utilized in infants and younger children (Table 2)⁵⁹. A GCS score of 13-15 is mild, 9-12 is moderate, and 3-8 is severe TBI. It is critical that the GCS be recorded on the initial medical record and re-assessed 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 then rapidly decrease over time secondary to an expanding epidural hematoma and impending herniation.

The pupillary exam is of paramount importance when assessing the neurological 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 ptosis⁵⁷. 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 oculomotor dysfunction. Bilateral mydriasis can be the result of ingestions (anti-cholinergics) or administration of atropine or adrenergic agonists such as epinephrine during resuscitation. A small pupil (miosis) is usually secondary to dysfunction of sympathetic innervation. Since 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 is an abnormal finding in children older than 6 months of age when the plantar reflex is tested- it is characterized by extension of the great toe and abduction of the remaining toes.

Diagnostic studies

The mainstay of the initial radiologic evaluation of the severely head-injured pediatric patient is computed tomography (CT) imaging- but **prior to** transport to CT scan, **“the ABC’s 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.

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 non-accidental trauma is suspected. Complete blood count (CBC) evaluating 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 performed, as well as chest radiographs for intubated patients to evaluate for right mainstem 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 non-accidental 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, transependymal flow and obliteration of the basal cisterns which are concerning 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 predictor of poor outcome ^{63,65}. Magnetic resonance imaging (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}. However, 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, a recent study is evaluating a “quick-brain” MRI to enhance image quality, such as the posterior fossa, and not have the potential risk of radiation associated with CT⁶⁷.

Therapeutic Options- The “Initial Golden Minutes” of Pediatric TBI Airway, Breathing, and Circulation (“ABC”)

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 ($\text{PaCO}_2 > 45 \text{ mmHg}$), $\text{GCS} \leq 8$, a decrease in $\text{GCS} > 3$ independent of the initial GCS , anisocoria $> 1 \text{ mm}$, cervical spine injury compromising ventilation, loss of pharyngeal reflex, and any clinical evidence of a herniation syndrome or Cushing's triad⁵⁷.

All patients should be assumed to have a full stomach and cervical spine injury, so the intubation should be utilizing 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 hypoxemia⁵⁷. Vigilant care of the cervical spine is especially advised during BVM ventilation due to an increased risk for cervical spine injury⁶⁸. 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 done 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 %, normocarbida ($35-39 \text{ mmHg}$) and not hyperventilation, confirmed by arterial blood gas and trended with an end-tidal CO_2 , and a chest x-ray showing the tracheal tube in good position above the carina (as right mainstem tracheal intubation is common) should be confirmed.

Unless the patient has signs or symptoms of herniation, prophylactic hyperventilation ($\text{PaCO}_2 < 35 \text{ mmHg}$) should be avoided. Hyperventilation causes cerebral vasoconstriction, which decreases cerebral blood flow and subsequent cerebral blood volume-this will lower ICP, but ischemia can also occur⁶⁹. 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 the other patients should usually receive lidocaine ($1-1.5 \text{ mg/kg}$) intravenously (IV) before intubation to help blunt the rise in ICP that occurs during direct laryngoscopy⁷⁰. For the hemodynamically unstable patient, the combination of lidocaine, etomidate ($0.2-0.6 \text{ mg/kg}$), and neuromuscular blockade with rocuronium (1 mg/kg) or vecuronium (0.3 mg/kg) IV is a popular choice. An alternative is the combination of lidocaine, fentanyl ($2-4 \text{ micrograms/kg}$), and rocuronium or vecuronium. In the hemodynamically stable patient, either of the above combination with fast-acting benzodiazepine, midazolam ($0.1-0.2 \text{ mg/kg}$) can be added. Another alternative in the hemodynamically stable patient is the combination of thiopental ($3-5 \text{ mg/kg}$), 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 laryngoscopy⁵⁷. 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 **re-assessment** 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 rates^{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 (i.e., hemorrhagic) shock. In severe TBI, rapid intravenous fluid resuscitation is the goal for hypovolemic shock. Isotonic solutions, such as 0.9 % NaCl solution and/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 both hypovolemic shock and intracranial hypertension should 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 etiology of hypotension. These patients may be bradycardic with shock. Both 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 IV 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, systemic hypertension), pupillary dysfunction, lateralizing extremity weakness, or extensor posturing, emergent treatment is needed.

Herniation

While the ABC's 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 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 ICP⁷³. Furthermore, the head should be midline to prevent obstruction of venous return from the brain. If these maneuvers don't relieve the signs and symptoms of herniation, such as 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), as described previously, can be administered emergently in this setting⁵⁷. During this time, the patient usually goes to the CT scanner and/or directly to the OR 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 TBI Guidelines and Beyond

The “guidelines for the acute medical management of severe TBI in infants, children, and adolescents” are summarized in Figures 1 and 2. While very informative and helpful, most of the recommendations are at the “Option” level or “Class III” evidence. As the number of evidenced-based pediatric studies were lacking, these authors made many recommendations after reaching a consensus based on published adult guidelines. Still, this important and seminal publication have been an important step in a better understanding of pediatric TBI and helping increase the number of clinical and experimental pediatric TBI studies.

Intracranial Hypertension Management: First-Tier Therapies

Once the initial resuscitation with the “ABC's” and 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 hypo-glycemia, electrolyte abnormalities, enlarging hematomas, coagulopathy, seizures, and hyperthermia).

As already discussed, 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, cerebral spinal fluid (CSF), and blood⁵⁷. 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 prevents 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 will then lead to brain ischemia and further edema, and ultimately lead to brain herniation.

Another important concept to understand is cerebral autoregulation and cerebral perfusion pressure. Under normal conditions, cerebral autoregulation provides constant cerebral blood flow (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 $CPP = MAP - ICP \text{ or } CVP$ ⁵⁷. After TBI, cerebral autoregulation can become “uncoupled” to 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 utilizing xenon CBF-CT studies in children after TBI demonstrated marked reductions in CBF within the first 24 hours after injury, which was associated with poor outcome, while the children with high CBF 24 hours after the injury exhibited improved outcome³⁴. However, because this type of study cannot measure minute-to-minute assessment of CBF changes, and due to the potential risk of transporting and performing 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 (Figure 1)¹. As discussed fully below, “first-tier” therapies include maintaining “age-appropriate” CPP, head position, sedation, analgesia, and 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 ≤ 8 , 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 ventricular catheter allows a potential therapeutic option of CSF drainage. Since clinical signs and symptoms of herniation are very late signs of intracranial hypertension, the use of ICP monitors allows early detection of intracranial hypertension before signs and symptoms of herniation are observed⁷⁴. However, ICP monitors can cause hemorrhage and infection. Coagulopathy needs to be corrected before ICP monitor placement and some centers use prophylactic antibiotics.

ICP and CPP

Treatment for intracranial hypertension should begin at an ICP ≥ 20 mmHg, as most pediatric TBI studies show poor outcome with ICP ≥ 20 mmHg, and aggressive treatment of intracranial hypertension is associated with improved outcomes in some studies⁷⁵⁻⁷⁸. 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 mmHg (since the MAP is lower) in order to optimize CPP (MAP-ICP).

It is currently unknown what the optimal or “age-appropriate” CPP for pediatric TBI is 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 that show that CPP ranging from 40 mmHg to 65 mmHg are associated with favorable outcome and a **CPP < 40 mmHg is associated with poor outcome**^{79,80,81}. As a result, the 2003 pediatric recommendations are that a CPP >40 mm Hg and an “age-related continuum” of CPP from 40 to 65 mmHg in infants to adolescents be maintained¹. In a recent study, CPP values of 53 mm Hg for 2-6 years old, 63 mm Hg for 7-10 years old, and 66 mm Hg for 11-16 years old, were suggested to represent minimum values for favorable outcome⁸². However, this study was limited by the fact that only the initial 6 hours of CPP data was analyzed, the specificity of the study was only 50 %, and no infants and children < 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, then 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 and/or vasopressors can be administered to augment the MAP in the hopes 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=0.08)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 > 50 mm Hg. In another study, aggressive treatment to lower ICP ≤ 20 mm Hg using systemic anti-hypertensive agents and aggressive maintenance of normovolemia (the “Lund concept”) revealed favorable outcomes⁸⁴. 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 CPP⁷³. While 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, and/or barbiturates are commonly used. There are virtually no randomized, controlled studies of 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 guidelines¹. 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 pre-treated with sedation and/or analgesics, and lidocaine (1mg/kg IV) should be considered to blunt rises in ICP.

Two drugs that are worth mentioning are ketamine and propofol. Ketamine is a potent cerebrovasodilator and increases cerebral blood flow⁸⁵. Ketamine markedly increases ICP, which can be reduced, but not prevented, by hyperventilation^{86,87}. While some recent clinical adult TBI studies have argued that ketamine may be safe⁸⁸⁻⁹⁰, there is no data on ketamine in clinical pediatric TBI. Though controversial, ketamine is thought to be contra-indicated in patients with increased ICP⁹¹. In our institution, we do NOT administer ketamine in pediatric TBI patients. A number of non-TBI and one TBI case reports have reported metabolic acidosis and death in pediatric patients on prolonged (24 hrs) continuous infusion of propofol⁹²⁻⁹⁴. 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 guidelines¹.

Neuromuscular blocking agents is thought to reduce ICP by reducing airway and intrathoracic pressure with improved cerebral venous outflow and by preventing shivering, posturing, or ventilator-patient asynchrony⁹⁵. 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 ICU length, and critical illness myopathy⁹⁵. The loss of clinical exam should be less concerning if ICP monitoring is used, as increases in ICP usually occur before changes in clinical exam.

Overall, it is very 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, we encourage the neurosurgeon to place a ventricular ICP monitor, unless contra-indications such as coagulopathy or very 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 than intermittent CSF drainage⁹⁶. Further study is warranted to see if

prolonged continuous CSF drainage will affect electrolyte balance or intravascular volume status. One potential concern of continuous CSF drainage is that ICP can only be monitored intermittently, but not continuously. Most importantly, whether either mode of CSF drainage improves outcome would be an important future study.

Hyperosmolar Therapy

The blood-brain barrier is nearly impermeable to both mannitol and sodium. While 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 2 mechanisms. It 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 requires an intact autoregulation^{97,98}. The second mechanism by which mannitol reduces ICP is via 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. While this effect is slower in onset (over 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 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 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 > 320 mOsm/l^{1,101}. Mannitol is administered in bolus doses of 0.25 g/kg to 1 g/kg IV¹.

Hypertonic saline has been gaining favor recently for 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 thought to preserve intravascular volume status¹⁰²⁻¹⁰⁴. 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 output¹⁰⁴⁻¹⁰⁶. 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 IV dose; while not well studied, 1-6 ml/kg IV has become a popular bolus dose (unpublished observations). Doses as high as 10 ml/kg IV bolus has been reported in the literature¹⁰⁷. In our pediatric institution, 2-6 ml/kg as an initial bolus dose is commonly used. Continuous infusions of 0.1 to 1 ml/kg/hour titrated to maintain ICP < 20 mmHg have also been reported^{108,109}. While the guidelines state that 3 % saline will not precipitate renal failure as long as serum osmolality is < 360 mOsm/l¹, caution should be exercised if the serum osmolality approaches 320 mOsm/l as there may be an increased risk for renal insufficiency⁶⁰. Another potential concern with the use of hypertonic saline is central pontine (demyelination of the pons) or extrapontine myelinosis (demyelination of the thalamus, basal ganglia, and cerebellum) that occurs with hypernatremia and/or rapid rise in serum Na¹¹⁰, although this has not been clinically reported. Another 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 has not been clinically reported. Rebound intracranial hypertension has been described clinically with the use of hypertonic saline bolus administration or after stopping the 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 ($\text{PaCO}_2 < 35 \text{ mmHg}$) in children should be avoided. Mild hyperventilation ($\text{PaCO}_2 30\text{-}35 \text{ mmHg}$) 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 cerebral blood flow may be decreased early following pediatric TBI and may be associated with poor outcome, and that prophylactic hyperventilation may cause further ischemia⁶⁹. 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

Unfortunately, refractory intracranial hypertension occurs as much as 42 % of cases of severe pediatric TBI and is associated with mortality rates 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, then the 2003 guideline recommends “second-tier” therapies (Figure 2), which includes aggressive hyperventilation, barbiturates, hypothermia, decompressive craniectomy, and lumbar CSF drainage¹.

Hyperventilation

Aggressive hyperventilation ($\text{PaCO}_2 < 30 \text{ mmHg}$) 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 utilized. Barbiturates reduce ICP by decreasing the cerebral metabolic rate¹¹⁸⁻¹²⁰. 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 hypotension¹¹³. 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 are patients with no episodes of sustained ICP $> 40 \text{ mmHg}$ before surgery and exhibited GCS > 3 at some point subsequent to injury. Other indications for decompressive craniectomy include secondary clinical deterioration or evolving cerebral herniation syndrome within 48 hours of injury¹. A randomized trial of very 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 ^{122,123,124,125}. Furthermore, decompressive craniectomy may be considered in the treatment of severe TBI and refractory intracranial hypertension in infants and young children with non-accidental head trauma or shaken-impact syndrome, as these patients had improved survival and neurological outcomes compared to 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. It is clear that further studies are clearly warranted on the timing, efficacy, safety, and the type of decompressive craniectomy (unilateral vs. bilateral) and the effects on long-term outcome.

Hypothermia

Post-traumatic hyperthermia is defined as a core body temperature $> 38.5^{\circ}\text{C}$, whereas hypothermia is defined as $< 35^{\circ}\text{C}$. 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. While 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 ($32\text{--}34^{\circ}\text{C}$) initiated within 6-24 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. Recently, a multi-center, 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 ¹³². The study reported a worsening trend with hypothermia therapy: 31% of the patients in the hypothermia group, as compared to 22% of the patients in the normothermia group, had an unfavorable outcome. Another multi-center, clinical trial is currently on-going 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 seizures can cause hyperthermia and intracranial hypertension. While prophylactic anticonvulsants may be considered a treatment option to prevent early post-traumatic seizures (occurring within 7 days following injury) in infants and young children, prophylactic anticonvulsants are not recommended for preventing late post-traumatic seizures (occurring after 7 days) as this has not been shown to improve outcome

^{133,134}. Future studies with newer anticonvulsants, 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. Similarly, a recent study revealed that S100 β was elevated early after children sustaining accidental TBI, but also in children sustaining non-accidental (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 non-accidental TBI or HIE. Furthermore, serum levels of myelin basic protein (MBP), a marker of white matter injury, revealed a delayed increase after accidental and non-accidental TBI, but not in the HIE group. These data suggest that the biochemical response of the developing brain to non-accidental 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 ^{139,140,141}. Interestingly, the potential use of urine biomarkers in pediatric TBI has recently been evaluated. Since serum S100 β has a short half-life which may limit their usefulness in detecting injury, a recent study revealed that urine S100 β levels were elevated in children with TBI ¹⁴². While further studies need to be addressed, with regards to the sensitivity and specificity of serum and urine biomarkers, such as the possibility of non-neuronal origin for some of these biomarkers, 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 both 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 to historical controls in their institution using ICP monitoring and therapy alone ¹⁴⁴. While the major limitation of this study was of the use of "historical controls", the potential advantage of PbO₂ monitoring and therapy mandates further evaluation. While 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 PbO₂ was increased in survivors ¹⁴⁵. One major limitation of the PbO₂ 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 "un-

injured” area vs. “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 the MRS is that it only provides information at a particular point in time and the potential risk of transporting a critically-ill patient to and from the MRS scanner. Limitations of cerebral microdialysis is 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

Arguably, nothing has garnered more investigation and discussion among anesthesiologists than the effects of anesthetics on the developing brain. There is increasing animal data which demonstrate that the administration of NMDA antagonist and/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^{146,147,148,149,150,151}. Following TBI in neonatal rats, the administration of NMDA antagonists also increased apoptotic cell death²⁵. Since 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 suggests beneficial effects of anti-excitotoxic agents. Following hypoxia-ischemia in neonatal rodents, administration of isoflurane was found to be neuroprotective^{152,153,154}. Similarly, following deep hypothermic circulatory arrest or low-flow cardiopulmonary bypass in newborn pigs, administration of desflurane improved neurologic outcome^{155,156}.

It is obvious that further research is of paramount importance on the role of anesthetics and apoptosis on 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, while NMDA antagonists promoted apoptosis in the neonatal rodent brain²⁵, the administration of isoflurane (an NMDA antagonist) provided neuroprotection in the adult rodent brain¹⁵⁹. Furthermore, while animal data suggest that anesthetics clearly promote apoptosis, it is unknown whether this is beneficial or harmful; is 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 combination 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 two NDMA-antagonist or two GABA-agonist agents to induce anesthesia ?

Most importantly, caution should be advised when extrapolating animal data to human data. While there are anecdotal cases of temporary neurological dysfunction after early exposure to anesthetics, most pediatric patients have been safely anesthetized and there is no published data on anesthetics causing long-term neurologic problems or structural brain abnormalities in infants and children¹⁵⁸. That said, further investigation is a must on the role of anesthetics on the developing brain in the lab and in the pediatric population.

Conclusions

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. While on-going 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, can not be overemphasized. Anesthesiologists must recognize the signs and symptoms of severe pediatric TBI and initiate appropriate therapeutic interventions.

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Figure 1. First tier. *GCS*, Glasgow Coma Scale; *ICP*, intracranial pressure; *CPP*, cerebral perfusion pressure; *HOB*, head of bed; *CSF*, cerebrospinal fluid; *CT*, computed tomography; *PRN*, as needed.

Figure 2.

Second tier. *ICP*, intracranial pressure; *CT*, computed tomography; *EEG*, electroencephalogram; *CBF*, cerebral blood flow; *SjO₂*, jugular venous oxygen saturation; *AJDO₂*, arterial-jugular venous difference in oxygen content.

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

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