Traumatic Brain Injury: A Primer for Primary Care Physicians

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Accidents are the leading cause of morbidity and mortality in children greater than 1 year of age and a major public health issue confronting health care providers. Traumatic Brain Injury (TBI) is the number one cause of death due to trauma in pediatric patients, and each year in the United States approximately 400,000 children suffer significant head injury. Of those, 30,000 require hospital admission, and more than 3000 children succumb to their injuries. To put these numbers into perspective, TBI will take the lives of 6 times the number of US children who will die from HIV/AIDS and 20 times the number of those who will suffer a fatal asthma attack.[1] In addition, TBI accounts for approximately 10 billion dollars per year in US health care spending. Unfortunately, there appears to be a noticeable disparity in care and outcome between children with health insurance and those without. Tilford and colleagues, in a study on hospitalization rates and outcomes for children with TBI, found that being uninsured conferred an increased mortality risk of 20%.[2] The reasons cited include delay in seeking treatment, decreased access to prehospital treatment, and less aggressive in-hospital treatment (as measured by utilization of invasive intracranial pressure monitoring).

Although the causes of head trauma vary by age (Table 1), in all age groups males are nearly twice as likely to experience head trauma as females. Currently, the three leading causes of serious head injury in children aged 0 to 14 years are falls, motor vehicle accidents, and intentional injury or assault. In children less than 1 year old, inflicted head injury continues to be a leading cause of death due to trauma and a significant source of morbidity in survivors (see section on *Shaken-baby Syndrome*). Adolescent males sustain the most injuries due to firearms of any age group, although motor vehicles continue to be the most frequent cause of injury.

Despite recent advances in our understanding of the mechanisms and treatment of TBI, close to one-third of children with serious head injuries will suffer permanent, debilitating neurologic complications and require prolonged inpatient rehabilitation and chronic care. The financial and emotional burdens these children place on the family, the health care system, and society cannot be overstated.

Without a doubt, the most effective approach to minimizing the impact of serious head injury in children is prevention, and according to latest figures, about 80% of pediatric head trauma is preventable.[3] To wit, the incidence of serious head injuries associated with moving vehicles, including bicycles, has slowly begun to decline since the introduction of primary prevention measures such as mandatory infant and toddler car seats, lower highway speed limits, automobile airbags, and bicycle helmet laws. That being said, large-scale, well-conducted research exploring the mechanisms and management of TBI in children is desperately needed.

Classification of Brain Injury

TBI is most often classified as mild, moderate, or severe, based on the Glasgow Coma Score (GCS) at presentation (Table 2). The utility of this scoring system in children is the subject of some debate for the two following reasons: (1) the initial GCS may be less prognostic in children than the score obtained 24 hours after the original injury; and (2) the validity of scores that rely on cognitive activities too sophisticated for infants and toddlers to perform (ie, localizing pain, verbal response) remains somewhat dubious. An alter-

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TABLE 1. Leading causes of pediatric HT by age and severity

Age (y)	All HT	Severe HT
0-1	Falls	Inflicted HT
2-14	Falls	Falls; MVA
15-24	MVA	MVA/Assault (FA)

*Adapted from: National Center for Injury Prevention and Control, Division of Injury and Disability Outcomes and Programs. TBI in the United States: Emergency Dept. Visits, Hospitalizations & Deaths. Centers for Disease Control and Prevention, October 2004.
HT, head trauma; MVA, motor vehicle accident; FA, firearms.

TABLE 2. The Glasgow Coma Scale and TBI classification

Adult/Standard	Score	Pediatric*
Eye opening		
Spontaneous	4	Spontaneous
To speech	3	To speech
To pain	2	To pain
None	1	None
Best verbal response		
Oriented	5	Coos, babbles
Confused	4	Irritable, cries
Inappropriate words	3	Cries to pain
Incomprehensible sounds	2	Moans to pain
None	1	None
Best motor response		
Obeys commands	6	Spontaneous movement
Localizes pain	5	Withdraws to touch
Withdraws to pain	4	Withdraws to pain
Abnormal flexion	3	Abnormal flexion
Extensor response	2	Abnormal extension
None	1	None

	Mild	Moderate	Severe
GCS	13-15	9-12	≤8

*Adapted from James HE. Neurologic evaluation and support in the child with an acute brain insult. Pediatr Ann 1986;15:16-22.

native system appropriate for infants and children has been developed,[4] but has not been tested extensively for accuracy and utility and has not been widely adopted.

Pathophysiology

Three basic tenets of normal brain physiology form the conceptual groundwork for our knowledge of the profoundly injured brain:

(1) The **Monro-Kellie Hypothesis** states that the skull is a rigid sphere occupied by noncompressible tissue components. The total volume in the cranial vault is equal to the sum of the volumes of the brain parenchyma, blood, and cerebral spinal fluid (CSF), and under normal conditions, is tightly controlled.[5] An increase in any one of these components will increase the total volume and therefore the pressure in the brain. Under normal physiologic conditions, constant intracranial volume is maintained by a variety of mechanisms including (1) alterations in the production and resorption of CSF; (2) shunting of CSF to the spinal subarachnoid space; and (3) shunting of venous blood away from areas of increased flow. Any acute change in intracranial volume due to "spontaneous, traumatic, or iatrogenic violation of the dura" may result in compression of the brain and increase the risk of herniation through the foramen magnum, or of leakage of CSF into the skull or spinal canal.[5]

(2) According to **Rosner's Conjecture**, brain injury occurs largely due to ischemia that results from "systemic and cerebral factors."[6]; Systemic factors include hypotension, hypoxemia, fever, hyperglycemia, and hypothermia. Cerebral factors include elevated intracranial pressure, decreased cerebral perfusion, edema, space-occupying lesions, and seizures. All of these factors must be addressed and treated in the management of TBI.

(3) **Cerebral autoregulation:** Under ordinary conditions, cerebral blood flow is maintained at constant levels when mean arterial pressures range between 50 and 150 mmHg. In patients with significant head trauma, this important function may be disturbed, either transiently or permanently, thus allowing for *pressure-dependent cerebral blood flow*. This pathologic state, in which fluctuations in blood pressure may lead to rapid alterations in cerebral blood flow, may result in permanent damage to previously healthy areas of the brain.

Currently, the most widely accepted conceptual model divides TBI into *primary* (largely irreversible) and *secondary* (potentially reversible) injury. Primary injury is the actual mechanical damage that occurs at the time of the inciting event. The primary injury may be due to linear or unidirectional *coup/contra-coup* forces, in which case parenchymal contusions and punctuate hemorrhages may result; or to rotational, nonlinear forces that disrupt axonal pathways in deeper brain structures. This *diffuse axonal injury* occurs when rapid acceleration and deceleration causes shearing of delicate neuronal pathways in the basal ganglia, thalamus, and corpus callosum, as these

structures move with a different momentum than more superficial areas of the brain.

Secondary injury begins within minutes of the primary insult as a result of respiratory, hemodynamic, and cellular disturbances. Traditionally, it was attributed largely to swelling that occurred as a consequence of iatrogenic interventions; however, recent advances in our understanding of the biomolecular events that occur in the brain after trauma suggest that the pathophysiology of secondary brain injury is far more complex. Alterations in vital biochemical pathways likely trigger destructive enzymatic cascades and upset the delicate balance usually maintained under physiologic conditions. Unfortunately, new insights into the molecular mechanisms of secondary brain injury have not thus far produced any magic bullets, and the focus of current treatment in patients with severe TBI continues to be on close monitoring, rapid and aggressive response to treatable problems as they arise, and impeccable supportive care.

Results from animal studies suggest that secondary injury involves four major mechanisms, as follows: (1) *ischemia* that results from vasoconstriction and alterations in cerebral blood flow as production and release of excitatory amino acids are increased; (2) *necrosis* and *apoptosis*; (3) *cerebral swelling* and *edema formation*; and (4) *inflammation,* which appears to be especially important in children. Each of these processes offers important potential targets for new therapies, and research involving interventions that may alter or reverse them is currently being conducted.

Mechanisms of Secondary Brain Injury

Cerebral Blood Flow Dysregulation

Under ordinary conditions, cerebral blood flow is maintained at constant levels when mean arterial pressure remains between 50 and 150 mmHg. This is termed *cerebral autoregulation*. There is evidence to suggest that, in some patients with severe TBI, this neuroprotective mechanism may be transiently or permanently disrupted,[7,8] leading to either ischemia (from inadequate cerebral blood flow during episodes of hypotension) or hyperemia (when blood pressures spike to dangerously high levels). Either of these extreme conditions may damage or destroy both injured and healthy brain tissue. Current evidence also suggests that at baseline cerebral blood flow is higher in children than in adults. This explains why the current paradigm for the management of early secondary TBI stresses the *prevention of hypoperfusion*, which is all too common during the first 24 hours after severe injury and is associated with poor neurologic outcome.[9] Inadequate perfusion is multifactorial in etiology, most often resulting from systemic hypotension, either relative or absolute, and from unchecked vasoconstriction of cerebral blood vessels. Unfortunately, cerebral perfusion often falls to its lowest levels just at the time when metabolic demands of the brain are at their greatest, and this disparity between supply and demand heightens the potential for ischemia and poor neurologic outcome.

Experimental models of TBI have shown that levels of nitric oxide, an endogenous vasodilator, may be depressed early after injury, while levels of endothelin-1, a potent cerebral vasoconstrictor, are markedly increased.[7,10] This suggests a shift in normal endogenous vasoregulation toward increased vascular tone. Analyses of CSF early after injury also reveal increased amounts of adrenomedullin and procalcitonin, both potent vasodilators[11] that likely represent compensatory responses to ischemia. These findings suggest that early and aggressive treatment of hypotension, along with the use of pharmacologic agents that promote cerebral vasodilation, may lead to improved functional outcome. To the best of this author's knowledge, no clinical trials utilizing cerebral vasodilators have yet been undertaken in adults or children.

Excitotoxicity

Excitotoxicity is the process by which supraphysiologic levels of excitatory amino acids cause cellular injury in the brain.[7,12] Excitatory amino acids are released in response to brain injury, and the highest levels are seen in infants after inflicted brain injury.[7,13] The binding of these neurotransmitters to their receptors sets into motion a series of reactions that may damage the blood-brain barrier and lead to neuronal swelling, edema, necrosis, and programmed cell death.

Glutamate is the most widely studied excitatory amino acid. The binding of glutamate to receptors on multiple brain cells alters both extracellular and intracellular sodium and calcium concentrations. Changes in sodium concentration may cause neuronal swelling, while alterations in intracellular calcium promote upregulation of lytic enzymes (proteases, lipases, and endonucleases) and reactive oxygen and nitrogen species. The net effect of this change in chemical balance

is damage to neuronal cellular machinery. In fact, there is now evidence to suggest that brain-injured patients with excessively high levels of CSF glutamate may be at greater risk of dying from their injury or may have a worse neurologic outcome if they survive.[7,12] However, in experimental animal models where production and release of *all* excitatory amino acids were *completely* blocked, the outcome was also poor, suggesting that the presence of low levels of excitatory amino acids may be somewhat protective in TBI.[7]

Though not yet fully understood, studies also suggest that *adenosine* may be an important neuroprotective agent in patients with severe TBI. Proposed mechanisms include decreasing intracellular calcium conductance and cerebral vasodilation. Furthermore, the binding of adenosine to specific receptors in the brain leads to increased levels of *vascular endothelial growth factor* in the CSF, which may confer additional neuroprotection.[14,15] Thus far, therapeutic interventions aimed specifically at blocking the production and activity of excitatory amino acids have not proven successful in clinical trials, although the timing of this intervention may be critical, and studies to date may have given these agents too late.[7,16]

Cerebral Swelling

By far, the best studied mechanism of secondary brain injury, swelling, contributes to intracranial hypertension, brain ischemia, and herniation. The importance of cerebral swelling in the pathogenesis of TBI in children is affirmed by the emphasis placed on the prevention and aggressive control of swelling and elevated intracranial pressure in current treatment regimens. Cerebral swelling is a complex process which is multifactorial in etiology, with edema and increased cerebral blood volume being two important contributing factors. The edema seen in patients after TBI can be *vasogenic*, *cytotoxic*, or a combination of the two. Cytotoxic edema occurs with increases in cellular osmotic load that result from breakdown of injured neurons, while vasogenic edema involves disruption of the blood-brain barrier and leakage of damaging substances into the brain. The blood-brain barrier seems to be more vulnerable in young children than in adults, and hypotension, hypoxemia, and the release of toxic metabolites by injured brain cells all serve to further weaken this essential protective structure.

The pattern of cerebral edema seen in children after TBI differs from that seen in adults. Whereas adults tend to have focal areas of edema and swelling, the edema in children is more diffuse. Explanations for this difference include increased susceptibility of the blood-brain barrier in children to disruption by free radicals, cytokines, and other vasoactive mediators, as well as increased sensitivity to inadequate oxygen supply, as occurs with hypotension and hypoperfusion.

Increased brain volume also appears to be an important mechanism in cerebral edema formation in children due to their increased cerebral blood flow at baseline. This may help to explain why treatments that emphasize aggressive control of intracranial pressure and cerebral swelling have yielded better outcomes in children.

Necrosis and Apoptosis

Both necrosis and apoptosis are evident in examination of the brains of patients with severe head injury. Mechanisms for both phenomena are currently being explored. Apoptosis is a complex, genetically regulated, enzyme-mediated process that disrupts DNA and leads to cell shrinkage, condensation, and death; whereas necrosis usually involves cellular swelling and lysis. Both processes are activated by a variety of triggers, including changes in cell membrane structure and function, activation of lytic enzymes (caspases and proteases), and *pro-apoptotic* proteins. Recent work suggests that apoptosis is triggered by both extrinsic and intrinsic cues. Extrinsic triggers include protein ligands that bind to cell-surface *death receptors* and ultimately lead to activation of an apoptotic cascade.[12,14] Intrinsic cues include DNA damage and other cellular triggers that signal mitochondria to initiate complex chemical reactions that lead to the creation of an *apoptosome*. Experimental models of programmed cell death support a larger role for extrinsic, ligand-receptor mechanisms in humans after severe head injury. In addition, levels of the *anti-apoptotic* protein bcl-2 are elevated to greater than four times normal in children after severe TBI. High levels of bcl-2 have been associated with increased survival, and it would appear that disabling apoptotic proteins may provide an additional therapeutic target.[7,12,17]

Oxidative Stress

Increased free-radical production occurs in patients with severe TBI due to (1) calcium influx and subsequent excitatory amino acid release; (2) elaboration of cytokines; and (3) activation of cascades that increase

phospholipase A-2 and cyclo-oxygenase production.[7] As a result, the balance between free radicals and antioxidants in the brain is upset, antioxidant pathways are overwhelmed, and cytotoxic oxygen and nitrogen radicals are available to form highly reactive, damaging substances. In fact, superoxide production is believed to be a major mediator of microvascular damage in patients after TBI.

Specifically, cell damage from free-radical formation occurs by lipid peroxidation, protein and DNA oxidation, and activation of proteins that upset cellular homeostatic mechanisms.

Some free-radical donors such as nitric oxide are thought to be neuroprotective by inhibiting apoptosis and excitotoxicity as well as by inhibiting lipid peroxidation. However, the presence of high levels of nitrite and nitrate (the final oxidation products of nitric oxide) is associated with an increased risk of mortality in patients with TBI.[18] Patients with TBI also have decreased levels of free-radical scavengers relative to the levels of free radicals, and this is thought to promote secondary brain injury. Despite clinical and experimental evidence demonstrating a role for oxidative stress in adults with severe TBI, human trials employing antioxidants have not demonstrated noticeable benefit. No trials in children have been undertaken thus far.

Inflammation

TBI initiates an inflammatory response that appears to be more pronounced in children than adults, for reasons that remain unclear. This exaggerated inflammatory response results in increased permeability of the blood-brain barrier and in the more diffuse pattern of injury seen in children with severe brain injury. An influx of inflammatory mediators, such as interleukins and soluble adhesion molecules, initiates a vicious cycle of cellular destruction. Studies performed on interleukin-1-b-converting enzyme-deficient mice, who are unable to mount an effective inflammatory response, show them to be resistant to cerebral ischemia, thus supporting the notion that inflammatory mediators contribute to secondary brain injury.[7] While too much inflammation is likely to be harmful to the injured brain, at least some inflammatory activity may be necessary for recovery and neuronal regeneration after TBI.[7,19]

Evaluation of the Child with Traumatic Brain Injury

Diagnostic Considerations

Initial evaluation of the child with suspected head trauma begins as all trauma assessments do, with rapid assessment of the ABCs and a focused history and physical examination. Any child with injuries to the face and/or neck should be evaluated for intracranial injury, and the presence of a skull fracture increases the likelihood that intracranial injury has occurred. The *primary survey* should identify all potentially life-threatening injuries and any vital sign instability, and if a diagnosis of TBI is likely, this supersedes all but the most severe injuries to other organ systems.

The need for neuroimaging in the child with mild head trauma (GCS 13-15) remains controversial, even when there is transient loss of consciousness or repeated emesis. Current acute care guidelines suggest that neuroimaging (computed tomography) may not be necessary in children who present to the emergency room with a history of minor head trauma, a GCS of 15, a nonfocal neurologic examination, and without evidence of headache, recurrent seizures, skull fracture, or scalp hematoma.[20] An important exception is the young, preverbal infant who presents with unexplained alteration in mental status; neuroimaging is essential to exclude occult or inflicted brain injury.

Head trauma is diagnosed using the three following modalities:

(1) The *Glasgow Coma Scale* is the initial screening tool used at the scene to classify head injury severity. (See text on page 318 and accompanying Table 2 for a more detailed description of GCS and its diagnostic and prognostic implications.)

(2) A *detailed neurologic examination*—Altered mental status with depressed level of consciousness that ranges from mild drowsiness to coma is a cardinal feature of TBI. Neither loss of consciousness nor recurrent emesis necessarily implies that the damage is severe, especially in children in whom both are quite common. Brief contact seizures following primary head injury are also quite common in children and do not necessarily portend a poor prognosis. However, the patient who does not regain consciousness or who demonstrates a waxing and waning level of consciousness must be closely observed and evaluated for more severe injury.

(3) The most commonly used diagnostic modality for evaluation of the child with head injury is noncontrast computerized tomography (CT), which is used to confirm the presence of mass lesions (with or without mid-line shift), hydrocephalus, edema, blood or CSF collections, as well as fractures of the skull, orbits, or facial bones. A CT should be obtained in all patients with persistent altered level of consciousness or focal neurologic findings, and before any procedure that is likely to mask changes in the neurologic examination (eg, general anesthesia for a surgical procedure or neuromuscular blockade for agitation). In addition, CT may be used to assess the cervical spine in patients who are unable to cooperate with clinical and radiographic examinations due to altered mental status or distracting injuries. The availability of head CT in many hospitals has decreased the morbidity and mortality from TBI and the need for surgical exploration.[21]

The utility of early CT in classifying TBI, guiding treatment decisions, and predicting outcome has been somewhat controversial. While it may offer a good snapshot of anatomic details at a single point in time, CT does not provide information about neurologic function, metabolic status of the brain, adequacy of cerebral blood flow, or events that may be occurring on a microscopic level. In addition, TBI is a dynamic process, and timing of the scan may limit its diagnostic sensitivity, since important findings, such as edema and ischemia, may not be evident in the immediate postinjury period, and may progress over a period of 48 to 72 hours.

Early classification of TBI severity based on CT findings was initially limited to two broad categories: mass lesions (mainly hematomas) and diffuse injury. Although this distinction had some important prognostic implications, it was recognized that patients with diffuse injury formed a heterogeneous group whose outcomes varied widely. Using outcomes data from the Traumatic Coma Data Bank, Marshall and coworkers developed the following system for classifying *diffuse* head injury based on CT findings[22]:

I. No evidence of pathology on CT (completely normal scan for age)
II. Cisterns present and open; midline shift 0 to 5 mm; no mixed or high-density lesions >25 mL in volume present (no mass effect)
III. Midline shift 0 to 5 mm, partial compression, or absence of basal cisterns; no high or mixed density lesions >25 mL in volume (prominent swelling)
IV. Midline shift >5 mm; compression or absence of basal cisterns; no lesions of high or mixed density >25 mL in volume (mass effect)

This system highlights the importance of the *volume status of the brain* in predicting outcome in TBI. Patients with diffuse injury and increased intracranial volume (Class III and IV), as evidenced by effacement of the mesencephalic cisterns, slit-like ventricles, and midline shift on CT, had mortality rates of 34 and 56.2%, respectively, compared with those in Class I and II where the mortality was 9.6 and 13.5%, respectively. This increased mortality is attributed to abnormal volume status of the injured brain, resulting in intracranial hypertension, which is currently believed to be the independent risk factor most responsible for poor outcome.

It is important to note that CT is not a good screen for detecting *diffuse axonal injury*. The presence of multiple punctuate hemorrhages in white matter tracts in deeper structures of the brain are suggestive, but not diagnostic.

MRI is seldom used in the initial evaluation of the patient with head injury due to the long time required to complete the study and because subtle soft-tissues findings rarely require emergent intervention.

Newer modalities for more precise assessment of neurologic damage include assays that measure serum and CSF markers released after head injury. Although no single marker has yet been identified, *neuron-specific enolase* (NSE), an enzyme found only in neuronal cytoplasm, and *Protein S100B*, which is specific to astrocytes and Schwann cells, are currently under investigation because of their specificity for cell destruction (neither is found in the extracellular space or circulating in the blood in the absence of nerve cell destruction). Detection of NSE in the peripheral blood likely indicates a breach of the blood-brain barrier, and increased levels of NSE have been demonstrated in patients after TBI. Furthermore, NSE levels that remain elevated 6 months after injury have been correlated with poor outcome.[23] Studies that compared the predictive value of GCS, loss of consciousness, and amnesia with Protein S100B levels suggest that only the latter can independently predict outcome.[24]

TABLE 3. Prognostic factors negatively affecting survival in pediatric head trauma

Cardiopulmonary arrest at scene
Prolonged hypoxemia early after injury
Hypotension from any cause
Treatment at a center without pediatric neurosurgical and trauma expertise
Refractory intracranial hypertension with ICP >20 mmHg
Cerebral perfusion pressure <40 mmHg for prolonged periods

TABLE 4. Classification of evidence

Class I evidence: Randomized controlled trials—the gold standard of clinical trials. Studies may be poorly designed with small numbers of patients and poor methodology.
Class II evidence: Both prospective and retrospective studies including observational, cohort, prevalence, and case-control studies.
Class III evidence: Studies with mostly retrospective data, including case series, case reports, and expert opinion.

Adapted from Adelson PD. Guidelines for the acute medical management of severe traumatic brain injury. Crit Care Med 2003.

Prognostic Indicators

The prognosis of children with severe TBI has been studied from both epidemiologic and physiologic perspectives and is summarized in Table 3.

Factors at the time of injury that increase the risk of poor outcome include (1) presence of severe injuries in organs other than the brain; (2) cardiopulmonary arrest at the time of injury, requiring CPR; (3) mechanism and location of injury, with inflicted head trauma having the worst prognosis; (4) care at a center without specialized pediatric trauma and neurosurgical capabilities; and (5) lack of medical insurance. Interestingly, although hospitalization rates for males with severe TBI are nearly double those for females, there is no significant difference in mortality rates by gender, each being approximately 22%.[2] The preponderance of males admitted with severe traumatic brain injury is likely explained by the larger number of males engaged in high-risk behaviors. The fact that mortality rates are not influenced by gender may suggest that the mechanism of injury has less to do with outcome than in-hospital/treatment factors.

The single, most important prognostic factor in determining neurologic outcome is thought to be *refractory intracranial hypertension*. Pediatric patients with intracranial pressures persistently greater than 20 mmHg have an increased risk of mortality. Those who survive will more than likely have profound neurologic impairment from prolonged hypoperfusion of both injured and healthy brain. The correlate to refractory elevation in intracranial pressure is inadequate *cerebral perfusion pressure* (CPP), which is the pressure that must be overcome to provide adequate cerebral perfusion. It is calculated by taking the difference between the mean arterial and the intracranial pressures. Although the precise CPP required to assure good neurologic outcome in children has not been determined, a goal of 50 to 60 mmHg is currently recommended, based largely on extrapolation from the adult literature.

Treatment of Children with Severe Traumatic Brain Injury

Great strides have been made in the management of children with TBI over the past two decades, due to a concentrated effort on the part of the medical and public health communities to develop evidence-based protocols that serve to standardize care and provide data for ongoing assessment. Although largely extrapolated from the adult Brain Trauma Foundation literature, and based mostly on case studies and anecdotal evidence, TBI is one of the few areas in which multidisciplinary involvement in the development of treatment guidelines specifically aimed at children has yielded results that have had a significant influence on current practice.

In February, 2002, the *Guidelines for the Acute Medical Management of Severe Traumatic Brain Injury in Infants, Children, and Adolescents*[25] were introduced. Endorsed by various highly respected groups such as the American Association for the Surgery of Trauma, the International Society for Pediatric Neurosurgery, the International Trauma Anesthesia and Critical Care Society, the Society for Critical Care Medicine, and the World Federation of Pediatric Intensive and Critical Care Societies, the document was intended to provide standard, evidence-based treatment guidelines for critically ill pediatric patients with severe TBI. All available pediatric data were reviewed and incorporated into the document, and where no data could be found, attempts were made to reach a consensus on the most plausible clinical approach. Given the limitations of the current available research in pediatrics, many of the recommendations are based mostly on Class II and Class III evidence (Table 4).

In addition to providing recommendations for treatment, the document's authors repeatedly acknowledge the paucity of credible evidence to support current standards of care in the management of pediatric

patients with head trauma, and in response, they developed a blueprint for future research as part of the project. With these caveats in mind, the guidelines still constitute the best attempt at compiling what is currently known about the acute management of pediatric patients with severe TBI, and they can be summarized as follows:

(1) Children with severe TBI are more likely to survive if they are treated in a pediatric trauma center with pediatric neurosurgeons available at all times. If transfer to a pediatric trauma center is not possible, an adult trauma center with resources available to accommodate pediatric patients is recommended. In large metropolitan areas, direct transport to a Pediatric Trauma Center may increase survival.[26]

(2) The best approach to prehospital airway management was reviewed but was left unresolved due to insufficient evidence. The studies that do exist find a slight improvement in survival in adults with severe TBI (GCS $\leq$8) who are intubated at the scene of the injury, although there appears to be little impact on neurologic outcome. The question of prehospital airway management is more complex in children, especially in infants and toddlers, given the skill required to correctly place an endotracheal tube by paramedics with limited training and experience in pediatrics. Although there is little doubt that prolonged hypoxia early after TBI worsens outcome in both adults and children, the utility of endotracheal intubation in the field remains largely unanswered. Newer methods for securing the airway may allow for more effective prehospital airway management and may ultimately improve outcomes by reducing hypoxemia early after injury. The *laryngeal mask airway* (LMA), a wide-bore endotracheal tube with a large inflatable cuff at its proximal end that rests over the entire retropharynx, can be placed rapidly by personnel with minimal pediatric experience and may offer a reasonable alternative to intubation.

(3) Addressing ABCs and correcting vital sign abnormalities quickly are essential in the early management of all patients with brain injury. The systemic conditions that appear to have the greatest impact on the injured brain are *hypoxia* and *hypotension*, and although large, randomized, controlled trials do not exist in children, there is consensus among experts that both must be reversed early and aggressively to insure the best possible neurologic outcome. Studies in adults with head trauma suggest that shock is rarely due to the head injury alone, but instead results from extracranial injuries such as long bone fractures and perforated viscous.[27]

(4) Early and aggressive *control of elevated intracranial pressure*, to maintain adequate cerebral perfusion pressure, remains the cornerstone of the current approach to patients with severe TBI. Available data suggest that patients who experience intracranial pressures greater than 20 mmHg, for even a relatively short period of time, are likely to have inadequate CPP and are at significantly increased risk of poor outcome.[28-31]

(5) In addition to careful monitoring and impeccable supportive care, a few simple, noninvasive measures are important in the management of all patients at risk for intracranial hypertension. These include *midline positioning* and *elevation of the head to 30°* to promote venous drainage, and avoidance of factors that increase cerebral oxygen consumption and metabolic demand, including agitation, fever, and seizures. Although the use of adequate sedation and analgesia continues to be endorsed, routine use of neuromuscular blockade in all patients with severe head injury is no longer recommended, since the inability to monitor neurologic status, especially in patients who do not have continuous electroencephalographic monitoring, is severely hampered. The routine use of pentobarbital coma for prophylaxis against intractable intracranial hypertension is still widespread in adults; however, the prolonged half-life and risk of hypotension and myocardial depression make it a less suitable option in children. It still constitutes an acceptable treatment option in patients with persistent intracranial pressures above 20 mmHg, although the effect of prolonged burst suppression on the immature, developing brain is not known, and a positive impact on neurologic outcome has not been established.

(6) The routine use of *prophylactic hyperventilation*, with PCO_2s of 25 to 30 mmHg, is no longer recommended. As mentioned previously, studies

in pediatric patients early after TBI demonstrate compromised cerebral blood flow, and hyperventilation only serves to worsen inadequate cerebral perfusion by promoting vasoconstriction. Therefore, the current recommendations are to maintain a state of *mild* respiratory alkalosis, with PCO_2s of approximately 30 to 35 mmHg and to reserve hyperventilation for impending herniation or refractory intracranial hypertension.[32]

(7) Although convincing evidence to suggest a positive impact on outcome is not yet available, current guidelines recommend placement of intracranial pressure monitoring devices to guide therapy and optimize cerebral perfusion pressure. ICP monitoring is recommended in patients with severe TBI (GCS≤8), and in those with evidence of edema, swelling, or risk of herniation on head CT. In addition, patients in whom monitoring by clinical examination is not possible, due to use of general anesthesia and/or neuromuscular blockade, should also have an ICP monitor placed. The choice of device (subarachnoid bolt, fiberoptic intraparenchymal probe, or ventriculostomy) is left up to the practitioner, although ventriculostomy appears to be most useful, since it not only monitors pressure, but can also relieve intracranial hypertension by draining CSF. Ventriculostomy placement can only be accomplished in patients with large, fluid-filled ventricles, and there is an increased risk of bleeding and infection when ventriculostomies are left in place for longer than 5 to 7 days.[28,33-35]

(8) Hyperosmolar Therapy—As stated previously, cerebral swelling and edema are both thought to promote secondary brain injury and increase the risk of cerebral herniation. Toward this end, mannitol (at a dose of 0.25 to 1 g/kg every 6 hours) has been used in the management of elevated intracranial pressure since the 1960s and continues to be an important pharmacologic adjunct in adults with TBI. It lowers ICP by two mechanisms: (1) by rapidly decreasing blood viscosity and blood vessel diameter, thus decreasing cerebral blood flow; and (2) by decreasing brain water through a slower osmotic effect in patients with an intact blood-brain barrier. When the blood-brain barrier is not intact, mannitol can enter the injured brain, reverse the osmotic gradient, and actually increase intracranial pressure. Mannitol therapy must be closely monitored since it induces a significant osmotic diuresis and frequent, large doses may result in hypovolemia, compromised cerebral perfusion pressure, and worsening of secondary brain injury. In part because of the above-mentioned risks associated with the use of mannitol, hypertonic saline (HTS) is gaining in popularity as an alternate osmotic agent.[36,37] In addition to being an effective osmolar agent, hypertonic saline offers the following advantages: (1) it maintains a state of euvolemia; (2) it may restore the normal volume and resting potential of neurons; (3) it increases atrial natriuretic peptide release and fosters brisk urine output; and (4) it has antiinflammatory properties.[37]

However, HTS must also be used with caution since animal studies have demonstrated central pontine myelinolysis, subarachnoid hemorrhage, renal failure, and an increased risk of rebound intracranial hypertension after its abrupt discontinuation. To date, no such events in children have been reported.[36,38]

Neither mannitol nor HTS has been proven to be superior in randomized, controlled trials, and current guidelines offer both agents as acceptable treatment options for controlling elevated intracranial pressure.

(9) There is little evidence to suggest that steroids improve the neurologic outcome of pediatric patients with severe head injury and they are not currently recommended for routine use in children with severe TBI. In addition, the increased susceptibility to infection, increased incidence of gastrointestinal bleeding, and suppression of the hypothalamic-pituitary axis associated with steroid use has led to the current recommendations against their use. This issue remains highly controversial, especially given the awareness of the role of inflammation in TBI in children, and the definitive answer will not be determined until well-conducted studies in large numbers of pediatric patients are completed.

(10) *Early*, *isolated* seizure activity after TBI is common, especially in children less than 2 years of age, and does not necessarily portend poor outcome. There is consensus that treatment with antiepileptic drugs is indicated for control of recurrent, posttraumatic seizures.[39] Although no

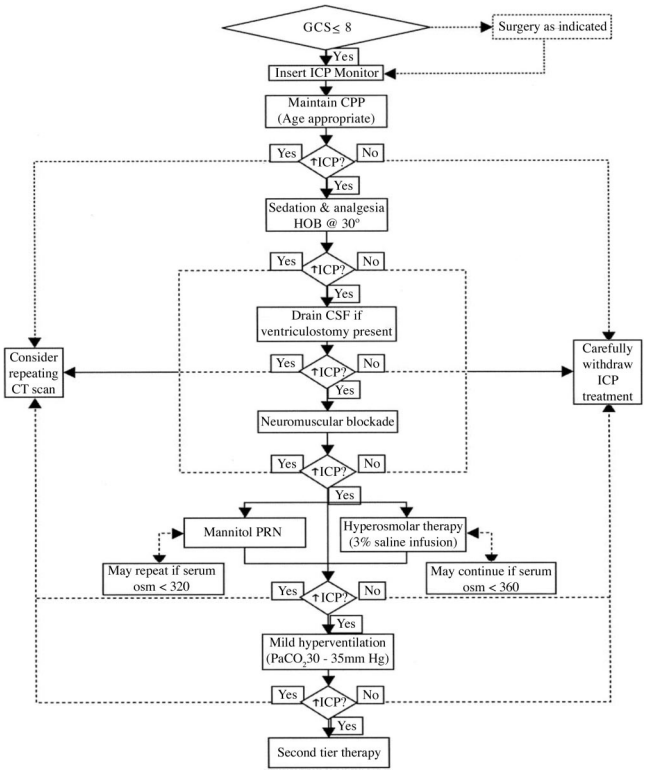

FIG 1. Critical pathway for the management of intracranial hypertension. *GCS*, Glasgow Coma Scale; *ICP*, intracranial pressure; *CPP*, cerebral perfusion pressure; *HOB*, head of bed; *CSF*, cerebral spinal fluid; *PRN*, as needed. (From Adelson PD.[40])

one specific agent has proven to be superior in this setting, fosphenytoin (15 to 20 mg/kg loading dose, followed by maintenance dose of 2.5 mg/kg twice daily) is the agent most often used, due to its relatively short half-life, its nonsedating properties, and ease of intravenous administration. The routine use of anticonvulsants to *prophylax* against late-onset seizures in adults or children is not currently recommended, as there is no evidence to suggest any impact on outcome.

(11) An important contribution to emerge from the management guidelines was a critical pathway for the treatment of elevated intracranial pressure (Fig. 1).[40]

Integral to this pathway is the recommendation that pediatric patients with severe TBI should have indwelling continuous ICP monitoring by which to guide treatment and that the focus of treatment should be the maintenance of adequate CPP. Again, the exact CPP that must be maintained to assure a favorable neurologic outcome in children has not yet been determined.

Table 5. Current recommendations for treatment of severe traumatic brain injury

Assess and stabilize ABCs. Determine severity of head injury using GCS, neurologic exam, and neuroimaging; if head injury is severe, insert ICP monitoring device
Utilize noninvasive measures to control ICP: maintain head midline and elevate to 30 degrees, provide sedation/analgesia, maintain normothermia, treat seizures
Maintain adequate systemic blood pressures to assure a cerebral perfusion pressure of 40 to 60 mmHg. Use vasopressors if necessary (norepinephrine, vasopressin) to increase blood pressure to the desired level
Ventilate to a pCO_2 of 32 to 37 mmHg and utilize hyperventilation only for impending herniation
Control refractory intracranial hypertension with CSF drainage, hyperosmolar agents, neuromuscular blockade, or burst suppression. If these interventions are not successful, consider mild hypothermia (32 to 34°C) or decompressive craniectomy

Armed with this invaluable tool, physicians treating children with TBI can now refer to a *consensus-based* series of recommended treatments (Table 5) with hopes that a more uniform approach will lead to improved outcomes, especially in children who cannot be cared for in specialized, pediatric trauma centers. It should be noted that until data compiled from pediatric centers are collected and analyzed, Class I evidence to support or dispute current treatment strategies remains elusive.

Studies looking at the impact of treatment guidelines on functional outcome *in adults* with TBI are limited in number and scope. In a retrospective analysis published by Bulger and coworkers[41] medical records of patients from 34 US trauma centers were reviewed for variations in trauma care, adherence to treatment guidelines, and outcomes as they related to treatment. Centers were categorized as "aggressive" or not based on whether intracranial pressure monitors were placed in at least 50% of patients with multiple trauma that included severe TBI (GCS ≤8). Outcomes measured included survival, length of hospital stay, and functional outcome at discharge. Bulger observed a significant decrease in mortality rate—27% in aggressive centers versus 45% in nonaggressive centers ($P = 0.01$)—but no significant difference in functional status at the time of discharge from acute care.

To date, there are only a few studies that address functional outcome[42,43] and no large population-based studies of the outcomes of TBI in children treated under the current guidelines. To begin to address this

important public health issue, and to determine appropriate allocation of resources, the National Center for Injury Prevention and Control at the Centers for Disease Control and Prevention (CDC) convened a working group in October 2000 to develop methods for assessing outcomes of TBI in children.[43] Studies are now in progress and results are forthcoming. Until definitive results are available, it would appear that aggressive control of intracranial pressure and maintenance of adequate cerebral perfusion pressure are essential to outcome of children with severe traumatic brain injury.

New Directions in Treatment

A deeper understanding of the molecular events that occur in TBI has given rise to new approaches to treatment. Some involve new applications of existing treatments, while others have not been widely used in adults or children. It is important to note that none of these interventions has been tested in large clinical trials or endorsed by expert consensus as first-line treatment for severe TBI. Therefore, current use of these treatment options should be limited to those patients in whom more conventional therapy has failed.

Hypothermia. Based on the observation that neurologic function in children who experience near-drowning in icy waters and in those undergoing open-heart surgery using deep hypothermic circulatory arrest is fairly well preserved, clinical trials employing mild hypothermia (32 to 34°C) in patients after severe TBI are currently in progress.[7,38] Trials in adults have yielded conflicting results. Of three trials conducted in patients with GCS of 3 to 7, only one trial demonstrated benefit, and only in patients with GCS between 5 and 7.[7] These studies suggest that early implementation and careful patient selection are needed to demonstrate overall benefit. Mild hypothermia provides some improvement in oxygen supply to the ischemic brain and may decrease ICP. It is also thought to preserve antioxidant and antiinflammatory function in the brain, and to decrease the brain's metabolic rate and demand for oxygen. Levels of excitatory amino acids may also be decreased, and hypothermia may protect against seizures. Coagulopathy is a well-known complication of prolonged hypothermia and presents an obvious risk to the child with head trauma who is already at risk for intracranial hemorrhage.

Decompressive Craniectomy. Removal of a portion of the skull to allow more room for expansion of a swollen, edematous brain makes intuitive sense, but studies incorporating this treatment modality have had mixed results. Although both experimental and clinical trials confirm the efficacy of lowering intracranial pressure,[7,12,38] there are currently no data to suggest that decompressive craniectomy results in improved long-term neurologic outcome, and in fact, it may lead to worsening cerebral edema and hemorrhage, thus negatively affecting outcome.[37]

A single prospective, randomized, controlled trial implementing early decompressive craniectomy, along with standard supportive care, showed a decrease in ICP and a trend toward improved functional outcome.[38,44] Additional trials with reproducible results are needed before decompressive craniectomy can be recommended as a helpful adjunct in the treatment of refractory intracranial hypertension.

Dexanabinol. A synthetic, nonpsychotropic canabinoid with antioxidant and antiinflammatory properties, dexanabinol blocks receptors for NMDA (an excitatory amino acid released in large quantities after head injury), thus lowering intracranial pressure.

It may also protect the integrity of the blood-brain barrier and decrease cerebral edema in patients after TBI. A phase 2 prospective trial in patients with severe TBI[12,38] demonstrated safety and tolerability of dexanabinol in adults, and a trend toward more rapid recovery. Unfortunately, improvement in neurologic outcome was not an endpoint included in the study.

Nonaccidental Brain Injury

It is not within the scope of this article to present a thorough and detailed review of the subject; however, intentional injury to children continues to be an important and troubling cause of pediatric TBI that deserves mention here. Inflicted brain injury presents both diagnostic and therapeutic challenges to physicians because of the long time lag between injury and medical intervention (these patients may not be brought to medical attention until severe, irreversible damage has occurred) and because of unwillingness on the part of the perpetrator to admit to having harmed a child. This delay in diagnosis may help to explain why outcomes in this subset of patients, most of whom are less than 1 year of age, continue to be dismal.

Risk factors for child abuse include young parental age, unstable family circumstances, low socioeconomic status, and prematurity and disability of the

victim.[45] In addition, the perpetrator is often male and may not be a first-degree relative of the victim.

The mechanism of brain injury is similar to that previously discussed for severe TBI and involves rotational movement of the brain inside the cranium, leading to disruption of important vessels and neuronal connections, and resulting in *subdural hemorrhage*, *cortical contusion,* and *diffuse axonal injury*. Forceful shaking while holding the infant at the waist allows the disproportionately large and heavy head to whip forward and back on the neck, hence the name *Shaken Baby Syndrome*. The shaking may be accompanied by thrusting of the infant's occiput against a hard surface (often a wall or floor), resulting in skull fractures and intracranial hematoma. For this reason, the name *Shaking-impact Syndrome* may be preferable. Regardless of the nomenclature, inflicted head trauma comprises a constellation of clinical and radiologic findings that help to distinguish it from accidental head trauma.

Cardinal features of Shaken Baby Syndrome (SBS) include skull fractures, subdural and/or epidural hematomas, retinal hemorrhages and/or detachment (in one or both eyes), and rib and long-bone fractures of differing ages. Infants often present with seizures, apnea, and/or depressed consciousness, but they may also present with vomiting, irritability, or lethargy. The differential diagnosis of these babies is quite broad and includes sepsis, coagulopathy, intracranial arteriovenous malformation, and metabolic disorders such as glutaric aciduria. Diagnostic evaluation almost always includes lumbar puncture which, in most instances, reveals bloody cerebrospinal fluid that does not clear. The history given by the family provides an important clue and is usually inconsistent or suggests an improbable explanation for the injury. A high index of suspicion is required to quickly arrive at the correct diagnosis, and careful documentation is essential to prosecute the perpetrator. It is important to note that the forces required to produce the injuries seen in infants with inflicted brain injury rarely occur during routine play.[45,46]

In addition to the usual diagnostic work-up, complete evaluation for suspected abuse includes a thorough and detailed birth, family health, and social history. Physical examination of all covered areas, including perineum and anus, and thorough ophthalmologic evaluation, with slit-lamp examination and documentation regarding the presence of retinal hemorrhages, are also required. Radiologic studies should include X-rays of all bones (skeletal survey), looking for fractures of varying ages and CT scan and/or MRI of the head, looking for skull fractures, hemorrhage, and loss of gray-white matter differentiation. In addition, perineal and rectal swabs, and stool samples for occult blood, should be obtained. Hematologic evaluation for evidence of congenital or acquired coagulation abnormalities, and a urine drug screen should also be performed. Where possible, photographic documentation of injuries provides support for claims of inflicted injury.

The examining physician is obligated by law to report any case of suspected abuse to the appropriate child protection agency to ensure the safety of the home, should the child be discharged, and to arrange for disposition of siblings who may also be in danger. If adequate assessment is not possible before the patient is medically cleared for discharge, admission to the hospital for social reasons is appropriate.

It is important to discuss openly with the patient's family any concerns about intentional injury to the child and to inform them of steps that have been taken to confirm these suspicions. In cases of severe harm to a minor, the local police precinct should be notified to initiate a criminal investigation.

Nonaccidental trauma in infants continues to be a difficult challenge for the health care community since prevention and surveillance are difficult, especially when the perpetrator may not be a part of the immediate family. Unfortunately victims often suffer repeated trauma and many are already known to authorities before they succumb to profound, irreversible neurologic injuries. It is therefore the responsibility of physicians to maintain a high index of suspicion, with close monitoring and follow-up of all at-risk patients, and to aggressively report any unexplained injuries or illnesses in these patients to the appropriate child welfare agencies.

Conclusion

Severe brain injury continues to be a major public health problem in children, consuming billions of health care dollars each year. In lieu of prevention, which is without a doubt the most effective intervention, much work is needed in the areas of diagnosis and acute and chronic management to improve the neurologic outcome of patients with TBI. The current approach to the care of children with TBI depends in

large part on acceptance of them as miniature adults, since age-specific data are scarce. However, research into the molecular biology and pathophysiology of pediatric brain injury suggests that significant developmental differences exist that are likely to impact prognosis and response to treatment. The recently released guidelines for the acute management of head injury in infants, children, and adolescents provide a reasonable first step by offering a uniform approach to care, and a solid foundation for future research. Clearly a great deal more work needs to be done before a noticeable positive impact on this widespread and troubling health problem can be realized.

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