Treatment of Traumatic Brain Injury in Pediatrics

Andranik Madikians, MD
Christopher C. Giza, MD

Corresponding author
Christopher C. Giza, MD
Division of Pediatric Neurology, Department of Pediatrics and Department of Neurosurgery, UCLA Brain Injury Research Center, Room 18-218B, Semel Institute, 10833 Le Conte Boulevard, Mattel Children's Hospital—UCLA, Los Angeles, CA 90095, USA.
E-mail: cgiza@mednet.ucla.edu

Current Treatment Options in Neurology 2009, **11:**393–404
Current Medicine Group LLC ISSN 1092-8480

Opinion statement

The primary goal in treating any pediatric patient with severe traumatic brain injury (TBI) is the prevention of secondary insults such as hypotension, hypoxia, and cerebral edema. Despite the publication of guidelines, significant variations in the treatment of severe TBI continue to exist, especially in regards to intracranial pressure (ICP)–guided therapy. This variability in treatment results mainly from a paucity of data from which to create standards and from the heterogeneity inherent in pediatric TBI. The approach to management of severe TBI based on the published guidelines should be focused on ICP control, which should ultimately improve cerebral perfusion pressure. After identifying and surgically evacuating expanding hematomas, the first-tier treatment approach requires placing an ICP monitor. This is accompanied by medical management of elevated ICP, initially with simple maneuvers such as elevating the head of the bed to improve venous drainage, instituting sedation and analgesia to decrease metabolic demands of the brain, and draining cerebrospinal fluid. If these measures fail, then further first-tier interventions include hyperosmolar therapy to decrease cerebral edema and controlled ventilation to decrease cerebral blood volume. For elevations of ICP resistant to first-tier therapies, treatment escalates to second-tier therapy, which includes more aggressive measures such as placing jugular catheters to measure cerebral oxygenation with moderate hyperventilation, placing lumbar drains to remove more cerebrospinal fluid, administering high-dose barbiturates to suppress cerebral electrical activity, inducing hypothermia as a protective measure, and performing decompressive craniectomy to open the cranial vault. To properly execute these interventions, appropriate neuromonitoring is essential, starting from standard physiological parameters such as ICP, mean arterial blood pressure, and temperature. Additional modalities of neurologic monitoring are becoming more readily available and can provide additional clinically useful information about the pediatric patient with TBI; these include cerebral oxygenation, continuous electroencephalography, noninvasive blood flow monitoring, and advanced neuroimaging.

Introduction

Traumatic brain injury (TBI) is the number one cause of death and disability in children and young adults in the United States. Because the human brain continues to mature into the early twenties [1] and because most TBI occurs in children and young adults [2], the effects of traumatic injury to a developing brain are particularly important considerations. Young patients who survive moderate to severe TBI may be left with significant neurologic and cognitive deficits and be forced to endure the lifelong burden of these impairments.

In the pediatric population, the mechanism of TBI varies by age [2]. A major cause of TBI in infants is nonaccidental TBI (also termed *abusive head trauma*), often associated with repeated, severe, diffuse injury and a delay in treatment that may cause associated hypoxic-ischemic injury. These characteristics make it distinctive among the many causes of TBI, and the outcome in these patients is generally worse than in other types of TBI [3]. Toddlers are more likely to be injured in falls, and motor vehicle accidents cause an increasing proportion of moderate to severe TBI in older age ranges, peaking in late adolescence and young adulthood.

TBI pathology is also age-dependent. Younger patients with TBI have fewer contusions and tend to have more subdural hematomas and diffuse cerebral edema. Using diffusion-weighted imaging, infants with abusive head trauma may show evidence of hypoxia-ischemia [4]. In adolescents, the injuries are more similar to those seen in adults, where predominant findings include contusions and diffuse axonal injury.

As one looks at the guidelines for treating pediatric patients with severe TBI (Fig. 1 and Fig. 2), one must not forget the fundamentals of patient care. Significant Class II and Class III evidence supports the avoidance of hypotension and hypoxia in these patients [5, Class III; 6, Class II]. Appropriate positioning of the patient, such as elevation of the head of the bed and maintaining the head in the midline, are important. These maneuvers will improve jugular venous drainage of the brain. Most patients with severe TBI also have other traumatic injuries, such as injuries to internal organs, lacerations, or orthopedic and cervical spine injuries. Some of these injuries could be life-threatening on their own, or if missed, could add significantly to morbidity and mortality. General hygiene—especially oral hygiene, skin care/decubitus prevention, and bowel and bladder care—is essential to prevent secondary infections.

Since the 2003 publication of the Guidelines for Acute Management of Severe Traumatic Brain Injury in Infants, Children, and Adolescents [7, Class II–III], there has been increasing interest regarding research pertaining to diagnostic evaluation, prognosis, pathophysiology, and treatment of pediatric TBI, but the treatment of severe TBI continues to vary, especially in regards to intracranial pressure (ICP)–guided therapy [8,9]. Appropriate knowledge of the pathophysiologic characteristics of the injury is key in correctly managing the TBI patient [10••]. Advanced neuroimaging techniques have shown promise in characterizing injury types better than conventional techniques. Hemorrhagic lesions associated with diffuse axonal injury are much more evident on susceptibility-weighted imaging [11]. Magnetic resonance spectroscopy is able to measure regional metabolic profiles in cerebral tissue, providing important functional data about the integrity of the tissue and thus offering early prognostic information [12]. Diffusion-weighted imaging, which is based on differences in diffusion of water molecules within the brain tissue, is extremely sensitive in the early detection of ischemic injury. Diffusion tensor imaging is a newer form of diffusion-weighted MRI that better evaluates the integrity of white-matter fiber tracts and thus can pick up white-matter abnormalities when conventional imaging appears normal [13].

Another area of expanding clinical interest is the use of biomarkers in cerebrospinal fluid (CSF), extracellular fluid (ECF), serum, and urine as tools for injury detection and prognostication. Most of the biomarkers that have been studied are protein mediators of the injury response, cellular damage, or cellular death, such as alpha II-spectrin, cytochrome c, myelin basic protein, neuron-specific enolase, and S100B [14–16]. Some of the questions regarding biomarkers involve their accessibility and specificity. Serum and urine levels may be contaminated by systemic (noncerebral) injury processes, but obtaining CSF or ECF levels is more invasive. CSF and ECF samples also depend on the location of sampling and factors that affect absolute protein values [17].

Treatment

Lifestyle

- Education is important in preventing TBI. Laws requiring seat belts, car seats, and helmets have been proven to significantly decrease the number and severity of TBIs [18]. Well-child visits at the pediatrician's office are an excellent setting in which to discuss preventive methods and anticipatory guidance. Similar instructions should be provided to families after emergency department visits or at discharge after a hospital admission.
- These instructions should include 1) the importance of using car seats and booster seats appropriate for the child's age and weight; 2) the correct placement of car seats for babies in the back seat, facing the rear of the car; 3) the use of helmets during bicycle riding, rollerblading, skiing,

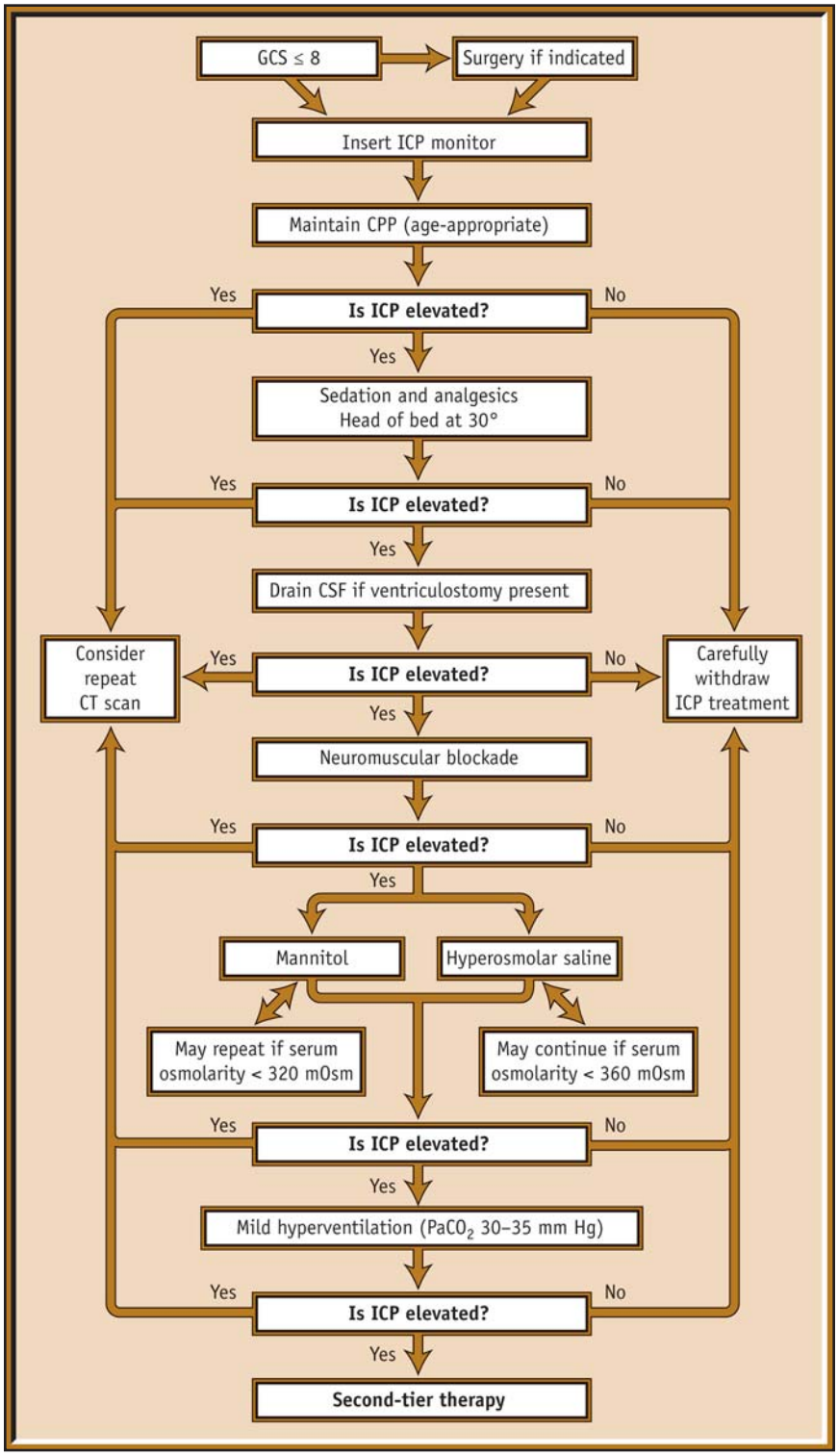

Figure 1. Algorithm for first-tier management of elevated intracranial pressure (ICP) in children following severe traumatic brain injury. CPP—cerebral perfusion pressure; CSF—cerebrospinal fluid; GCS—Glasgow Coma Scale. (*Adapted from* Adelson et al. [7].)

and other sports activities with a significant risk of head injury, including contact sports; and 4) the dangers of drug and alcohol use during driving or recreational activities such as skiing and swimming.

Pharmacologic treatment

- Medication use in TBI consists of two approaches, one specific to treating increased ICP, and one using medications in a supportive manner.

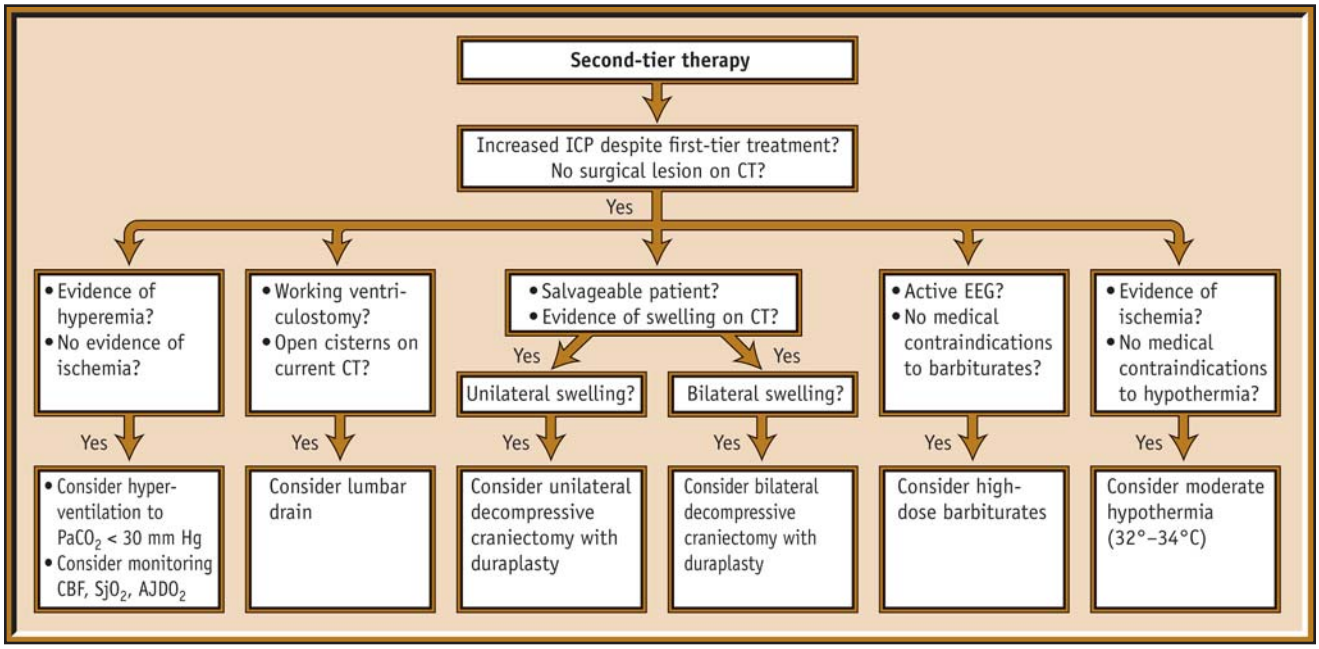

Figure 2. Algorithm for second-tier management of elevated intracranial pressure (ICP) in children following severe traumatic brain injury, showing options for treatment of increased ICP intractable to first-tier interventions. $AJDO_2$—arterial–jugular venous difference in oxygen content; CBF—cerebral blood flow; EEG—electroencephalogram; SjO_2—jugular venous oxygen saturation. (*Adapted from* Adelson et al. [7].)

Hyperosmolar therapy

- Hyperosmolar therapy is a first-tier therapy [19, Class II–III] used after initiating measures of ICP control such as elevation of the head of the bed, sedation, analgesia, CSF drainage, and neuromuscular blockade. Because of a lack of sufficient evidence, there are no standards regarding hyperosmolar therapy, but both mannitol and hypertonic saline have been used effectively in lowering ICP [20].
- In essence, hyperosmolar therapy causes movement of fluid from intracellular space into the extracellular space. This action results in volume loss of the brain tissue with subsequent decrease in ICP [21]. Osmotic agents are also thought to cause an increase in blood pressure (increased intravascular volume), thus leading to autoregulatory vasoconstriction with a resultant decrease of the cerebral blood volume. Both mannitol and hypertonic saline decrease blood viscosity by hemodilution, reducing the red blood cell volume and the rigidity of red blood cell membranes, further helping to lower cerebral blood volume [22]. Animal studies have also shown evidence that both mannitol and hypertonic saline have some antioxidant activity in TBI [23].

Mannitol

	Mannitol is a large sugar molecule, which acts as an osmotic agent. One of the important properties of mannitol is that it remains extracellular and does not cross the blood-brain barrier, so it extracts both intracellular and interstitial fluid.
Standard dosage	0.25–1 g/kg intravenously every 4–6 hours.
Contraindications	Caution should be exercised if serum osmolarity is 320 mOsm or higher.
Main side effects	Forced diuresis can occur; without careful volume repletion, the result can be hypovolemia and hemodynamic instability. Also, mannitol can potentially cross the blood-brain barrier if the vasculature is not intact, causing rebound intracranial hypertension [20].
Special points	A Foley catheter is necessary because of diuresis.

Hypertonic saline

	Although there are no standards regarding the concentration, dose, and timing of hypertonic saline use, it remains a commonly used adjuvant therapy to treat increased ICP. Hypertonic saline does not cause diuresis, so the intracellular and interstitial volumes within the vascular compartment are maintained.
Standard dosage	The published guidelines suggest a dosing range from 0.1 to 1.0 mL/kg per hour of 3% saline [19]. Peterson et al. [24] reported that a similar dosage of 11 to 27 mL/kg per day was well tolerated, and that the mortality rate was significantly lower than predicted from the Trauma and Injury Severity Score (TRISS).
Main side effects	Rebound intracranial hypertension may result from rapid correction of the hyperosmolar state. Pontine myelinolysis or renal failure is a theoretical risk, but these are not limiting problems in practice.
Special point	Serum osmolarity levels of up to 360 mOsm are well tolerated [19].

Supportive medications

Phenytoin/fosphenytoin

	These medications are used as anticonvulsants and for acute seizure prophylaxis.
Standard dosage	15–20 mg/kg intravenously as a loading dose, then 5 mg/kg per day in two divided doses for maintenance. When used for prophylaxis, these drugs should be administered for only the first 7 days [25].
Contraindications	Hypersensitivity to phenytoin or other hydantoins, heart block, sinus bradycardia.
Main drug interactions	May interfere with metabolism and protein binding of many drugs.
Side effects	Acute adverse effects include hemodynamic instability and skin rash.
Special points	May cause skin necrosis at the intravenous site, so avoid intravenous administration in small veins. Administer slowly.

Lidocaine

	Lidocaine is used to blunt cough and the gag reflex.
Standard dosage	0.5–1 mg/kg per dose intravenously or via the endotracheal tube; do not repeat within 2 hours. The maximum dose is 4.5 mg/kg per dose.
Contraindications	Stokes-Adams attacks, heart block.
Main drug interactions	May affect metabolism of various drugs. Amiodarone may decrease metabolism of lidocaine.
Main side effects	Hypotension, asystole, seizures.
Special points	Do not use lidocaine mixed with epinephrine. Use extreme caution in patients with hepatic disease, heart failure, atrial fibrillation, or heart block.

Pentobarbital

	Pentobarbital is used to induce barbiturate coma to control intractable ICP or seizures. It may also reduce cerebral metabolic rates and confer neuroprotective qualities. Use of barbiturates is a second-tier intervention for control of ICP.
Standard dosage	5–10 mg/kg intravenously over 1 to 2 hours, then 1–3 mg/kg per hour as an infusion to achieve and maintain burst suppression on electroencephalography (EEG). Titration to burst suppression is recommended, as it results in maximal reduction of cerebral metabolism and blood flow while preserving systemic arterial pressure and cardiac output [26]. Very young children and infants may be more prone to these systemic side effects.
Contraindications	Hypersensitivity to barbiturates, marked liver dysfunction, or latent porphyria.

Main drug interactions	May increase the metabolism and protein binding of multiple drugs.
Main side effects	Respiratory depression, hemodynamic instability, thrombocytopenia, Stevens-Johnson syndrome.
Special points	May cause hemodynamic instability requiring inotropic and pressor support. Requires continuous EEG monitoring.

Epinephrine

	Epinephrine is used to support hemodynamics, and also may be used to increase mean arterial blood pressure to increase cerebral perfusion pressure (CPP). Improvement of the CPP depends on intact autoregulation, and when autoregulation is disrupted, increasing the mean arterial pressure could be detrimental. Impaired autoregulation can be assessed clinically by observing parallel movement of the ICP and blood pressure, which happens because the cerebral blood vessels lose the ability to constrict and maintain a stable blood flow. Therefore, as the arterial blood pressure increases, the cerebral blood volume and ICP passively increase. The use of transcranial Doppler to measure the autoregulatory index is a newer alternative to allow more quantitative assessment of autoregulation [27].
Standard dosage	0.05–1 mcg/kg per minute as a continuous intravenous infusion; titrate to effect.
Contraindications	Cardiac arrhythmias, hypersensitivity to epinephrine. Use with caution in patients with diabetes or tachycardia.
Main drug interactions	May enhance the effects of other sympathomimetics.
Special points	Must be administered via a central line.

Phenylephrine

	Phenylephrine is used to support hemodynamics and also may be used to increase mean arterial blood pressure to improve CPP in the setting of intact autoregulation, as discussed in the Epinephrine section.
Standard dosage	0.1–0.5 mcg/kg per minute as a continuous intravenous infusion; titrate to effect.
Contraindications	Pheochromocytoma, severe hypertension.
Main drug interactions	May enhance toxic effects of other sympathomimetics.
Main side effects	Tremors, reflex bradycardia.
Special points	Should be administered via a central line.

Interventional procedures

Intracranial pressure monitoring and cerebrospinal fluid drainage

	One of the most common questions that arises in taking care of patients with severe TBI is the optimal method of measuring ICP. As pointed out by the guidelines [28, Class III], there are insufficient data to create a standard for therapy. This problem is further complicated by a lack of data on optimal CPP, which is calculated by subtracting the ICP from the mean arterial pressure. Recently, Chambers and colleagues [29•] published age-specific thresholds but excluded patients under the age of 2 years.
Standard procedure	**Ventriculostomy** was the original mode of ICP monitoring [30•] and continues to be a common form of monitoring. A ventricular catheter is placed through a burr hole into a lateral ventricle, and CSF pressure is measured via a transducer. This system also allows for pressure wave form analysis. The main advantage of this system is that it allows therapeutic CSF drainage when ICP rises. Disadvantages include the possibility of CSF leak around the catheter site, hemorrhage along the catheter tract, or CSF infection, which subsequently limits the period of monitoring. There may also be difficulty with catheter placement if there is significant cerebral edema or midline shift. Lastly, if there is air within the ventriculostomy

system, it may create an airlock, rendering the measurement unreliable. **Intraparenchymal microsensors**, the most commonly used systems today, are very reliable [31]. Their major shortcoming is the inability to drain CSF if necessary. This system is placed via a burr hole into the brain parenchyma; some neurosurgeons prefer to place them on the uninjured side.

Contraindications Coagulopathy and thrombocytopenia are relative contraindications; both may be corrected prior to placement of these devices.

Complications The risks associated with direct ICP monitoring are shared between both approaches. The most concerning complications are hemorrhage and infection. Device failure is also possible, from surgical technique when placing the device or from accidental removal by the patient or a caregiver.

Special points The hemorrhagic complication rate with intraventricular catheter placement is higher (up to 15%) than with intraparenchymal devices [32]. Infection rates are also higher with intraventricular catheters (up to 5%), compared with about 2% with intraparenchymal devices [33]. In circumstances of intractable elevated ICP with a working ventriculostomy in place, open basal cisterns, and no major mass lesions or shift, the use of a **lumbar drain** is considered a treatment option [34], but this technique is not widely used.

Mechanical ventilation

As noted in the guidelines, the use of mild hyperventilation ($PaCO_2$ 30–35 mm Hg) is an optional therapy in the first-tier management of severe pediatric TBI, and aggressive hyperventilation ($PaCO_2$ < 30 mm Hg) is a second-tier therapeutic option [35, Class II].

Complications The most common complications are nosocomial pneumonia, tracheal irritation and excoriations due to frequent and aggressive suctioning, and accidental extubation. Overly aggressive hyperventilation may result in ischemic injury.

Special points Caution should be exercised when using hyperventilation, as it causes hypocapnia, which leads to vasoconstriction, which subsequently may lead to global or regional ischemia. When using more aggressive hyperventilation, monitoring of jugular venous oxygen saturation, arterial-venous oxygen difference, brain tissue oxygen, and/or cerebral blood flow (CBF) is recommended to identify ischemia, if present.

Like any other intubated patient in the intensive care unit (ICU), pediatric patients with severe TBI require frequent suctioning of the endotracheal tube to optimize gas exchange and prevent ventilator-associated pneumonia [36]. However, the act of suctioning induces the cough and gag reflex, which in turn increases the ICP and decreases CPP [37]. Instillation of lidocaine endotracheally will attenuate this response [38, Class II].

Surgery

Evacuation of mass lesions

Surgical intervention should play a major role in severe TBI if space-occupying lesions are compressing the brain and causing elevated ICP.

Decompressive craniectomy

Decompressive craniectomy is presented as a second-tier treatment option in the guidelines. Sahuquillo and Arikan [39•, Class II–III], in a Cochrane review, reported that, although there were insufficient data to determine the benefits of this therapy in adults, there was modest evidence for its effectiveness in pediatrics. In a randomized clinical trial of pediatric patients, Taylor and colleagues [40, Class II–III] reported more favorable outcomes in patients receiving decompressive craniectomy than in patients treated medically.

Standard procedure	Although there is still debate about the proper procedure, decompression is most often performed on the side ipsilateral to the more severe injury or space-occupying lesion. At times, bilateral craniectomies may be performed in the presence of significant global cerebral edema.
Complications	Complications of decompressive craniectomy include alterations of CSF dynamics leading to hydrocephalus, collection of subdural and subgaleal fluid [41], paradoxic herniation [42], and external brain tamponade as a result of subgaleal fluid collection [43]. More common complications include infections and surgical wound bleeding.
Contraindications	Severe coagulopathy may be considered a relative contraindication, as it could be corrected with blood products and replacement of procoagulation factors.

Assistive devices

CT scanning

CT is a critical assistive device for initial management and periodic reassessment of the pediatric patient with moderate to severe TBI. Initially a noncontrast head CT scan is essential to rule out a surgically treatable lesion. Subsequently, if the patient's clinical status deteriorates or ICP increases, CT should be part of the workup to ensure that delayed hemorrhage has not occurred. This procedure is incorporated into the algorithm accompanying the consensus guidelines (Fig. 1).

Continuous EEG

Continuous EEG (cEEG) increasingly is being used in the monitoring of critically ill patients of all ages in the ICU. It may be used to detect subclinical or subtle seizure activity and distinguish seizure from nonseizure episodes, to titrate barbiturate coma, to evaluate the level of sedation, and to monitor for ischemia. In studies of adults, the rate of subclinical seizures detected on cEEG ranged from 18% to 22% [44]. Improved methods of displaying these data help to make them more accessible to non–EEG-trained intensivists, but interpretation and intervention are best performed in consultation with pediatric neurologists.

Cerebral blood flow monitoring

Quantitative determination of CBF has long been performed with xenon CT scanning, but the use of this method in pediatric patients has been limited because of the radioisotope required [45]. Noninvasive measures using transcranial Doppler can give surrogate measures for CBF or the cerebral autoregulatory index and are beginning to be implemented in the study and management of pediatric patients with TBI [27].

Tissue oxygen monitoring

This modality uses a tissue oxygen sensor to give early warning of worsening cerebral ischemia in the vicinity of the probe. This device has been shown to be safe and may prove to be a helpful tool in treating pediatric patients with TBI [46]. One advantage of this technology is that it can give real-time readings of changes in tissue oxygenation. Disadvantages include the very focal nature of the tissue oxygen readings, the need for calibration of the device, and drift of the values over time.

Standard procedure	The fiberoptic device is placed surgically via a burr hole, generally within brain tissue that is free from overt injury. There is some controversy, however; it has been argued that the probe should be placed in "at-risk pericontusional tissue." The position of the probe can be verified by head CT.
Complications	Complications include infection and bleeding.
Contraindications	Severe coagulopathy may be a relative contraindication, but blood products and procoagulation factors can be administered to correct the problem.

MR imaging

As discussed in the Introduction, various modalities of MRI could be of significant benefit in patients whose clinical examination is not reflected in their CT findings, providing insight into underlying injury pathophysiology and additional prognostic information.

Other treatments

Hypothermia

In the face of intractable cerebral hypertension, induced hypothermia may also be used as a treatment option [47••]. Although the use of hypothermia in pediatric patients with TBI has been shown in some studies to reduce ICP [48] and to safely improve outcomes to some degree [49, Class II], a large multicenter study by Hutchison et al. [50•, Class I] recently reported that hypothermia increased mortality in pediatric patients with TBI and did not improve neurologic outcome. These conflicting results lead to significant controversy regarding the use of hypothermia in severe pediatric TBI. Before this controversy can be settled, certain questions need to be answered, such as the proper parameters for hypothermia treatment. In particular, the rate of rewarming may be important, because rapid rewarming has been reported to cause rebound increase of ICP [49, Class II]. Duration of hypothermia beyond 24 hours may also be desirable.

Posttraumatic seizure prophylaxis

Early posttraumatic seizures (EPTS) have been described as occurring within the first week after injury. Occurrence of EPTS may contribute to secondary injuries by increasing ICP, elevating cerebral metabolic demands, and causing hyperthermia. Studies have shown that prophylactic use of phenytoin may prevent EPTS but does not prevent the ensuing development of epilepsy [51, Class I]. Because EPTS are more common in younger patients [52], phenytoin prophylaxis for 1 week after injury is suggested by the guidelines [25, Class II–III]. It is important to keep in mind that antiepileptic medications may have particular toxicities in the immature brain. Multiple animal studies report increased apoptotic cell death [53], and some clinical pediatric studies [54] show abnormal cognitive development following treatment with anticonvulsant medications. Preclinical studies suggest that the newer antiepileptic medications topiramate and levetiracetam do not show this toxicity when used at therapeutic doses [55•].

Nutritional support

Adequate nutritional support is paramount in any critically injured pediatric patient. TBI may create a hypermetabolic state that not only affects the early phase of the injury but also may continue into the convalescent phase [56]. Currently, there are no recommended standards for an approach to nutrition in the pediatric population with TBI. The published guidelines suggest starting nutritional support by 72 hours and reaching full caloric replacement status by 7 days.

Tight glucose control has been shown to improve outcome in critically ill adult patients, including (but not limited to) patients with significant neurologic disease [57, Class I]. In animal models of TBI, hyperglycemia has been shown to worsen ischemic brain injury [58]. However, it has also been demonstrated that tight glucose control can lead to significant reductions in extracellular brain tissue glucose concentrations and relative hypoglycemia [59•, Class II–III].

Emerging therapies

- As articulated above, most standard therapies currently in use for pediatric TBI management lack solid Class I or Class II data. Future studies to strengthen these recommendations and provide age-dependent modifications are certainly warranted.
- Innovative analyses of continuous physiologic data (ICP, CPP) have resulted in improved age-dependent critical thresholds as measures for therapeutic intervention [29•]. In addition, algorithms are being developed that may ultimately lead to individualized CPP thresholds to help direct ICU management of elevated ICP [60].
- Because indiscriminate administration of standard anticonvulsants may be toxic to the developing brain [53] and because subclinical seizures may be missed, targeted seizure prophylaxis aided by cEEG monitoring [44] may provide a valuable strategy to detect and treat seizure-related secondary injury. In addition, the use of less developmentally toxic anticonvulsants after acute brain injuries is only beginning to be studied.

Disclosure

No potential conflicts of interest relevant to this article were reported.

References and Recommended Reading

Papers of particular interest, published recently,
have been highlighted as
- • Of importance
- •• Of major importance

1. Toga AW, Thompson PM, Sowell ER: **Mapping brain maturation.** *Trends Neurosci* 2006, **29:**148–159.
2. Centers for Disease Control and Prevention: **Traumatic brain injury in the United States: assessing outcomes in children.** Available at http://www.cdc.gov/ncipc/tbi/tbi_report/index.htm. Accessed August 18, 2009.
3. Barlow KM, Thomson E, Johnson D, et al.: **Late neurologic and cognitive sequelae of inflicted traumatic brain injury in infancy.** *Pediatrics* 2005, **116:**e174–e185.
4. Suh DY, Davis PC, Hopkins KL, et al.: **Nonaccidental pediatric head injury: diffusion-weighted imaging findings.** *Neurosurgery* 2001, **49:**309–318.
5. Mayer TA, Walker ML: **Pediatric head injury: the critical role of the emergency physician.** *Ann Emerg Med* 1985, **14:**1178–1184.
6. Michaud LJ, Rivara FP, Grady MS, et al.: **Predictors of survival and severity of disability after severe brain injury in children.** *Neurosurgery* 1992, **31:**254–264.
7. Adelson PD, Bratton SL, Carney NA, et al.: **Guidelines for the acute medical management of severe traumatic brain injury in infants, children, and adolescents.** *Pediatr Crit Care Med* 2003, **4:**S1–S75.
8. Keenan HT, Nocera M, Bratton SL: **Frequency of intracranial pressure monitoring in infants and young toddlers with traumatic brain injury.** *Pediatr Crit Care Med* 2005, **6:**537–541.
9. Morris KP, Forsyth RJ, Parslow RC, et al.: **Intracranial pressure complicating severe traumatic brain injury in children: monitoring and management.** *Intensive Care Med* 2006, **32:**1606–1612.
10. •• Saatman KE, Duhaime AC, Bullock R, et al.: **Classification of traumatic brain injury for targeted therapies.** *J Neurotrauma* 2008, **25:**719–738.

The concept of moving toward a pathophysiologic classification of TBI is introduced. Acute neuroimaging can help with this classification and may ultimately lead to treatments based upon underlying neurobiologic mechanisms.

11. Tong KA, Ashwal S, Holshouser BA, et al.: **Diffuse axonal injury in children: clinical correlation with hemorrhagic lesions.** *Ann Neurol* 2004, **56:**36–50.
12. Babikian T, Freier MC, Ashwal S, et al.: **MR spectroscopy: predicting long-term neuropsychological outcome following pediatric TBI.** *J Magn Reson Imaging* 2006, **24:**801–811.
13. Wilde EA, McCauley SR, Hunter JV, et al.: **Diffusion tensor imaging of acute mild traumatic brain injury in adolescents.** *Neurology* 2008, **70:**948–955.
14. Berger RP, Adelson PD, Richichi R, et al.: **Serum biomarkers after traumatic and hypoxemic brain injuries: insight into the biochemical response of the pediatric brain to inflicted brain injury.** *Dev Neurosci* 2006, **28:**327–335.
15. Cardali S, Maugeri R: **Detection of alphaII-spectrin and breakdown products in humans after severe traumatic brain injury.** *J Neurosurg Sci* 2006, **50:**25–31.
16. Satchell MA, Lai Y, Kochanek PM, et al.: **Cytochrome c, a biomarker of apoptosis, is increased in cerebrospinal fluid from infants with inflicted brain injury from child abuse.** *J Cereb Blood Flow Metab* 2005, **25:**919–927.
17. Shore PM, Thomas NJ, Clark RS, et al.: **Continuous versus intermittent cerebrospinal fluid drainage after severe traumatic brain injury in children: effect on biochemical markers.** *J Neurotrauma* 2004, **21:**1113–1122.

18. Wesson DE, Stephens D, Lam K, et al.: **Trends in pediatric and adult bicycling deaths before and after passage of a bicycle helmet law.** *Pediatrics* 2008, **122:**605–610.
19. Adelson PD, Bratton SL, Carney NA, et al.: **Guidelines for the acute medical management of severe traumatic brain injury in infants, children, and adolescents. Chapter 11. Use of hyperosmolar therapy in the management of severe pediatric traumatic brain injury.** *Pediatr Crit Care Med* 2003, **4:**S40–S44.
20. Diringer MN, Zazulia AR: **Osmotic therapy: fact and fiction.** *Neurocrit Care* 2004, **1:**219–233.
21. Donato T, Shapira Y, Artru A, et al.: **Effect of mannitol on cerebrospinal fluid dynamics and brain tissue edema.** *Anesth Analg* 1994, **78:**58–66.
22. Burke AM, Quest DO, Chien S, et al.: **The effects of mannitol on blood viscosity.** *J Neurosurg* 1981, **55:**550–553.
23. Yilmaz N, Dulger H, Kiymaz N, et al.: **Activity of mannitol and hypertonic saline therapy on the oxidant and antioxidant system during the acute term after traumatic brain injury in the rats.** *Brain Res* 2007, **1164:**132–135.
24. Peterson B, Khanna S, Fisher B, et al.: **Prolonged hypernatremia controls elevated intracranial pressure in head-injured pediatric patients.** *Crit Care Med* 2000, **28:**1136–1143.
25. Adelson PD, Bratton SL, Carney NA, et al.: **Guidelines for the acute medical management of severe traumatic brain injury in infants, children, and adolescents. Chapter 19. The role of anti-seizure prophylaxis following severe pediatric traumatic brain injury.** *Pediatr Crit Care Med* 2003, **4:**S72–S75.
26. Kassell NF, Hitchon PW, Gerk MK, et al.: **Alterations in cerebral blood flow, oxygen metabolism, and electrical activity produced by high dose sodium thiopental.** *Neurosurgery* 1980, **7:**598–603.
27. Vavilala MS, Lee LA, Boddu K, et al.: **Cerebral autoregulation in pediatric traumatic brain injury.** *Pediatr Crit Care Med* 2004, **5:**257–263.
28. Adelson PD, Bratton SL, Carney NA, et al.: **Guidelines for the acute medical management of severe traumatic brain injury in infants, children, and adolescents. Chapter 6. Threshold for treatment of intracranial hypertension.** *Pediatr Crit Care Med* 2003, **4:**S25–S27.
29.• Chambers IR, Jones PA, Lo TY, et al.: **Critical thresholds of intracranial pressure and cerebral perfusion pressure related to age in paediatric head injury.** *J Neurol Neurosurg Psychiatry* 2006, **77:**234–240.

This paper extends the rationale of delineating and following age-specific physiological thresholds to guide management of pediatric TBI.

30.• Wiegand C, Richards P: **Measurement of intracranial pressure in children: a critical review of current methods.** *Dev Med Child Neurol* 2007, **49:**935–941.

This is a comprehensive review of methods, physiology, utility, and complications of ICP monitoring in children.

31. Gelabert-Gonzalez M, Ginesta-Galan V, Sernamito-Garcia R, et al.: **The Camino intracranial pressure device in clinical practice. Assessment in a 1000 cases.** *Acta Neurochir (Wien)* 2006, **148:**435–441.
32. Rossi S, Buzzi F, Paparella A, et al.: **Complications and safety associated with ICP monitoring: a study of 542 patients.** *Acta Neurochir Suppl* 1998, **71:**91–93.
33. Pople IK, Muhlbauer MS, Sanford RA, et al.: **Results and complications of intracranial pressure monitoring in 303 children.** *Pediatr Neurosurg* 1995, **23:**64–67.
34. Adelson PD, Bratton SL, Carney NA, et al.: **Guidelines for the acute medical management of severe traumatic brain injury in infants, children, and adolescents. Chapter 10. The role of cerebrospinal fluid drainage in the treatment of severe pediatric traumatic brain injury.** *Pediatr Crit Care Med* 2003, **4:**S38–S39.
35. Adelson PD, Bratton SL, Carney NA, et al.: **Guidelines for the acute medical management of severe traumatic brain injury in infants, children, and adolescents. Chapter 12. Use of hyperventilation in the acute management of severe pediatric traumatic brain injury.** *Pediatr Crit Care Med* 2003, **4:**S45–S48.
36. Young PJ, Ridley SA: **Ventilator-associated pneumonia. Diagnosis, pathogenesis and prevention.** *Anaesthesia* 1999, **54:**1183–1197.
37. Gemma M, Tommasino C, Cerri M, et al.: **Intracranial effects of endotracheal suctioning in the acute phase of head injury.** *J Neurosurg Anesthesiol* 2002, **14:**50–54.
38. Bilotta F, Branca G, Lam A, et al.: **Endotracheal lidocaine in preventing endotracheal suctioning-induced changes in cerebral hemodynamics in patients with severe head trauma.** *Neurocrit Care* 2008, **8:**241–246.
39.• Sahuquillo J, Arikan F: **Decompressive craniectomy for the treatment of refractory high intracranial pressure in traumatic brain injury.** *Cochrane Database Syst Rev* 2006, CD003983.

This meta-review of decompressive craniectomy for management of elevated intracranial pressure following TBI concludes that the strongest evidence in favor of this procedure comes from a pediatric study.

40. Taylor A, Butt W, Rosenfeld J, et al.: **A randomized trial of very early decompressive craniectomy in children with traumatic brain injury and sustained intracranial hypertension.** *Childs Nerv Syst* 2001, **17:**154–162.
41. Aarabi B, Hesdorffer DC, Ahn ES, et al.: **Outcome following decompressive craniectomy for malignant swelling due to severe head injury.** *J Neurosurg* 2006, **104:**469–479.
42. Oyelese AA, Steinberg GK, Huhn SL, et al.: **Paradoxical cerebral herniation secondary to lumbar puncture after decompressive craniectomy for a large space-occupying hemispheric stroke: case report.** *Neurosurgery* 2005, **57:**E594.
43. Akins PT, Guppy KH: **Sinking skin flaps, paradoxical herniation, and external brain tamponade: a review of decompressive craniectomy management.** *Neurocrit Care* 2008, **9:**269–276.
44. Vespa P: **Continuous EEG monitoring for the detection of seizures in traumatic brain injury, infarction, and intracerebral hemorrhage: "to detect and protect."** *J Clin Neurophysiol* 2005, **22:**99–106.
45. Muizelaar JP, Ward JD, Marmarou A, et al.: **Cerebral blood flow and metabolism in severely head-injured children. Part 2: Autoregulation.** *J Neurosurg* 1989, **71:**72–76.
46. Stiefel MF, Udoetuk JD, Storm PB, et al.: **Brain tissue oxygen monitoring in pediatric patients with severe traumatic brain injury.** *J Neurosurg* 2006, **105:**281–286.
47.•• Polderman KH: **Induced hypothermia and fever control for prevention and treatment of neurological injuries.** *Lancet* 2008, **371:**1955–1969.

This exhaustive review of the use of hypothermia and fever control for neuroprotection following acute neurologic injuries identifies critical treatment variables that may affect trials of efficacy for hypothermia, including systemic complications and rebound intracranial hypertension.

48. Biswas AK, Bruce DA, Sklar FH, et al.: **Treatment of acute traumatic brain injury in children with moderate hypothermia improves intracranial hypertension.** *Crit Care Med* 2002, **30:**2742–2751.
49. Adelson PD, Ragheb J, Kanev P, et al.: **Phase II clinical trial of moderate hypothermia after severe traumatic brain injury in children.** *Neurosurgery* 2005, **56:**740–754.
50.• Hutchison JS, Ward RE, Lacroix J, et al.: **Hypothermia therapy after traumatic brain injury in children.** *N Engl J Med* 2008, **358:**2447–2456.

This is the largest currently published series of hypothermia for neuroprotection after pediatric TBI; the authors concluded that hypothermia was associated with worse outcomes when implemented by this protocol, but with several methodologic caveats.

51. Temkin NR, Dikmen SS, Wilensky AJ, et al.: **A randomized, double-blind study of phenytoin for the prevention of post-traumatic seizures.** *N Engl J Med* 1990, **323:**497–502.
52. Annegers JF, Grabow JD, Groover RV, et al.: **Seizures after head trauma: a population study.** *Neurology* 1980, **30:**683–689.
53. Bittigau P, Sifringer M, Genz K, et al.: **Antiepileptic drugs and apoptotic neurodegeneration in the developing brain.** *Proc Natl Acad Sci U S A* 2002, **99:**15089–15094.

54. Dessens AB, Cohen-Kettenis PT, Mellenbergh GJ, et al.: **Association of prenatal phenobarbital and phenytoin exposure with small head size at birth and with learning problems.** *Acta Paediatr* 2000, **89:**533–541.

55.• Kaindl AM, Asimiadou S, Manthey D, et al.: **Antiepileptic drugs and the developing brain.** *Cell Mol Life Sci* 2006, **63:**399–413.

This preclinical review shows dosage–toxicity graphs for many of the common anticonvulsants used for acute posttraumatic prophylaxis and also indicates that some newer anticonvulsants may best protect the young brain from medication-induced apoptosis.

56. Pepe JL, Barba CA: **The metabolic response to acute traumatic brain injury and implications for nutritional support.** *J Head Trauma Rehabil* 1999, **14:**462–474.

57. van den Berghe G, Wouters P, Weekers F, et al.: **Intensive insulin therapy in critically ill patients.** *N Engl J Med* 2001, **345:**1359–1367.

58. Cherian L, Goodman JC, Robertson CS: **Hyperglycemia increases brain injury caused by secondary ischemia after cortical impact injury in rats.** *Crit Care Med* 1997, **25:**1378–1383.

59.• Vespa P, Boonyaputthikul R, McArthur DL, et al.: **Intensive insulin therapy reduces microdialysis glucose values without altering glucose utilization or improving the lactate/pyruvate ratio after traumatic brain injury.** *Crit Care Med* 2006, **34:**850–856.

These observations suggest that tight systemic glucose control using insulin may have deleterious consequences in TBI patients by causing critical reductions in intracerebral glucose concentrations.

60. Brady KM, Lee JK, Kibler KK, et al.: **Continuous time-domain analysis of cerebrovascular autoregulation using near-infrared spectroscopy.** *Stroke* 2007, **38:**2818–2825.