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Neurointensive care of the nonaccidentally injured child

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Head injury is the leading cause of traumatic death in infants, accounting for more than 7000 deaths annually [1], 1000 of which are attributed to nonaccidental trauma (NAT) [2]. Those children who survive their initial injury come to the attention of neurosurgeons and neurointensivists as critically ill patients, often with multisystem injuries. From the moment that these children arrive in hospital, an aggressive, multidisciplinary approach to their care is mandatory, involving neurosurgeons, pediatric neurointensivists, general surgeons, ophthalmologists, orthopedic surgeons, and pediatricians. Outcomes after NAT with severe traumatic brain injury (TBI) are poor, with mortality rates ranging from 12% to 65% [3], and nearly all of those who survive suffer some neurologic disability. Despite the seemingly dismal prognosis, the authors advocate an aggressive treatment strategy for victims of NAT because it has been their experience, and the experience of others, that a number of children survive to have a meaningful recovery if given the opportunity. What follows is a discussion of the neurointensive care of infants and in particular, the nonaccidentally injured child with a TBI. This article includes the initial evaluation and resuscitation, a brief overview of the radiologic and laboratory work-up, the indications and rationale behind neurophysiologic monitoring, and finally the neurosurgical critical care of these children with a focus on intracranial pressure (ICP) management and prevention of secondary brain injury.

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Initial evaluation and resuscitation

The child presenting with NAT should be assumed to have multisystem trauma, and aggressive and comprehensive evaluation and resuscitation are mandatory. Consistent with advanced trauma life support guidelines, the "ABCs" of trauma resuscitation are given priority over the perhaps more obvious neurologic dysfunction. It is important to keep in mind that severe injury to the brain sets in motion a cascade of potentially life-threatening secondary sequelae that unless anticipated and treated lead to a worsened neurologic outcome or death. In addition, the most common contributing factors to mortality and poor outcome after TBI are hypoxia and hypotension [4,5]. These should be addressed aggressively at the scene and throughout the hospital course.

Airway, breathing, and circulation

An adequate, protected airway is critical to provide for proper oxygenation and preventing hypercarbia. Although not every child requires assisted ventilation, a low threshold for intubation should exist in all NAT patients. Young children and infants often have apnea following a concussive injury or suffer a seizure that can compromise the child's airway. Orotracheal intubation obviously protects the airway and is indicated in the following situations [6,7]:

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1. Glascow Coma Score of 10 or less
2. A decrease in Glascow Coma Score of greater than 3, regardless of initial score
3. Anisocoria greater than 1 mm
4. Apnea
5. $Paco_2$ greater than 45 mm Hg
6. Spontaneous hyperventilation causing $PaCO_2$ less than 25 mm Hg
7. Loss of pharyngeal reflex
8. Cervical spine or orofacial injury compromising ventilation

Rapid-sequence intubation, ideally using neuroprotective agents, is the procedure of choice in head-injured children. All children with TBI are assumed to have a concomitant cervical spine injury making in-line stabilization of the cervical spine mandatory during intubation. If possible, the bag-valve-mask technique should be avoided because cervical spine manipulation may be increased with this procedure [8]. In addition, because all head-injured children should be assumed to have increased ICP and a full stomach, precautions should be taken to avoid inducing hypotension and hypoxia during intubation. The pharmacologic agents used for rapid-sequence intubation of the brain-injured child are chosen to avoid laryngeal stimulation during laryngoscopy, hypotension, aspiration of gastric contents, and provide cerebral protection. Thiopental (4 to 5 mg/kg), a barbiturate, reduces cerebral metabolic rate for oxygen by up to 50% within 15 seconds after injection [9], making it an excellent short-acting sedative for intubating the head-injured child. Fentanyl (2 to 4 μg/kg) or other narcotics, in combination with lidocaine, 1 mg/kg, reduces catecholamine release during laryngoscopy [7], and provides additional sedation. Finally, a paralytic, such as vecuronium (0.1 mg/kg), is recommended for muscle relaxation because it is short acting and helps reduce the elevation of ICP with intubation.

Circulatory compromise with inadequate tissue perfusion secondary to multiorgan injury and shock is common after TBI, especially in children 4 years or younger [10,11]. Vascular access should consist of two large-bore intravenous lines, one of which is preferably central. Initial resuscitation should begin with 20 mL/kg of 0.9% normal saline without dextrose. Hypotonic fluids should be avoided so as to prevent fluid shifts into the injured brain. Colloid or packed red blood cells need only be given if indicated by initial laboratory studies, ongoing hemorrhage, or lack of response to crystalloid fluid resuscitation.

Until proved otherwise, hypoperfusion after NAT must be assumed to be hemorrhagic in nature, and extracranial sources of blood loss must be sought. The abdomen, retroperitoneal space, pelvis, and long bones are potential sites for occult blood loss in the infant, and should be investigated by CT or ultrasound if circulatory compromise is present. With the exception of the subgaleal space where there can be a fairly sizeable hematoma in children under the age of 1 year or obvious scalp hemorrhage, hemorrhagic shock is never usually caused by intracranial or intracerebral injury.

Neurologic assessment

As part of the initial resuscitation and primary survey, a rapid, yet thorough, evaluation of neurologic function must be obtained. Initial treatment and outcome prognosis are based largely on the neurologic status of the child at presentation. If at all possible, the neurologic status of the child before hospital arrival should be obtained from family members, first responders, or paramedics. This information is particularly important when the child is intubated or sedated before arrival.

The initial neurologic examination can be performed within minutes and should consist of the age-appropriate Glasgow Coma Scale (GCS) score, cranial nerve, motor, sensory, and reflex examinations. There have been some concerns that the GCS does not adequately reflect the severity of injury in the infant. More recently, the Infant Face Scale may more accurately reflect the response of the injured infant to cerebral injury [12]. In addition, the scalp and skull should be examined to identify lacerations, abrasions, skull depressions, and other external signs of intracranial injury. Otorrhea, rhinorrhea, retrotympanic blood, Battle's sign, and raccoon eyes are all external signs of a potential basilar skull fracture.

It is common for the child to arrive intubated or sedated, either from emergency response personnel or from prior treatment at another facility. In this setting, a pupillary examination may be all that can be performed to assess clinically the patient's neurologic status. In these instances, a neurologic examination should be obtained when the initial medications have worn off and before resedating or paralyzing the child. After the child has been initially assessed and stabilized through the resuscitation, a CT scan should be urgently obtained to evaluate the intracranial extent of injury. The CT is often prognostic and useful

when determining the course of action (e.g., surgery or aggressive medical management).

Radiologic assessment

Plain radiographs

Initial radiographs should be performed before more involved studies, such as CT, to identify potentially life-threatening injuries. Every child suffering from NAT should have at least a lateral cervical spine radiograph, anteroposterior (AP) chest, and AP pelvis films. The lateral film must clearly show the C7-T1 disk space to be considered complete. The child should remain in cervical spine precautions immobilized in a size-appropriate rigid cervical collar until a full cervical spine series can be obtained later that consists of an AP, lateral, and odontoid (open mouth or submentovertex) film. Unless the patient is awake, alert, and cooperative enough to undergo clinical examination, the rigid collar should be left in place despite a radiographically cleared cervical spine. The AP chest film is mandatory in all NAT patients, because a number of injuries and complications of treatment can be identified quickly. In addition to confirmation of endotracheal tube and central venous catheter placement, the AP chest film should be evaluated for pneumothorax and hemothorax; aortic injury (widened mediastinum); pneumoperitoneum; rib fractures; clavicular fracture; and shoulder dislocation. An AP pelvis film reveals fracture or dislocation of the femoral head and pelvic fractures. Once stabilized, a skeletal survey should be obtained to diagnose any occult fractures, and to search for evidence of old fractures.

CT

A CT scan of the head is indicated in all NAT patients with a GCS of 14 or less, a focal neurologic deficit, clinical evidence of basilar skull fracture, an obvious skull deformity, or any patient who is undergoing prolonged sedation or anesthesia. Classic CT findings in NAT include thin-rimmed subdural hematomas with a predilection for the posterior interhemispheric fissure; subarachnoid hemorrhage; and skull fractures (particularly parieto-occipital) [3]. An ominous finding on CT is the cerebellar reversal sign, where the supratentorial brain is diffusely hypodense with respect to the cerebellum. An indicator of a concomitant second severe hypoxic or ischemic insult to the primary cerebral injury, this CT finding portends a dismal prognosis [13].

A CT of the abdomen and chest should also be considered in those patients suspected of having intra-abdominal or intrathoracic injury. Bruising found in these areas at the initial resuscitation, falling blood counts, hypotension, and so forth requires the full imaging evaluation to ensure against soft tissue, organ, or retroperitoneal injury. Similarly, suspected cervical spine or lower spine injuries should be imaged either through CT in abnormal areas seen on the plain radiographs or based on neurologic examination.

MRI

In the acute setting, MRI is rarely indicated. The time required acquiring images and the relative isolation of the patient during imaging limits the use of this imaging modality. One scenario that may warrant MRI involves the patient with a neurologic examination that is markedly worse than predicted by CT images. MRI is superior to CT in imaging the posterior fossa and brainstem, revealing brainstem injury that may be missed on CT. Also, diffuse axonal injury, with white matter signal abnormalities in the corpus callosum and brainstem, is often apparent on MRI. Despite the added information that can be gained with MRI, CT scanning is the imaging modality of choice in the acute setting. The MRI is most useful for prognostic purposes and better understanding as to the extent of the injury

Laboratory studies

Screening laboratory studies should be obtained in every case of NAT on presentation. Although no particular laboratory abnormality is associated with NAT, the diffuse and severe nature of the injury warrants a nonspecific laboratory work-up. Serum electrolytes, blood urea nitrogen, creatinine, and glucose studies should be obtained immediately, and abnormalities aggressively corrected. Hyperglycemia, as part of a systemic stress response to head injury, can potentiate cerebral ischemia and is clearly linked to worsened neurologic outcome [14–16]. Hypokalemia is another common electrolyte abnormality in children with TBI [17], and is also linked to poor neurologic outcome [15]. Correction of glucose and electrolyte abnormalities should begin as soon as they are recognized. In addition to injury-related electrolyte abnormalities, patients with NAT are often

suffering from chronic neglect, which may include malnutrition and dehydration, the evidence of which may be suspected based on serum electrolytes.

A complete blood count, including platelet count, is often the first indication of internal hemorrhaging. It cannot be overemphasized that hypovolemia and a subnormal hemoglobin and hematocrit indicate hemorrhage outside of the central nervous system and the source should be sought aggressively. In the setting of intracranial injury, a platelet count of greater than 80,000/μL is indicated, with platelet transfusions given as required. Nearly 75% of all children with head injuries have laboratory evidence of coagulopathy, 32% of which meet criteria for disseminated intravascular coagulation [18], making a prothrombin time and partial thromboplastin time mandatory. Further coagulation studies (fibrinogen, fibrin-split products, and so forth) for disseminated intravascular coagulation can be obtained as necessary. Correction of coagulation abnormalities should begin with fresh-frozen plasma, vitamin K, cryoprecipitate, or other factors as indicated. It is also recommended that liver function tests, amylase, and lipase be assessed to exclude intra-abdominal injury, such as liver or pancreatic laceration.

A number of biochemical mediators of TBI have been described, and the list is growing almost daily. Excitatory amino acids (glutamate and aspartate) [19–21] and cytokines (interleukin-1, -6, and -10) [22] have been shown to be elevated after TBI in children, and current research efforts are focused on the roles of these molecules in secondary injury after TBI. In addition, inflammatory responses, such as complement activation [23], microglial activation [24], and leukocyte infiltration [25], are well documented after experimental brain injury. Although these and other molecules hold great promise for future diagnostic and therapeutic studies, their use in the diagnosis and management of acute NAT is limited today. Quinolinic acid, however, a macrophage-derived neurotoxic metabolite of the tryptophan-kynurenine pathway, has the potential to be a marker for timing an injury or injuries and is found to be elevated in cerebrospinal fluid (CSF) 3 days after injury [26]. Quinolinic acid was found in a subset of patients to be elevated at or within only a day or two after presentation in the CSF. All of these children with early quinolinic acid elevations were victims of NAT. This seems to indicate that these children were likely at least to have been injured earlier and had a delay to presentation or repeated injuries. Although this molecular marker of brain injury is still investigational, the possibility of a laboratory test for NAT is becoming a possibility. Other promising molecules that the authors are investigating as markers to evaluate for trauma in situations with no history of trauma are neuron-specific enolase and S-100B [27]. It is hoped that these markers of injury will be useful for the earlier identification of children with NAT and be useful in prognosis and treatment of these children.

ICP monitoring

Despite the acceptance of ICP as standard of care in the management of adult severe TBI [28], no randomized controlled studies have proved its efficacy in altering the outcome from these injuries in children. Although the monitoring of ICP and treatment reduced the mortality rate after TBI from 12% to 53% [29], this nonrandomized case series did not include infants or children. It is still believed that the ability to detect and treat elevated ICP is critical to the intensive care of the NAT patient. Clinical signs are notoriously inaccurate in detecting elevated ICP, and modern neurologic critical care relies heavily on accurate continuous ICP monitoring. ICP monitoring is recommended in adults with an abnormal admission CT and an initial GCS of 3 to 8 [28], and these recommendations are also believed to be appropriate for children. The optimal ICP monitor is accurate, reliable, and has therapeutic potential. Five different classes of ICP monitors are currently in general use:

1. Intraventricular devices and external ventricular drains
2. Intraparenchymal devices
3. Subdural devices
4. Subarachnoid devices
5. Epidural devices

In the authors' experience, external ventricular drains (EVD) most closely fulfill the criteria of the optimal ICP monitor. By coupling the CSF pressure in the lateral ventricle to a fluid-filled strain gauge, the EVD provides a direct reading of the pressure within the skull. Numerous studies have concluded that the most accurate means of measuring ICP is by EVD [30–32], including children [33], and an analysis of the literature by the Brain Trauma Foundation concluded that ventricular pressure should be the standard for accurate ICP monitoring in trauma patients. The potential for inaccuracy exists when the catheter tip becomes

obstructed (by blood, brain, or choroid plexus), but in most cases flushing the catheter can clear the obstruction or the catheter can be replaced. The reported accuracy of intraparenchymal monitors is less than with an EVD [30,32,33], and unlike EVDs, intraparenchymal monitors, once inserted, cannot be recalibrated reliably, making them less dependable. When the lateral ventricles cannot be catheterized because of obliteration from swelling or intraventricular hemorrhage, it may necessitate the use of an intraparenchymal catheter rather than an EVD. Subarachnoid, subdural, and epidural monitors, in the authors' opinion, are indicated only in the setting of coagulopathy where hemorrhage from catheter passage becomes more concerning. They are notoriously inaccurate and of an older technology. Despite its accuracy in the measure of ICP, the reason to recommend the use of EVDs over other ICP monitoring technologies is its ability therapeutically to drain CSF. The EVD can be used to drain CSF, either continuously or intermittently as needed in the setting of intracranial hypertension. The authors have found it useful continuously to drain the ventricles at a low pop-off pressure (3 cm above midbrain) to decrease clogging of the catheter and to keep the brain as relaxed as possible for as long as possible. Although it is the rare NAT patient that is able to maintain normal ICPs with only intermittent CSF drainage, removing fluid from the intracranial compartment lessens the requirement for other ICP-lowering treatments.

Complications from EVD placement include infection, hemorrhage, and malfunction. Although significant intracranial infection related to EVD placement is exceedingly uncommon [34,35], colonization of the catheter can occur. At least two reports suggest that the risk of colonization increases significantly after 5 days [34,36], and some have recommended the routine changing of catheters every 5 days to prevent colonization leading to meningitis [37]. The practice of many pediatric neurosurgeons, including the authors', is to monitor CSF from the EVD on a daily basis and remove or replace the catheter when colonization or infection is suggested by an increasing leukocyte count or decreasing glucose or confirmed by a positive Gram stain. Review of the literature reveals an average rate of EVD colonization of approximately 5% [28]. EVD placement also carries the risk of hemorrhage with a reported rate of catheter-related hemorrhage of 1% [35,36,38], although the true rate may be higher if incidental hemorrhages are included.

Cerebral blood flow

Unique to the pediatric TBI population, diffuse cerebral swelling is seen in 44% of children after severe TBI [10]. In the 1970s and early 1980s, this diffuse swelling was believed to be caused by vasomotor paralysis, cerebrovascular dilation, and an overall increase in cerebral blood volume (CBV), not edema [39]. Recent advances in the measurement and monitoring of cerebral blood flow (CBF) after TBI has called the posttraumatic hyperemia concept into question in both children and adults. Studies in adult TBI patients revealed acute hypoperfusion, rather than an increase in CBF, often at, or below, ischemic threshold (<18 mL/100 g/min). Subsequent elevations of CBF seem to indicate that the late hyperemia might be contributory to the late intracranial hypertension. Studies in children suggest that in the acute phase after TBI, cerebral hypoperfusion with a resultant reduction in oxygen delivery occurs more commonly than was once believed [40–42], with one third at or below ischemic threshold. These studies revealed that posttraumatic elevation of CBF or hyperemia is a delayed phenomenon, occurring 24 hours after injury. CBF becomes uncoupled from the cerebral metabolic rate of O_2 and CBF increases. This hyperemia is further evident by a lowered arteriovenous difference of O_2 [43]. The significance for this has come into question because higher levels of CBF were associated with a good outcome [44].

The clinical assessment of CBF is rapidly changing both the understanding and management of TBI. Three techniques are currently in use (stable xenon CT, ^{133}Xe techniques, and transcranial Doppler) and several new technologies hold promise for the future. With the proper equipment coupled to a CT scanner, inhaled xenon gas can be used to provide a physiologic CT scan with quantitative CBF measurement in the NAT patient [44]. The authors prefer the xenon-CT method because an anatomic image is obtained as part of the study, allowing the comparisons of the anatomic imaging and functional CBF values in the injured brain. More than a diagnostic or prognostic study, xenon CT can help guide therapy and gauge the child's response to therapy [45,46]. By obtaining xenon-enhanced images before and after a physiologic manipulation, such as changing $PaCO_2$ or blood pressure, the response to these manipulations can be evaluated rapidly [47,48]. Optimal treatment strategies to prevent cerebral ischemia and further brain injury

can then be tailored to each patient and response to these manipulations closely followed.

^{133}Xe (radioactive xenon), initially used in adult TBI patients [49], has also been used in the pediatric population [39,50,51]. Like xenon-enhanced CT, this technology is able to provide regional, quantitative measurements of CBF. An advantage of ^{133}Xe over xenon CT is its portability and ease of use at the bedside, making this study ideal for the unstable patient where traveling to a CT scan may pose significant risk. The major disadvantage of this CBF technology is the lack of anatomic correlation with the physiologic data provided. Transcranial Doppler, a measure of blood flow velocity rather than perfusion, has limited use in the child with NAT. This study is usually used to assess middle cerebral artery flow velocity, and at best serves as a marker of a potential trend toward hypoperfusion.

Neurointensive care

After resuscitation and initial diagnostic studies, a decision must be made as to whether emergent craniotomy is required. Most children with NAT proceed directly to the neurointensive care unit (NICU) rather than the operating room, because a focal mass or operative hematoma from this injury is rare. Intracranial hematomas in NAT are classically thin and diffuse with a predilection for the interhemispheric fissure, contributing little to increased ICP [3]. More focal NAT, such as from blunt force trauma to the head with depressed skull fracture or epidural hematoma, may require emergent craniotomy, the details of which are beyond the scope of this article. If ICP monitoring is indicated, in the absence of other indications for surgical intervention, it is the authors' practice to place EVDs in the NICU where the procedure can be performed rapidly under sterile conditions. In addition, performing EVD placement in the NICU allows the pediatric intensivists to begin their work concomitantly, obtaining intravenous and arterial access, assessing the patient, and beginning medical treatment. The authors have not experienced an increased complication rate with this practice, and see no distinct advantage to performing this procedure in the operating room. Proper preparation of the site and sterile technique do not lead to any increased risk of complication. The operating room is used for EVD placement if the child required a craniotomy or other operative intervention (e.g., exploratory laparotomy). In these instances, where general anesthesia is required for an extended period of time, the monitoring of the ICP intraoperatively can give warning of a problem that can either be treated or needs immediate diagnostic studies at the end of the surgery.

The authors routinely treat all NAT patients with evidence of brain injury with prophylactic antiepileptic medication. The incidence of seizures within the first 7 days after TBI is 4% to 25% [52], but can be upward of 80% in infants following even minor trauma. It is clear that seizures during the early period after injury are detrimental to the already injured brain [53]. Seizures create a hypermetabolic state that the injured brain may not be able to regulate, creating a second insult. The authors often monitor young children and infants with a severe TBI in the event that they are having subclinical seizures and often need to use multiple medications to get the posttraumatic seizures in these children under control.

The management of the injured patient and the severely injured victim of NAT patient involves achieving and maintaining physiologic stability, recognizing and treating elevated ICP, and preventing secondary brain injury. A stepwise approach to these issues is suggested and continuous surveillance for a change in the patient (neurologic or physiologic) is required.

Pediatric neurophysiology

Although it is believed that the injured pediatric brain has far more potential for recovery, reassignment of function, and plasticity than the adult, infants and young children are well known to have very poor outcomes [5,11]. Although it is unclear as to the exact etiologies, the protocols for treatment for children have followed the adult guidelines with little toward pediatric-specific approaches. There is a lack of literature in this area, so physiologic support and optimizing the posttrauma environment are also the goals in pediatric TBI. It is vitally important to prevent secondary injury, and an understanding of pediatric neurophysiology is central to this goal. The complex metabolic derangements following adult head injury are poorly understood [54], and even less is known in children. Only recently has attention turned to the effects of TBI on the immature brain [55], and it is becoming clear that children are not small adults.

Central to the management of the injured child, as in the adult, is the lessening of secondary injury (e.g., hypoxia, ischemia, and elevated ICP). After

NAT, similar to the adult, oxygenation or O2 saturation should be kept above 94% and blood pressure should be maintained above 2 standard deviations below the mean for age. Most of this can be co-managed with direction with the pediatric intensivist or pediatric trauma surgery teams. Supplementation with appropriate ventilatory support, fluid management, and pressor support is necessary to maintain adequate cerebral perfusion and oxygenation for the injured brain to recover. Meticulous adherence to details lessens the impact of avoidable second insults.

Cerebral perfusion pressure: mean arterial pressure

Cerebral perfusion pressure (CPP) by definition is the difference between mean arterial pressure (MAP) and ICP and must be maintained at an adequate level to prevent secondary ischemia and cerebral death. In adults, a CPP of 70 mm Hg is suggested as a minimum value to prevent secondary ischemia [28], although this is controversial and some consider 50 mm Hg adequate. It should be noted that CPP is a calculated parameter reflecting a global perfusion pressure; even with an adequate CPP of 70 or more, focal areas of injured brain may still be ischemic [53]. The lower limit of cerebral autoregulation is age dependant [56–58], making a recommendation for a threshold value for CPP in the pediatric patient difficult.

The authors use the mean MAP for age minus the ICP for age as a guide for CPP. Despite the lack of conclusive data, the authors recommend a goal CPP of 40 to 50 mm Hg in infants and toddlers and 50 to 60 mm Hg in older children [9]. To achieve this goal, MAP or ICP can be manipulated, often concomitantly. Hypotension is clearly associated with poor outcome in adults [59] and children [60] after TBI, and efforts are made to prevent any episode of hypotension. Despite the role of MAP in the CPP equation, no study has shown that induced hypertension has any impact on the final outcome after TBI. Assuming an intact cerebral autoregulatory mechanism, hypotension leads to cerebral vasodilatation with a resultant increase in CBF and ICP. By artificially increasing MAP, cerebral vasoconstriction occurs, leading to a decreased CBV and ICP with preserved CBF [61]. Because of the variability in age and size of the pediatric NAT patient, an ideal MAP is not a single value for all patients; treatment must be tailored to the child and changes made as response to treatment is closely monitored. As a general guide, systolic blood pressures at or below the 50th percentile for age should be considered significantly hypotensive and aggressively treated. In the setting of elevated ICP, low MAP, and forced hypertension, central venous access with central venous pressure monitoring capability and an arterial blood pressure line are mandatory. The authors do not routinely place Swan-Ganz catheters in infants and young children, but the information gained from this monitoring can be very useful in a select group of patients, such as those with neurogenic pulmonary edema. Before the introduction of vasopressors, adequate volume resuscitation hematologic indices (hematocrit and hemoglobin) should be confirmed. Once the patient is adequately hydrated (as assessed by central venous pressure and urine output) and hematologically stable, vasopressor agents should be added if systolic pressures are still below the 50th percentile for age. Dopamine is generally the first-line agent of choice, and doses of 10 μg/kg/min are optimal to obtain the α-adrenergic vasoconstriction needed to increase MAP. Dopamine should not be used in this setting at doses less than 5 μg/kg/min in head-injured patients because cerebral vasodilatation can occur with resultant elevation in ICP.

CPP: ICP

The second variable in the CPP equation is ICP. It has become standard to use 20 mm Hg as the threshold above which the ICP is considered elevated. This value is based on adult head-injury studies that clearly show that patients with ICPs greater than 20 mm Hg, even for a brief period of time, have significantly worse outcomes than those who maintain ICPs less than 20 mm Hg [62]. Some argue that ICPs above 15 mm Hg should be treated aggressively [29,63], ideally avoiding ever reaching the threshold of 20 mm Hg. As with most critical neurointensive care issues in head injury, few studies exist to validate the adult findings in children. Until this issue is critically examined in the pediatric population, the authors recommend using a threshold of 15 mm Hg as the upper limit of normal for infants and toddlers and 18 mm Hg for children greater than 5 years.

Neurointensive care: control of elevated ICP

As monitoring lines are being placed, and physiologic stabilization beginning, an aggressive, focused effort should be made toward lowering

elevated ICP. The treatment of elevated ICP follows a stepwise algorithm (Fig. 1), with continual monitoring for response to treatment. NAT should be considered multisystem trauma until proved otherwise, and concomitant injuries may require deviation from the protocol or omission of certain steps. In most cases of NAT, however, it is the brain injury that dictates the course of treatment, with other injuries evaluated and treated in the midst of aggressive neurointensive care. The ICP treatment algorhythm assumes that there are no surgical mass lesions present, or that a surgical mass lesion has been addressed in the operating room. Before progressing to each successive step on the algorhythm, a CT scan is recommended to ensure that a surgical mass lesion has not appeared to explain the lack of effectiveness of treatment. Each step on the ICP treatment algorhythm should be given opportunity to demonstrate effectiveness, or lack thereof, before making the decision to escalate therapy. No further escalation of therapy is required once a period of 24 hours has passed with ICP less than 15 mm Hg. Once a period of 24 hours has passed without any additional treatment to maintain ICP below 15 mm Hg, the algorithm can be followed in reverse, thereby decreasing the intensity of treatment in the opposite order that it was escalated. In general, a period of 24 hours should elapse with stable ICPs before decreasing therapy further. If the ICP becomes elevated during this de-escalation period, therapy should again be intensified in a stepwise manner until a new 24-hour period has elapsed with stable ICPs. The most critical piece of monitoring equipment during elevated ICP treatment is the EVD, and removal should be the last ICP treatment to be discontinued.

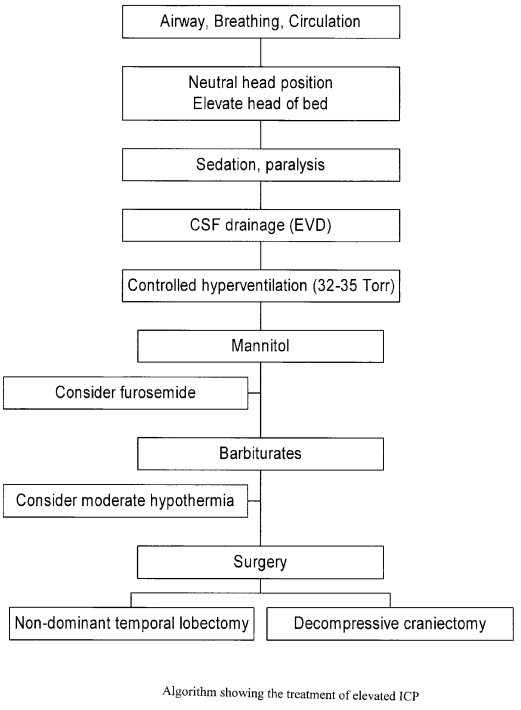

Fig. 1. Algorithm showing the treatment of elevated intracranial pressure.

Head position

Assuming no thoracolumbar fractures are present, all children with elevated ICP should have the head of their bed elevated 30 degrees and their necks maintained in neutral position. In so doing, cerebral venous (and possibly CSF) drainage is optimized, thereby lowering CBV and ICP. In a prospective randomized study of 22 severely head-injured adults, these maneuvers significantly reduced both ICP and mean carotid arterial pressure, although there was no change in CPP or CBF [64]. Somewhat controversial in that the clinical effect is rarely dramatic, and no study has ever been performed demonstrating effectiveness in children, head positioning is nonetheless recommended as a simple means of optimizing intracranial physiology.

Sedation and neuromuscular blockade

Once appropriate monitoring, most importantly an ICP monitor, is in place, elevated ICP is treated by sedating and paralyzing the brain-injured child. By reducing the noxious stimulation encountered in the ICU setting, lessening pain, and eliminating the effect of muscle tension on ICP, sedative and paralytic medications are effective in reducing ICP. Although no controlled trial of specific drug regimens has been performed, short-acting agents are preferred to allow for a short emergence time once the medications are discontinued. Fentanyl (1 to 4 μg/kg) or morphine (0.1 to 0.3 mg/kg) in combination with vecuronium (0.5 to 1 mg/kg/h with titration to paralysis) is recommended as the agents of choice in the pediatric population. Single-agent sedation, in contrast to a combination of narcotic with benzodiazepines or barbiturates, simplifies the drug regimen and allows for predictable, relatively rapid, emergence. To eliminate the peaks and troughs of sedation-paralyzation that occur with intermittent dosing, the authors routinely use constant infusions of

these agents, titrating them as needed to achieve lower ICPs. The level of neuromuscular blockade can be assessed easily at the bedside by the use of a twitch monitor; the authors strive for 0 to 0.25 twitches. The adequacy of sedation can be determined by heart rate, blood pressure, and most importantly, ICP.

CSF drainage

By draining CSF in a controlled manner by an EVD, total intracranial volume, and secondarily pressure, is reduced. In addition, by decreasing the CSF fraction of total intracranial volume, this may improve perfusion from the compromised CBF. Despite the simplicity of this concept, little scientific evidence exists that it is efficacious in treating elevated ICP, especially in children. A small number of studies have reported the positive effect of CSF drainage on CBF [65,66] and ICP [65] in adults; studies in children show similar results [29,63]. Two schools of thought exist as to how best to drain CSF: intermittently as needed to lower ICP when threshold (15 mm Hg) is reached or continuously. To date, no controlled study exists to show that one method is superior to the other, but the authors' practice is to drain continuously at 5 mm Hg. If intermittent drainage is used, the drain should be opened every time ICP is sustained above 15 mm Hg for greater than 5 minutes.

Controlled hyperventilation

Long a topic of debate in TBI, controlled hyperventilation exploits the cerebrovascular response to changes in $PaCO_2$ by inducing vasoconstriction at the arteriolar level, thereby decreasing CBV and ICP. A 1 mm Hg change in $PaCO_2$ results in a 3% change in CBF in adults [49]. It has been suggested that hyperventilation alone could be used to control elevated ICP in children [39]; however, this concept has recently been questioned. Animal studies have shown this effect to be short-lived [67], and with chronic use hyperventilation produces a loss of the bicarbonate buffer in CSF making the cerebrovasculature exquisitely more sensitive to changes in $PaCO_2$ [9]. More importantly, the decrease in CBF induced by hyperventilation puts the brain at risk for ischemia. In the acute setting, hyperventilation has been shown to induce global hypoperfusion and ischemia [44,68,69], and one randomized, controlled study demonstrated worsened outcomes after TBI when profound hypocarbia was induced in adults [43]. Based on the available evidence, most of which is based on the adult brain, it is recommended that moderate hyperventilation ($PaCO_2$ 32 to 35 mm Hg) be used in the early period after severe NAT to aid in control of elevated ICP; more profound levels of hypocarbia should be guided by the clinical setting and CBF monitoring.

Osmotic therapy

Of the osmotic diuretics used to control elevated ICP, mannitol and furosemide are the most widely used. Mannitol lowers ICP by two main mechanisms. By rapidly reducing blood viscosity, mannitol immediately reduces CBV without changing CBF [70]. This can be understood by considering Poiseuille's law, which when applied to the cerebrovascular system, states that reducing blood viscosity is balanced by a decrease in vessel diameter resulting in a constant CBF. This effect is transient, however, and only operates when cerebral autoregulation is intact. If cerebrovascular autoregulation is dysfunctional, the decreased blood viscosity leads to an increase in CBF, and no change in vessel diameter, CBV, or ICP. If given too rapidly, this situation can be made worse by causing systemic hypertension leading to a transient rise in CBV and ICP. The second mechanism by which mannitol exerts it's ICP-lowering effect is by osmotically dehydrating the brain through an intact blood-brain barrier. Despite this seemingly simple osmotic dehydration concept, considerable controversy exists as to the exact mechanism by which mannitol is able to lower ICP, although a rheologic effect with the potentiation of metabolic autoregulation is the most likely contributor [71,72].

Despite the controversy surrounding its use, in the authors' experience mannitol is an effective and safe ICP-lowering therapy if used properly. Initial doses of 0.25 g/kg effectively lower ICP and allow for dose escalation if the patient becomes refractory to this low starting dose. Dosing can be intermittent as needed to lower ICP, although the authors place the child on a scheduled dose every 4 to 6 hours as needed for a particular threshold of ICP. Before initiating mannitol therapy, it is important to ensure euvolemia, because systemic dehydration and hypovolemia may result. Additionally, careful attention must be paid to serum electrolytes and osmolality, because serum osmolality greater than 320 mMol/L is associated with the potential for renal failure [73]. A recent report suggests that higher serum osmolalities may be better tolerated in the pediatric population [74], but

until further evidence becomes available, the authors recommend discontinuing mannitol therapy once serum osmolality reaches 320 mMol/L. Furosemide, a loop diuretic, is occasionally used to potentiate the effectiveness of mannitol. The authors have found this regimen useful in setting of an attenuated response to mannitol alone, but do not give furosemide routinely.

Barbiturate therapy

In the setting of NAT and elevated ICP, barbiturates have two primary effects on the injured brain. First, barbiturates have long been known to be neuroprotective by decreasing the metabolic demands of the brain [75]. By lowering the metabolic demands of the injured brain, ischemic levels of CBF are tolerated for longer periods of time. Second, the reduction of cerebral metabolic demand leads to a decrease in CBF and CBV, with a subsequent decrease in ICP. As with other aspects of TBI therapy, barbiturates are surrounded by controversy. Numerous studies point to the effectiveness of barbiturates in treating refractory elevations in ICP [28], and there is evidence that detrimental excitatory amino acid concentrations are lowered with barbiturates [76]. In contrast, a randomized, controlled clinical trial in adults failed to demonstrate a positive effect on outcome after TBI [77]. To date, no clinical trial of barbiturate therapy has been conducted in the brain-injured child, and no standard exists to guide therapy. Barbiturates are generally reserved for refractory cases of intracranial hypertension, but their use should not be withheld if other treatments methods have failed. Before beginning barbiturate therapy, euvolemia must be achieved, and a normal MAP must be present. Barbiturates are profound cardiac depressants, and their indiscriminate use may lead to cerebral ischemia and systemic circulatory collapse. The authors recommend the use of continuous electroencephalography (EEG) monitoring to guide treatment response and as a gauge to determine when further dosing is ineffective. Barbiturate coma is achieved when 10 to 20 seconds of burst suppression is noted on EEG [53], and further dosing is not likely to make a significant impact on ICP. It should be noted that barbiturate coma or total burst suppression are not the goals of barbiturate therapy, but an end point to its usefulness. Barbiturates should be dosed based on ICP, not EEG. The authors' protocol involves pentobarbital (thiopental also has been used successfully) dosed initially at 5 mg/kg every 4 to 6 hours or intermittently as needed. Very often, intermittent doses of pentobarbital control ICP and no dose escalation is required. If, however, the dosing interval is decreasing, or ICP remains refractory to intermittent dosing, full coma can usually be achieved with a loading dose of 10–15 mg/kg given slowly over 1–2 hours followed by continuous infusion of 1–2 mg/kg/hour. This may require an increase to 2–3 mg/kg/hour in order to maintain burst suppression on EEG. It is important to monitor blood pressure and respiratory rate when high-dose pentobarbital is used; vasopressors are often required to maintain MAP. The end point of treatment is up to a 90% burst suppression on EEG or hypotension refractory to vasopressors.

Hypothermia

Hypothermia in the treatment of TBI was first reported in children in 1959 [78], but other than scattered reports, scientific rigor had never been applied to the technique. Recently, however, renewed interest in therapeutic hypothermia after TBI has prompted randomized, controlled clinical trials and basic research. In adults, moderate hypothermia (32 to 34°C) has produced significant ICP reductions [79,80], improved CPP [80], and trends toward improved outcomes [79–81]. A more recent study shows improved neurologic outcomes in adult patients treated with moderate hypothermia at 3 and 6 months after injury [82]. The multicenter study in adults failed to show efficacy, although the data did suggest an age-related effect with younger adults (<40 years) doing better than older patients. Because no children were included in this study, a phase II multicenter trial of therapeutic moderate hypothermia in children is currently underway. Because of the lack of data, it is difficult to make solid recommendations about the use of therapeutic hypothermia in pediatric NAT patients. Before beginning the multicenter therapeutic hypothermia trial at the authors' institution, their practice was to cool patients to 32 to 34°C when ICP was refractory to barbiturate coma. Further study is needed to make more concrete recommendations for the use of this treatment modality.

Surgical treatment of refractory ICP

Once all medical treatments for control of elevated ICP have proved ineffective, the last option available to regain control of intracranial hyper-

tension is surgical. Initially described by Cushing in 1905 [83], decompressive craniectomy for refractory ICP has always been a controversial topic. No controlled studies have been performed in adults or children, but several reports indicate good results with this procedure, with the most success seen in children and young adults [84–86]. Another surgical option, and the one used at the authors' institution in selected cases of uncontrollable intracranial hypertension, is nondominant temporal lobectomy. The authors prefer this procedure to decompressive craniectomy for two reasons. First, by removing the temporal lobe, room is created in the intracranial compartment for the remaining parenchyma to fill. Additionally, the most concerning vector of compression, the temporal lobe into the midbrain, is removed. Second, decompressive craniectomy can set the stage for the brain to herniate out of the skull and become strangulated by the bone edge producing large volumes of infarcted brain. Some have reported success in children in these instances but no controlled trial has shown efficacy yet for this method. It should be noted that once a child with diffuse brain injury, as is seen in most cases of NAT, has reached this point, the chances for a meaningful outcome are minimal and serious consideration should be given as to whether surgical treatment of ICP is in the best interests of the patient. As a rule, the authors do not perform surgery on victims of NAT if they become refractory to medical management. The ethics of such surgery are beyond the scope of this article, and a decision to undertake such surgery should be tailored to the clinical and social situation.

Summary

Childhood victims of NAT with severe brain injury require a multidisciplinary approach to their management if a good outcome is to occur. Despite the grave prognosis of these patients, an initial aggressive treatment strategy is warranted, because enough children go on to a meaningful life. A vigilant evaluation for multisystem injuries and vigorous resuscitation should be followed by prompt surgical intervention as indicated. Most NAT victims do not require surgical treatment of their brain injury, but do require ICP monitoring. A stepwise approach to the treatment of elevated ICP optimizes CPP, minimizes secondary brain injury, and increases the chances of a meaningful recovery. The future holds promise for these patients because a concerted effort is underway to understand pediatric TBI on a molecular level, and targeted therapies based on current basic research will certainly improve the neurointensive care, and eventual neurologic outcomes, of these children.

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