Management of Traumatic Brain Injury

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KEYWORDS

- Traumatic brain injury • Neurotrauma • Secondary injury • Intracranial monitoring
- Intracranial pressure • Craniotomy • Craniectomy • Decompression

KEY POINTS

- The diagnosis of severe traumatic brain injury is based on a variety of clinical and radiographic data and encompasses a wide heterogeneity of structural and physiologic insults.
- The concept of treatment thresholds is somewhat outdated; although there are specific physiologic ranges at which secondary injury clearly takes place, treatment of an individual patient's physiology at a given point in time must take into account numerous concurrent events, including the evolution of extracerebral injuries, structural brain lesions, cerebral edema, and cerebral hypoxia/ischemia.
- The options for treatment of severe traumatic brain injury are just as varied as the presenting pathologies and may include surgery for evacuation of mass lesions or decompression of herniating or compressed cerebral tissues, drainage of cerebrospinal fluid, pharmacologic sedation and paralysis, ventilator management, hyperosmolar euvolemic therapy, and prophylaxis against seizures, thromboses, and a variety of other complications.

INTRODUCTION

According to the Centers for Disease Control and Prevention, injury remains the leading cause of death in the United States for all persons aged 1 to 44 years, is the third leading cause of death for those aged 45 to 64 years, is the fifth most common cause of death for infants less than a year of age, and ranks seventh in those 65 years and older.[1] Traumatic brain injury (TBI) comprises the cause of death for approximately one-third of people with multitrauma.[2] The public health importance of TBI, therefore, cannot be overestimated.

RELEVANT ANATOMY AND PATHOPHYSIOLOGY

Severe TBI (sTBI) has traditionally been defined as those presenting with head trauma and brain injury with a postresuscitation Glasgow Coma Scale (GCS)[3] score of 3 to 8, although other classification schema exist. Patients with sTBI, and some with

so-called moderate TBI, that is, a GCS score of 9 to 12, require intensive care, sometimes for several days to a few weeks. The pathophysiology of TBI involves the initial blow (primary injury) that may result in numerous structural pathologies as well as initiation of the chemical, electrical, and inflammatory cascade of physiologic events that comprise the secondary injury of the brain. Furthermore, secondary insults, such as hypotension, hypoxia, seizure, and other physiologic events, have a profound impact on the degree of secondary injury sustained and ultimately the functional outcome of patients. Patients with polytrauma and sTBI represent a significant challenge because of the potential for ongoing secondary insults from other organ injuries and vascular and musculoskeletal trauma.

Thus, the treatment of sTBI must begin the moment that patients are assessed by first responders. Emergency personnel and physicians in multiple specialties must be conversant with the diagnosis and management of severe TBI so as to prevent secondary insults to the degree possible, to rapidly coordinate the surgical care of structural injuries requiring surgery, and to minimize secondary cerebral injury to improve long-term outcomes after sTBI.

Structural cerebral injury occurring as part of the primary injury cannot currently be repaired, but the effects of structural injury must be mitigated. Surgical repair of a variety of structural injuries is often undertaken early (in the case of compressive lesions causing pressure on the brain) or later in the course (as in the case of evolving cerebral edema, craniofacial repairs, and treatment of cerebrospinal fluid [CSF] leak or infection). Mass lesions may be classified as extra-axial (outside the brain tissue but inside the cranium) or intra-axial (within the brain tissue). Certain intracranial hematomas require immediate surgical intervention, generally those with sufficient volume to create outright cerebral herniation or cerebral compression that is symptomatic, that is, causing coma, neurologic deficit, or intracranial hypertension.

Management of intracranial pressure (ICP) in the face of hemorrhagic lesions and cerebral edema can be challenging, depending on the space occupied in the intracranial compartment by hematomas and edematous brain tissue. The Monroe-Kellie hypothesis states that the intracranial compartment has fixed volumes of the following components: cerebral tissue, cerebral blood, and CSF. As one compartment increases in volume or a mass lesion is added to the compartment, compensation must occur to maintain a normal ICP. This compensation initially involves displacement of CSF and venous blood into the spinal canal; but once a critical volume is reached in the intracranial compartment, cerebral compliance decreases and elastance increases, resulting in larger changes in ICP with smaller changes in volume. Therefore, small reductions in CSF can have a large impact on ICP control at this stage; likewise, removing mass lesions or increasing the size of the cranial compartment via craniectomy and duraplasty can very effectively control ICP.

CLINICAL PRESENTATION

Patients with sTBI by definition present in coma. They often arrive at the hospital having been intubated in the field because of suppression of respiratory function caused by the brain injury and/or inability to protect the airway because of the depressed level of consciousness. Trauma patients with TBI must be assessed for the presence of other injuries and should be presumed to have them until proven otherwise, given their inability to report history or symptoms.

Depending on the mechanism of injury, other injuries may be rather self-evident or occult. Typical high-speed motor vehicle crash patients or a pedestrian struck by a vehicle will often present with gross signs of trauma, including abrasions, contusions,

lacerations, degloving soft tissue injuries, and a variety of musculoskeletal deformities suggesting fractures, dislocations, or tendon or ligamentous injuries of the spine, thorax, pelvis, or extremities. Many of these injuries may cause sufficient internal or external blood loss resulting in hypotension and hemodynamic instability. Internal abdominal organ injuries may manifest as an acute abdomen with hypotension and abdominal distension and tympany, whereas hemopneumothorax manifests as respiratory insufficiency or cardiac arrest; cardiac or large vessel injuries may present with hypotension or cardiac arrest. Fall patients may show minimal signs of external trauma (especially for lower heights) but harbor significant internal injuries. Those presenting after assault may present with multiple missile entries and exits, stab wounds, manifestations of blunt trauma, or combinations of these. Recreational injuries may present in any number of ways, and workup requires an accounting of the activity involved and details of the mechanisms of injury.

DIAGNOSIS
Airway, Breathing, and Circulation

As with all injured patients, assessment and treatment (done simultaneously) begins with the ABCs: management of patients' *airway*, *breathing*, and *circulation* first. The next, or *D* portion of the assessment, is for *disability* (neurologic status). A GCS score is assigned both before and after resuscitation based on patients' responsiveness with respect to eye opening, motor activity, and speech (**Table 1**). As part of the motor examination, any lateralizing signs must be noted, as these can signal the location of intracranial lesions or the presence of a concurrent spinal cord injury (as can a neurologic deficit at a particular spinal level).

Glasgow Coma Scale

The GCS has been used for decades and has both high interrater reliability and prognostic value for mortality and morbidity for large populations. Prognosis relies on the postresuscitation score, and the motor examination is most sensitive. However, any given patient presenting with a specific GCS score may ultimately have a wide range of outcomes, depending on the type of structural injury, the relative degree of secondary injury burden, the development of neurologic or systemic complications,

Table 1
The Glasgow Coma Scale

GCS Component	Examination Finding	Score
Eye opening	Spontaneously	4
	To sound	3
	To pressure	2
	None	1
Verbal response	Oriented	5
	Confused	4
	Words not sentences	3
	Sounds not words	2
	None	1
Motor response	Obeys commands	6
	Localizes to pain	5
	Normal flexion	4
	Abnormal flexion	3
	Extension	2
	None	1

and a host of known and unknown genetic and epigenetic factors. Ergo, treatment is aimed at maximizing the healing milieu and minimizing detrimental events; an initial survey of traumatic findings associated with TBI must be done as rapidly as possible.

Pupils

Additional neurologic signs include the size, symmetry, and reactivity of the pupils, as abnormalities are not only helpful in determining the presence of cerebral herniation requiring emergency interventions but are also associated with other forms of trauma, including blunt vascular injury (Horner syndrome), direct trauma to the globe, or direct injury of the third nerve (as opposed to compression caused by cerebral herniation). Pinpoint pupils may signify a brainstem injury. Other factors affecting the level of consciousness, such as the presence of certain intoxicants, can also affect the pupillary examination. The absence of brainstem reflexes, such as corneal and gag reflexes, after adequate establishment of perfusion and oxygenation from resuscitation and restoration of normothermia, portends a poor prognosis but is sometimes reversible with ongoing stabilization.

Cranium

After the rapid neurologic examination and GCS score are obtained, signs of trauma to the head and neck must be identified. External signs of head trauma must be carefully sought and documented, sometimes requiring clipping of hair to determine the nature and extent of scalp abrasions, contusions, and lacerations and the presence of open depressed skull fractures within lacerations. The presence of mastoid ecchymoses (Battle's sign) or bilateral periorbital ecchymoses (raccoon eyes) are often associated with basilar skull fractures. The calvarium should be palpated for deformities signifying closed skull fractures.

Eyes

Early survey including pupillary examination and assessment of corneal reflexes and the presence of periorbital ecchymoses has been mentioned. Periorbital edema may make the ocular examination more difficult; head elevation, application of iced-saline-soaked gauze pads, and the use of instruments to evert the eyelids may aid the examination. Extraocular movements should be assessed as soon as patients are able to follow commands, as cranial nerve palsies may be due to impingement in the orbit, compression within the cranium, or primary damage to the nuclei. Gaze deviation may signal the presence of nonconvulsive seizure activity/status epilepticus. The presence of important signs should be noted. For example, hyphema (typically an ophthalmologic emergency) or subconjunctival hemorrhage indicate direct trauma to the globe and conjunctival petechiae may indicate hypoxemia. For those with the most devastating of injuries resulting in brain death, the presence of oculocephalic and oculovestibular reflexes needs to be assessed.

Ears and Nose

The presence of hemotympanum or external auditory canal hemorrhage on otoscopic evaluation should be investigated for cause and associated injuries (eg, skull fracture, ruptured tympanic membrane, or trauma to the ossicles and other structures of the ear). The presence of CSF otorrhea or rhinorrhea signifies skull base fracture and dural laceration and is a risk factor for later development of meningitis. Although most skull base fracture-associated CSF leaks resolve spontaneously and do not require any treatment (including lumbar drainage or administration of antibiotics), some CSF leaks may require later lumbar drainage; others may require immediate or delayed open or

endoscopic surgical repair, especially those associated with frontal sinus fractures. Except for transoral gunshot wounds, antibiotics are generally reserved for perioperative surgical patients (as per standard practice for craniotomy), so as to avoid selection of resistant organisms should infection occur. Epistaxis must be controlled, especially if arterial; this may require careful packing or interventional embolization.

Face

Concomitant facial fractures and soft tissue injuries are common and may impact surgical decision-making, so a thorough assessment of these injuries is mandatory, including imaging when needed and careful repair and control of active bleeding. Cranial integrity in multiple fractures relies on craniofacial bone structural integrity; however, fracture repair is often delayed because of the presence of brain edema, so surgical approaches must be coordinated among specialists.

Neck

Coincident blunt vascular injury (BVI) may occur and should be suspected in the following clinical scenarios[4]:

- Neurologic deficit unexplained by brain computed tomography (CT)
- Monoparesis in alert patients without brachial plexus injury suspected
- Lucid interval followed by neurologic deterioration
- Isolated dysphasia
- Unilateral headache after trauma
- Arterial epistaxis
- Horner syndrome (ptosis, miosis, anhidrosis)
- Neck hematoma, ecchymosis, or crepitus

Risk factors for blunt cerebrovascular injury include[5]

- Cervical hyperextension injury, especially with rotation
- GCS of 8 or less
- Seatbelt injury to the neck, hanging, or strangulation mechanism
- Skull base fracture, especially through the foramen lacerum or carotid canal
- Facial fractures, especially Le Fort II and III
- Cervical spine fracture
- Other vascular injuries, for example, thoracic aorta

Maintaining a high index of suspicion and evaluating for blunt vascular injury (BVI) in appropriate cases is important, as the consequences of dissection, thromboembolism, and occlusion are avoidable secondary insults to the brain resulting in potentially large territories of ischemia, which can not only add to the neurologic deficit burden but may also be fatal.[6,7]

Secondary Surveys

As soon as patients are testable, more detailed assessments should be done, including tests of all cranial nerve functionality, sensory and motor abilities (including tremor and coordination), speech (for dysarthria, expressive and receptive dysphasia), and cognition (multiple domains, especially awareness and memory early on).

DIAGNOSTIC PROCEDURES

Systemic causes of a depressed level of consciousness must be ruled out, including hypoxia, hypoperfusion, hypoglycemia or hyperglycemia or the presence of

intoxicants. Arterial blood gases, serum electrolytes and glucose, serum alcohol level, and urine toxicology tests are, therefore, commonly needed emergently to gauge the impact of physiologic derangements on the neurologic examination.

Neuroimaging

Once patients have been adequately hemodynamically stabilized, the mainstay of diagnosis for sTBI is CT of the brain and skull. This imaging may be augmented by CT angiography for potential blunt craniocervical vascular injury and CT of the face (to fully evaluate craniofacial fractures and degree of pneumocephalus) and should always also include high-quality, thin-cut, 3-dimensional reconstructed views of the cervical spine, if available, in order to diagnose any comorbid cervical column injuries (common). MRI of the brain is not typically used in the workup of acute trauma because of the safety of the scanner environment, the length of time to obtain the study, and the lack of meaningful additional information to guide emergency management. Diagnostic cerebral angiography is not used in the diagnosis of brain injury itself but may be needed to assess blunt vascular injuries more fully in the hours or days after presentation. Advanced neuroimaging with PET or single-photon emission CT is sometimes used in the intensive care phases of sTBI management in research centers or high-acuity centers with advanced imaging and other treatment modalities available. The timing and number of follow-up CT scans depends on patients' presenting clinical and radiographic findings, presence of antithrombotic drugs or coagulopathy, trends in neuromonitoring values, age, and ability to obtain adequate serial neurologic examinations.

Neuromonitoring

After initial stabilization and treatment of patients with sTBI, consideration is given to the use of invasive and noninvasive neuromonitoring techniques. Such monitoring devices may be intraparenchymal (fiber-optic catheters inserted through the lumen of a bolt secured to the skull) or intraventricular. These catheters may be used to measure continuous ICP; from that value, the cerebral perfusion pressure (CPP) may be calculated as the difference between mean arterial pressure and ICP. The advantages of parenchymal catheters include ease of placement and ultralow complications rates.

Numerous studies have demonstrated improvements in mortality and outcome with ICP monitoring and goal-directed treatment,[8–11] although rigorous scientific conclusions have been somewhat inhibited by their retrospective nature or other limitations in study design.[12] Although one prospective controlled trial[13] at 6 hospitals in South America randomizing patients with sTBI to either ICP monitor-guided treatment or treatment guided by frequent clinical reexamination and radiographic studies showed no statistically significant difference in 6-month outcome (as assessed by the Glasgow Outcome Scale-Extended), this study is not an indictment of the use of ICP monitoring; rather, it highlights that primary use of numerical electronic ICP values or signs of intracranial hypertension on examination or radiographic studies may be equally as important in driving ICP-related decision-making. Practically speaking, such decisions are made on a daily basis through the synthesis of numerical ICP data, clinical examination changes, and radiographic imaging evolution.

External ventricular drainage catheters may be used in a therapeutic manner as well as diagnosticly. There are 2 forms available; one is a simple ventricular catheter and a fluid-coupled transducer to measure ICP and monitor the ICP waveform. The disadvantage of this method is that during periods when the catheter is open to drainage for therapeutic purposes (to remove CSF volume and, therefore, decrease ICP), an

accurate reading cannot be obtained. Thus, a second technology has been developed that contains a fiber-optic transducer at the tip of the catheter that can read ICP continually, even when the system is open to drain CSF. Disadvantages of EVD in general include higher infection and hemorrhage rates than for parenchymal monitors.

In addition to ICP monitoring, there are multiple other advanced neuromonitoring options for patients with sTBI. These options include parenchymal catheters to measure brain tissue oxygen (pB_tO_2)[14] and brain temperature and cerebral microdialysis to monitor extracellular glutamate,[15] lactate, and pyruvate (among other molecules) to assess for excitotoxicity and tissue ischemia.[16,17] Additionally, intravenous jugular bulb catheters to assess jugular venous saturation of oxygen ($S_{jv}O_2$) as an estimation of cerebral extraction of oxygen are sometimes used.[18–20] Parenchymal pB_tO_2 monitoring techniques tend to be used in patients with worse injuries requiring more intensive care interventions, and the use of the technique has been associated with improvement in outcomes.[21–26] Microdialysis techniques tend to be used only in highly specialized centers or research settings, but preliminary work suggests that using data derived from microdialysis techniques may help predict outcomes (both mortality and functional outcome at 6 months). The use of $S_{jv}O_2$ monitoring in sTBI requires a fair amount of troubleshooting and interpretation. Any maneuver or physiologic event that results in decreased oxygen delivery to the brain or increased oxygen extraction by the brain will result in low $S_{jv}O_2$, provided the device is reading the venous saturation properly, so the values cannot be interpreted in isolation. The technique must be used in conjunction with other assessments (systemic hypoxia, ventilator settings, pB_tO_2 measurements, and so forth) to put the $S_{jv}O_2$ values into context to drive clinical decision-making. That being said, some studies have shown improvements in outcome when the technique is used to guide treatment of jugular venous desaturations.[18,19] Parenchymal probes to assess regional cerebral blood flow (CBF) are also available,[27] though not yet in common usage; however, as techniques become more reliable and more data become available, the addition of direct measurements of blood flow in the injured brain will likely prove to be a valuable adjunct in the intensive care management of sTBI. Finally, the use of electroencephalography (EEG), particularly continuous EEG, in comatose intensive care unit (ICU) patients with TBI plays an important role in diagnosing subclinical seizures so that they can be treated in a timely fashion to prevent secondary injury.[28,29]

MANAGEMENT OPTIONS AND OUTCOMES
Treatment Thresholds

The concept of treatment thresholds has been an important part of decision-making for decades; however, understanding the physiology behind these thresholds and acting accordingly is more important than blind adherence to maintaining a particular set of numeric values.

Hypotension has long been known to have an adverse effect on patient mortality after TBI (mortality being 35% in those admitted with TBI and systolic blood pressure [SBP] of less than 85 mm Hg vs 6% without hypotension in a seminal study from the 1980s).[30] This concept was confirmed in a Traumatic Coma Data Bank study demonstrating a doubling of mortality (from 27% to 55%) in patients with sTBI experiencing early hypotension (any measurement of SBP <90 mm Hg).[31] Avoiding any SBP less than 90 mm Hg requires a higher average SBP than 90 mm Hg, and for decades maintenance of SBP well greater than 90 to 100 mm Hg has been a mainstay of therapy (as long as autoregulatory collapse does not cause major elevations in ICP). In young healthy patients, permissive hypertension can sometimes be used. Pain or

dysautonomia must be considered for those with persistent hypertension and no pre-morbid hypertension diagnosis. Age is a factor in determining appropriate blood pressure thresholds, and recent data suggests that for patients 50 to 69 years of age, SBP should be maintained at greater than 100 mm Hg and greater than 110 mm Hg for patients 15 to 49 years of age or greater than 70 years of age.[32] In general, the strict avoidance of hypotension and concomitant hypoperfusion of the brain is a critical aspect of sTBI management. Hypoxia is also to be avoided, as any episode of hypoxia (defined as $Pa_{O_2} \leq 60$ mm Hg or apnea or cyanosis in the field) is independently associated with a poor outcome after sTBI.[33]

ICP has variably been considered to be normal at less than 20 or 25 mm Hg in sTBI studies. Traditionally, ICP target ranges of less than 20 mm Hg have been used; but slightly higher values are tolerable as long as CPP is adequate (60–70 mm Hg or greater), ICP waveforms are not pathologic, and/or significantly higher or sustained elevations are not occurring. In decades past, aggressive attempts to artificially elevate the CPP to sustained levels higher than 70 mm Hg using fluid and pressors led to systemic complications, most notably adult respiratory distress syndrome[20,34], so global application of that technique has largely been abandoned for nearly 2 decades. However, a specific patient may require higher CPP if, for example, there are consistent pressure-dependent examination changes or neuro-monitoring parameters suggest cerebral ischemia.

Surgical Management

Rapid evacuation of mass lesions causing neurologic compromise most commonly occurs shortly after arrival to the hospital. Although each patient must be considered individually for his or her surgical indications, size and volume criteria as well as guidelines based on midline shift, appearance of cisterns, and other markers of mass effect have been published.[35–39] Occasionally, patients are managed nonoperatively initially, but expansion of mass lesions in the first hours or days after admission will prompt surgical evacuation. This decision may be based on uncontrollable ICP, new or worsening neurologic deficit, and/or new or worsening findings on CT.

When patients are taken for craniotomy and evacuation of mass lesions, the decision must be made whether or not to replace the bone flap. This decision is usually made based on a combination of factors, including but not limited to the occurrence of hypotension or hypoxia, the presence of a major vascular injury, the degree of cerebral edema on CT scan (including midline shift out of proportion to extra-axial hematoma thickness and compressed or absent cisterns), the degree of hemorrhage and hemispheric swelling seen at surgery, the degree of observed intraoperative coagulability, the presence of extracranial injuries that are expected to produce ongoing problems with hypotension or hypoxia, and others. When the bone flap is left out, it must comprise a large fronto temporoparietal craniotomy with squamous temporal craniectomy to the middle fossa floor, and duraplasty of some form must be performed to avoid hemispheric compression.

Delayed decompressive craniotomy/craniectomy may be done in cases of medically refractory intracranial hypertension. Two randomized controlled clinical trials of surgical decompression have been performed,[40,41] with variable results due to differences in methodological considerations. However, many prior studies have demonstrated the effectiveness of this technique in controlling ICP, and the practice of decompressive surgery in these patients is commonplace. The potential for meaningful recovery based on patient values is a critical part of decision-making, so careful patient selection is most important.

Medical Management

Medical management of TBI centers on several principles, namely, reduction of cerebral edema and ICP, avoidance of tissue hypoxia and ischemia, neuroprotection via mitigation of inflammation and reduction in metabolic demand, correction of coagulopathies and avoidance of hemorrhagic progression, and prevention of systemic complications (primarily pulmonary, infectious, nutritional, thromboembolic, musculoskeletal, and neurologic, such as seizure). The critical care management of sTBI involves meticulous attention to the maintenance of adequate CBF for oxygen and glucose delivery, which is practically managed by keeping ICP low and CPP adequate. Because, to date, numerous clinical trials of neuroprotective agents for sTBI have failed,[42] clinical care must rely on providing the best environment for healing to occur while avoiding complications.

Treatments aimed at controlling ICP include sedation and neuromuscular paralysis. Ideal sedative agents would have neuroprotective effects on the brain and not aggravate the neurochemical cascades leading to excitotoxicity and secondary injury. Any agent used for this purpose should be short acting to allow for neurologic assessment, should not increase ICP, and should not decrease cerebral perfusion. Unfortunately, no one agent meets these criteria. Propofol[43] and narcotics are the most commonly used agents for sedation in sTBI, with benzodiazepines a less ideal alternative. However, caution with high doses of propofol is warranted; adequate intravascular volume should be ensured in an effort to avoid the rare complication of propofol infusion syndrome,[44] which is characterized by cardiovascular collapse, renal failure, metabolic acidosis, and rhabdomyolysis. In difficult-to-control intracranial hypertension, barbiturate coma may be used; but it is not used prophylactically.[45–47] Barbiturate therapy also reduces cerebral metabolism. Patients may be responders or nonresponders; before initiating a barbiturate coma, test doses may be given to ensure that the desired effect on ICP is present, because of the risk of morbidity associated with barbiturate coma (infection, hypotension). Any patient being considered for a barbiturate coma should have confirmation of adequate intravascular volume before initiation, should be hemodynamically stable without hypotension, and should undergo continuous EEG to monitor for adequate effect (burst suppression). Short-acting neuromuscular paralytics (intermittent doses or low-dose continuous infusions) may rarely be required to help control ICP, typically in difficult-to-ventilate patients.

The use of osmotic agents to reduce cerebral edema is also commonly used, namely, mannitol for the acute reduction of increased ICP, and hypertonic saline (HTS) for multiple effects. Mannitol has multiple mechanisms of action in addition to reduction of interstitial edema via osmotic gradients, including increasing CBF and decreasing blood viscosity via hemodilution and alterations in red blood cell viscosity (potentially increasing oxygen delivery) as well as reducing ICP via reductions in blood volume from arteriolar constriction and inhibition of CSF production.[48,49] HTS may also decrease ICP, in addition to serving as a microresuscitation fluid for improved microcirculatory CBF and as a mitigator of inflammation.[50] The two therapies are not necessarily mutually exclusive and may be used at different time points or even simultaneously during the management of a single patient. Further research is needed to define optimal hyperosmolar euvolemic therapeutic laboratory values and physiologic parameters to guide therapy as well as modes of delivery, that is, rapid bolus of very concentrated formulae, slower boluses or self-limited drips, or continuous drips, all of which are in clinical usage for different situations.

Although hypothermia has shown significant promise in preclinical research and early clinical studies,[51,52] it has not borne out in large clinical trials as a viable

therapeutic alternative due in part to methodological considerations, that is, time to target temperature not being achieved, possibly suboptimal rewarming rates, and the like.[53–55] However, some centers with expertise in its use do use the technique in select patients. Furthermore, certain subsets of patients may benefit, including those with evacuated subdural hematoma; ongoing research is being done in this area (the Hypothermia for Patients requiring Evacuation of Subdural Hematoma: A Multicenter, Randomized Clinical [HOPES] Trial). What is clear is the detrimental effect of hyperthermia and elevated core brain temperature[50]; therefore, active attempts to keep patients with sTBI euthermic should be used, at a minimum.

Although prolonged, prophylactic hyperventilation is not recommended in patients with sTBI because of the potential for harm,[56] hyperventilation is still an acceptable temporizing measure in the setting of elevated ICP.[12] Hyperventilation to reduce the systemic P_{CO_2} results in cerebral vasoconstriction (via pH changes in the blood) and a reduction in CBF and volume leading to acute decreases in ICP. Hyperemic patients may respond particularly well to this intervention. However, careful use is essential so as to avoid cerebral tissue ischemia. Oxygenation monitoring (pB_tO_2 or $S_{jv}O_2$) is a useful adjunct when using hyperventilation.

Corticosteroids are not used in the treatment of sTBI. The Corticosteroid Randomisation After Significant Head Injury (CRASH) trial[57,58] demonstrated deleterious effects in patients with sTBI and was halted early. This study of 10,008 patients, 3966 of whom had sTBI, led to the only current evidence-based level I recommendation in sTBI, namely, that the use of steroids is not recommended to improve outcomes or control ICP in sTBI. In addition, high-dose methylprednisolone is associated with increased mortality in sTBI patients and is, therefore, contraindicated.[12]

Early nutritional replacement to meet the increased metabolic needs of coma is critical in the management of sTBI and may reduce cerebral inflammation. Early nutritional replacement (within 5 days) has been demonstrated to reduce 2-week mortality after sTBI[59] and reduce the incidence of ventilator-associated pneumonias (VAPs).[58] Certainly, the critical care and trauma literature on early nutritional replacement for the avoidance of the systemic inflammatory response[60] and infectious complications[61] also applies to patients with sTBI. Transpyloric feeding is favored over gastric feeding because of the decreased incidence of VAPs.[62]

Strict glycemic control has been espoused as a mechanism to reduce the complications of hyperglycemia in critical care patients; however, in sTBI hypoglycemia may be detrimental to the injured brain, because cerebral metabolism relies on a steady supply of glucose for oxidative metabolism. No differences in mortality have been shown with various glycemic control protocols in sTBI, although there has been some evidence of improved outcome[63] when hyperglycemia is avoided. However, studies have also shown increased frequency of hypoglycemic episodes[64,65] in the more strictly controlled groups. In general, euglycemia is targeted in critical care patients with sTBI, with great care taken to avoid hypoglycemic episodes.

Coagulopathy is common in sTBI, both from acute blood loss from polytrauma and resuscitation-related hemodilution as well as release of tissue factor and other proteins from damaged brain tissue.[66] Standard coagulation panels, including partial thromboplastin time, prothrombin time, and the international normalized ratio, may need to be performed serially within the first 72 hours of injury or longer. Full disseminated intravascular coagulation panels should be done for uncorrectable coagulopathies as evidenced by abnormal laboratory values or excessive and protracted bleeding at surgery or from injuries. Studies of platelet function, such as thromboelastography, are also sometimes required, particularly for patients with major blood loss, patients on antiplatelet medications, or those with chronic alcohol abuse.

Correction of coagulopathy (including those on anticoagulants for comorbidities) is particularly important for those patients undergoing cranial surgery, intracranial monitor placement, and for those harboring significant intracranial hemorrhage, in general (Table 2). Administration of platelets for patients on antiplatelet therapy is reserved for surgical patients, as there is no strong evidence that administration of platelets in these patients is effective at improving outcomes or reducing lesion progression.[67,68]

Infection prevention in patients with sTBI is difficult, and a significant proportion of patients admitted to the ICU with sTBI will have some form of infection. Prolonged mechanical ventilation increases the risk of pneumonia, as does prolonged immobilization. Although oral care with povidone-iodine has been promulgated as a means of reducing VAP risk for orally intubated patients over the last several years, there is at least some evidence that it may contribute to increased infectious risk as well as the development of adult respiratory distress syndrome.[69] Early tracheostomy may afford some degree of protection from VAP in patients with sTBI in that mechanical ventilation days can be reduced,[70] although actual VAP incidence and mortality rates have not been shown to be directly affected.[70,71] Again, the benefits of early tracheostomy as seen in general trauma patients apply as well to patients wutg sTBI, as long as the procedure does not lead to deleterious effects on ICP, brain edema, and so forth, which have largely been reduced with rapid surgical technique and minimally invasive tracheostomy techniques that can be used in the ICU. In addition to reduced ICU length of stay, these benefits include avoidance of vocal cord injury and stenosis, improved pulmonary toilet, reduced work of spontaneous breathing, and enhanced ability to wean mechanical ventilation (ability to go on and off of the ventilator). Surgical complications are unusual and include infection and hemorrhage as well as tracheal stenosis. For patients with sTBI whose return to consciousness is generally expected to be greater than 7 days, consideration for tracheostomy between days 3 and 7 should be given.

The potential for central nervous system infection related to surgery, monitoring procedures (especially EVD), or the primary injury (especially for penetrating injuries, open depressed skull fractures, and dural laceration with CSF leak) requires extra vigilance. Two meta-analyses[72,73] have concluded that the use of antibiotic-impregnated catheters significantly reduced catheter-related infections; however, when considering only studies with adequate allocation concealment, this difference was not seen in one of these analyses.[72]

Table 2
Structural intracranial injuries

| Extra-Axial Hematomas	Intra-Axial Hematomas	Primary Brain Injuries
Epidural hematoma	Intraparenchymal hemorrhage Contusion Hematoma	Intraparenchymal hemorrhage Contusion Hematoma
Subdural hematoma	Intraventricular hemorrhage[b]	Cerebral laceration
Subarachnoid hemorrhage[a]		Diffuse axonal injury

[a] Although traumatic subarachnoid hemorrhage (tSAH) is technically a form of extra-axial hemorrhage, the presence of diffuse tSAH portends a poor prognosis, as it can be a marker of structural damage to the underlying cerebral tissue.
[b] Although intraventricular hemorrhage is often classified as intra-axial because of the deep location within the ventricles of the brain, it is technically not within the substance of the brain, and the ventricular space and CSF are in communication with the subarachnoid space.

Venous thromboembolism (VTE) prophylaxis is particularly important in patients in a prolonged coma and its resultant immobility. Clinical questions of timing, choice of agent, and duration of therapy persist. Expectations for intracranial monitor or ventricular catheter insertions and removals and cranial surgeries impact the timing and choice of agent. Surgical staving of cerebral arteriolar and venular bleeding relies on the use of careful bipolar cautery to minimize brain tissue trauma, and adequate clotting is required for cautery to be effective. Surgery on patients who already have significant tissue trauma with friable brain tissue can be adversely affected by the presence of anticoagulants, in particular low-molecular-weight heparin (LMWH). LMWH used early has also been shown to significantly increase hemorrhagic progression on imaging after blunt TBI, with a proportion of those patients requiring surgery for the hemorrhagic progression.[74] Another study showed no difference in radiographic progression but suffered from the grouping of subcutaneous heparin and LMWH together as "chemoprophylaxis."[75] An examination of VTE rates in patients with sTBI treated with early or late LMWH (enoxaparin) prophylaxis showed no difference in VTE rate.[76] Most studies on this subject are limited by their retrospective nature. The utilization of a protocol for initiation of chemoprophylaxis alone may be sufficient to improve VTE rates.[77] The protocol used by the senior author is demonstrated in Fig. 1.

Posttraumatic seizures (PTSs) are classified into 3 categories: immediate, early (within 7 days of injury), or late (after 7 days). Posttraumatic epilepsy is defined as recurrent seizures occurring in the late seizure period. The incidence of clinical PTSs may be as high as 12%, with the rate of subclinical seizures detected on EEG

For Severe Traumatic Patients with Brain Injury Expected Prolonged Coma
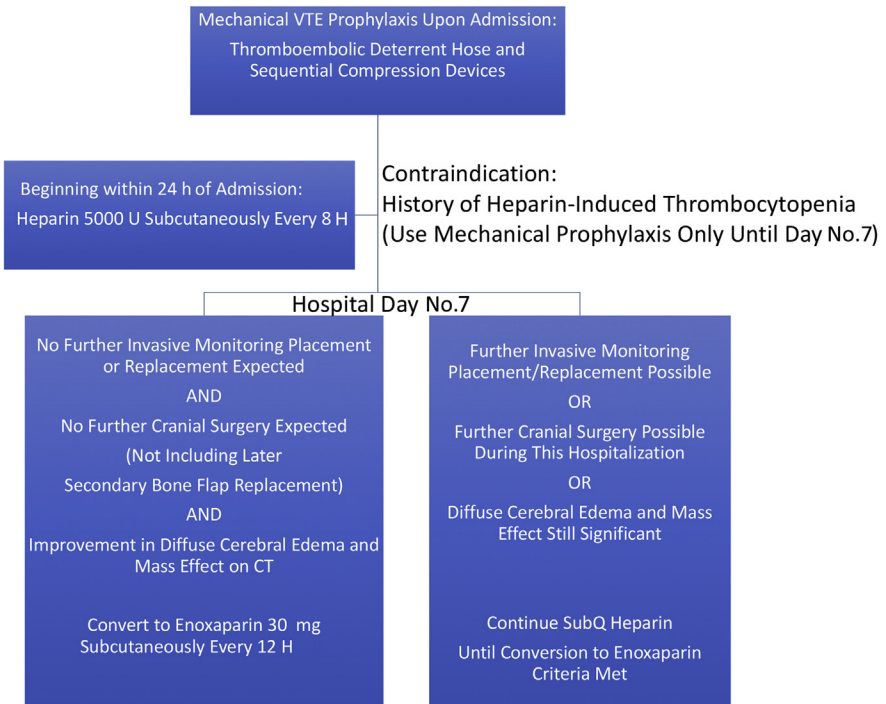
Fig. 1. Senior author's protocol for VTE prophylaxis in patients with sTBI. SubQ, subcutaneous.

being even higher.[28,78] To date, the largest randomized controlled clinical trials have shown that phenytoin significantly reduces the incidence of early but not late seizures,[79] with no differences in 12-month neuropsychologic testing outcomes.[80] Valproic acid has similar efficacy for the prevention of early PTS but not late PTS but is associated with higher mortality.[81] Phenytoin is, therefore, indicated for prevention of early PTS. Strong evidence for the use of levetiracetam in the prevention of early PTS in patients with sTBI is so far lacking. Late PTS is treated with a broader array of antiepileptic drugs (AEDs), congruent with the treatment of new-onset epilepsy from other causes, until further evidence is forthcoming. No anticonvulsant is free from side effects. Phenytoin may be associated with excessive sleepiness and if levels become too high, ataxia and imbalance. Levetiracetam has been independently associated with mood and behavioral side effects (depression, nervousness, agitation, anger, and aggression) and other adverse effects, such as upset stomach and sleep disturbance.[82] A thorough familiarity with the medication kinetics and adverse effect profiles for any AED under consideration for the prevention of early PTS or treatment of late PTS is of critical importance, as many of the adverse effects mimic the sequelae, signs, and symptoms of TBI (eg, confusion, depression, anxiety, somnolence, anger and aggression, sleep disturbance, ataxia, and more). Age and prior neuropsychiatric disease also play roles in AED selection.

SUMMARY

The management of patients with sTBIs requires meticulous attention to a variety of details and involves team members from a variety of specialties. A thorough understanding of the pathophysiology of cerebral edema and secondary injury cascades is a critical foundation for determining therapeutic decisions, particularly in areas where evidence is lacking.

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