HHS Public Access

Author manuscript

Semin Neurol. Author manuscript; available in PMC 2015 August 25.

Published in final edited form as:

Semin Neurol. 2015 February ; 35(1): 42–49. doi:10.1055/s-0035-1544238.

Pathophysiology and Clinical Management of Moderate and Severe Traumatic Brain Injury in the ICU

Faheem G. Sheriff, MD[1] and **Holly E. Hinson, MD**[1,2]

[1]Department of Neurology, Oregon Health Science University, Portland, Oregon

[2]Department of Emergency Medicine, Oregon Health Science University, Portland, Oregon

Abstract

Moderate and severe traumatic brain injury (TBI) is the leading cause of morbidity and mortality among young individuals in high-income countries. Its pathophysiology is divided into two major phases: the initial neuronal injury (or primary injury) followed by secondary insults (secondary injury). Multimodality monitoring now offers neurointensivists the ability to monitor multiple physiologic parameters that act as surrogates of brain ischemia and hypoxia, the major driving forces behind secondary brain injury. The heterogeneity of the pathophysiology of TBI makes it necessary to take into consideration these interacting physiologic factors when recommending for or against any therapies; it may also account for the failure of all the neuroprotective therapies studied so far. In this review, the authors focus on neuroclinicians and neurointensivists, and discuss the developments in therapeutic strategies aimed at optimizing intracranial pressure and cerebral perfusion pressure, and minimizing cerebral hypoxia. The management of moderate to severe TBI in the intensive care unit is moving away from a pure “threshold-based” treatment approach toward consideration of patient-specific characteristics, including the state of cerebral autoregulation. The authors also include a concise discussion on the management of medical and neurologic complications peculiar to TBI as well as an overview of prognostication.

Keywords

severe traumatic brain injury; pathophysiology; multimodality monitoring; intensive care unit

Few diseases impact global heath to the extent that traumatic brain injury (TBI) does. It is the leading cause of morbidity and mortality among young individuals in high-income countries.[1] Close to 52,000 patients with TBI die each year,[2] and moderate to severe TBI disables 80,000 persons per year.[3]

Classification

Traumatic brain injury may be classified by etiology or severity. Classification by etiology includes blunt closed head injuries, penetrating head injuries, and blast head injuries.

Address for correspondence Holly E. Hinson, MD, 3181 SW Sam Jackson Park Road, CR-127 Portland, OR 97239-3098 (hinson@ohsu.edu).

Traumatic brain injury may also be classified by severity into mild, moderate, and severe. A Glasgow Coma Score (GCS) of 13 to 15 is considered mild, 9 to 12 moderate, and GCS of 8 or less severe.[4] An alternative method of classification divides TBI into focal and diffuse. Focal injury constitutes extra-axial hematomas (subdural and epidural), intraparenchymal hematomas, and hemorrhagic contusions.[5] Diffuse brain injury involves widespread damage to axons, diffuse micro\vascular injury, hypoxic ischemic injury, and brain swelling.[5] Axonal injury (also referred to as diffuse axonal injury) is the result of shear, tensile, and compressive forces within brain tissue due to heterogeneity in tissue consistency and degree of fixation. It usually occurs in the setting of high-velocity motor vehicle accidents.

Pathophysiology

Traumatic brain injury may be divided into two major phases: the initial neuronal injury (or primary injury) followed by secondary insults (secondary injury).[3] The primary injury is the initial neuronal injury that occurs immediately and is a direct result of the traumatic event. The primary injury may not always be treatable and thus often proves fatal. On the macroscopic level, damage includes shearing of white matter tracts, focal contusions, hematomas, and diffuse edema. At the cellular level, early sequelae of neurotrauma include microporation of membranes, leaky ion channels, and stearic conformational changes in proteins. Blood vessels can be torn at higher shear rates, causing microhemorrhages.[1] It cannot be overemphasized that the mainstay of minimizing damage due to primary injury is through prevention.

The secondary injury develops over hours to days, and includes neurotransmitter release (excitotoxicity), free radical generation, calcium-mediated damage, gene activation, mitochondrial dysfunction, mass affect, ischemia, and inflammatory responses.[1]

The pathophysiology of TBI both focal and diffuse is multifaceted and heterogeneous, a fact that must be taken into account when designing neuroprotective treatments. This fact might partly explain why neuroprotective therapies to date have not shown significant clinical benefit in humans.

Diagnosis

Traumatic brain injury is a clinical diagnosis, relying on symptoms such as documented loss of consciousness, confusion, or amnesia (anterograde or retrograde) after an impact to the head.[1] The preliminary neurologic exam at the scene should focus on the Glasgow Coma Scale (GCS) and pupillary exam.[6,7] Neuroimaging should be performed as soon as hemodynamic stabilization is achieved, but should be expedited if the patient is comatose or has a focal neurologic deficit.[6] Magnetic resonance imaging (MRI) is seldom useful in the acute phase of TBI. However, in the diagnosis of diffuse axonal injury (DAI), MRI offers better detection of white matter lesions.[8] Magnetic resonance imaging also has specific prognostic applications that will be discussed later in this review.

Intensive Care Unit Monitoring

Given the fact that secondary brain injury is an ongoing process exacerbated by inadequate cerebral perfusion and oxygenation, the focus of care in the intensive care unit (ICU) is on monitoring parameters, which act as surrogates of brain ischemia and hypoxia. In the following sections, we will address these parameters in greater detail.

Neurologic Examination

The neurologic exam is the cornerstone of physiologic monitoring of TBI patients in the ICU.[9] Sequential clinical evaluation is crucial. The most important aspects are assessment of consciousness, usually performed by using the GCS, with a score of 8 or less defining coma. The full outline of unresponsiveness (FOUR) score includes assessment of pupillary light and corneal reflexes, breathing pattern examination, and motor and eye exams; it may be superior to the GCS in predicting in-hospital mortality after TBI.[9–11] Despite the advent of multimodality monitoring (MMM), the neurologic exam remains indispensable in the ICU monitoring of TBI patients and complements other modalities.

Intracranial Pressure and Cerebral Perfusion Pressure

Measuring intracranial pressure (ICP) and cerebral perfusion pressure (CPP) are also important. Conventionally, ICP greater than 20 mm Hg is considered intracranial hypertension (ICH), and was associated with worse outcomes in the Traumatic Coma Data Bank (TCDB) upon retrospective analysis.[12,13] The principle aims of ICP monitoring are to enable early detection of secondary hemorrhage and to guide therapies that minimize ICH.[13] Also important is the use of ICP to calculate CPP, using the following equation: CPP = MAP − ICP.

In light of the BEST-TRIP trial,[14] there is now greater understanding that treatment based solely on ICP is insufficient to influence TBI outcomes. Although one singular value (20 mm Hg) as a threshold for intervention is likely not correct for all patients, ICP monitoring should not be abandoned. Tailoring treatment to specific patient characteristics is likely a superior strategy. Additionally, treatment of ICP when a numerical threshold is reached may be an oversimplification because cerebral hypoxia and metabolic dysfunction may still occur with normal ICPs. Instead, ICP may be better managed when considered in the context of parameters such as compliance, ICP waveform morphology, cerebral autoregulation, and ICP impact on cerebral blood flow (CBF) and brain metabolism, and vice versa.[9,15] The Brain Trauma Foundation (BTF) outlined the indications for ICP monitoring in their guidelines published in 2007.[16] These indications are as follows:

- Severe TBI (GCS 3–8) after resuscitation and an abnormal computed tomography (CT) scan: the later included CT scans that revealed hematomas, contusions, swelling, herniation, or compressed basal cisterns.[17,18]
- Severe TBI and normal CT if two or more of the following exist: age ≥ 40 years, unilateral or bilateral motor posturing, or systolic blood pressure < 90 mm Hg.[18]

- Decompressive craniectomy and evacuation of acute supratentorial intracranial hematomas to help guide further management may be considered; however, these neurosurgical interventions are not included in guidelines.[19]

Intracranial pressure is best monitored invasively with a ventricular catheter or an intraparenchymal monitor.[9,16] Invasive techniques, in particular external ventricular drains (EVDs), offer the additional advantage of being able to drain CSF as a therapeutic measure to control elevated ICP. Cerebral perfusion pressure is among the most important factors in the preservation of cerebral blood flow (CBF), and is the stimulus to which the autoregulatory response of cerebral vasculature occurs.[20] Treatment aimed at CPP (in addition to ICP) is therefore superior to traditional techniques that focused on ICP alone.[20] Achieving optimal CPP is associated with favorable outcome after TBI. Optimal CPP was calculated using the pressure-reactivity index, which is a marker of autoregulation.[21] This is additional evidence against a pure “threshold-based” treatment approach to ICP/CPP without considering other parameters.

Cerebral Blood Flow

Cerebral blood flow (CBF) can be measured by different techniques. These include transcranial Doppler ultrasonography (TCD), thermal diffusion flowmetry, and laser Doppler flowmetry. Although TCD is the most commonly used technique, it is operator-dependent and may have technical limitations depending on the size of the temporal bone window.

Brain tissue oxygenation is another parameter to be followed. There are four general methods to measure brain oxygenation: jugular venous bulb oximetry, direct brain tissue oxygen tension measurement (PbtO2), near-infrared spectroscopy (NIRS), and oxygen-15 positron emission tomography (PET).[9] Cerebral hypoxia (defined as brain tissue oxygen [$PbtO_2$] < 10 mm Hg) is associated with worse out-comes after severe TBI.[22] However, though some studies show that combined ICP/CPP and $PbtO_2$-based therapy is associated with better outcomes after severe TBI than ICP/CPP-based therapy alone,[23,24] other studies demonstrated no significant difference.[25] BOOST-2 is a randomized, controlled trial aimed at determining whether interventions directed at $PbtO_2$ result in improved outcomes after severe TBI. Its results are expected imminently. Another controversial issue is which side the probe should be inserted on. Placement of the device on the side of the lesion (injured hemisphere) yields quite different results compared with placement on the contralateral (noninjured) hemisphere, and needs to be studied further.[26] Near-infrared spectroscopy is a promising newer noninvasive technique that may have additional uses, such as in the assessment of cerebral autoregulation.[9] Jugular venous bulb oximetry measures $SjvO_2$ (oxygen saturation at the jugular bulb), allowing assessment of global brain oxygenation as opposed to more focal or regional assessment with $PBtO_2$ probes.

Cerebral Metabolism

Cerebral metabolism can be assessed at bedside using cerebral microdialysis, which measures extracellular brain chemistry with an intraparenchymal probe. Importantly, changes in these analytes can precede changes in other physiological variables such as ICP.[27,28] Lactate and pyruvate concentrations provide information about the relative

contributions of aerobic and anaerobic metabolism.[9] Cerebral microdialysis is largely used for research purposes at present, but can be useful for prognostication.

Electrophysiology

Nonconvulsive seizures may occur in up to 40% of severely brain-injured patients, and contribute to worsening secondary brain injury.[29] Various epileptiform discharges are seen in patients with TBI and may precede actual seizures.[30] Quantitative electroencephalography (EEG) using fast Fourier transformation, in which raw EEG signal is converted into a digital form, has made continuous EEG monitoring practical and its interpretation easier in the ICU.

Biomarkers

Several biomarkers have been examined in TBI; however, the ideal brain marker does not yet exist. The existing biomarkers can be categorized according to their source as primarily neuronal, astroglial, or microglial. Of special importance is the role of genetic factors, in particular the ApoE4 allele, which has been linked in several studies with poorer neurologic outcomes, including death, after TBI.[31]

Treatment

As discussed earlier, the main goal of ICU therapy of moderate to severe TBI is the prevention of secondary brain injury by maintaining adequate cerebral perfusion, which involves targeting ICP/CPP as well avoiding cerebral hypoxia. In addition, optimizing medical management and preventing systemic complications in the ICU plays a crucial role in improving outcomes.

Therapies to Control Intracranial Pressure

The target value for ICP is < 20 mm Hg, and for CPP is 50 to 70 mm Hg.[6] However, as discussed earlier, TBI management in the ICU is moving away from a pure “threshold-based” treatment approach and relies more on a proper understanding of the Monroe Kelly doctrine and the contribution of the different compartments in the cranium to ICP. These compartments include venous blood, arterial blood, CSF, brain parenchyma, and mass lesions; they are discussed below.

Venous blood can be allowed to drain more effectively by elevating the head of the bed to 30 to 45 degrees and ensuring the neck is straight. Other measures include avoiding insertion of internal jugular catheters, especially during an ICP crisis because placement requires laying the patient supine at 180 degrees, which may impair venous drainage and venous obstruction; thus, congestion may occur with catheters in the jugular position.

Reducing intracranial arterial blood is another strategy to reduce ICP. This can be done by techniques that include hyperventilation, optimizing MAP (target 60 mm Hg) and decreasing metabolism by sedation, and in refractory cases, by cooling. Hyperventilation (HV) causes hypocarbia and vasoconstriction, which reduces CBF and subsequently CBV. However, aggressive HV ($PaCO_2$ of < 28 mm Hg) can cause severe vasoconstriction resulting in decreases in CBF to ischemic levels. For acute ICP management, clinicians

should aim for a $PaCO_2$ goal of 34 to 36 mm Hg. If ineffective, hyperventilation may be titrated to a goal of 28 to 32 (moderate HV). For recalcitrant ICP, the $PaCO_2$ goal can be advanced to 25 to 30 mm Hg usually with concomitant jugular venous bulb oximetry or $PbtO_2$ monitoring. If invasive monitoring is not feasible, continuous monitoring of endtidal CO_2 is essential to ensure regulated hypocarbia.[6] Hyperventilation should be tapered as soon as possible and prolonged HV should be avoided, particularly in the first 24 hours. Prolonged HV has been shown to worsen outcomes.[16,32] Given the association between CBF and cerebral metabolism (flow-metabolism coupling), the use of sedation reduces ICP by reducing cerebral metabolism.

Pharmacological coma may be considered for patients in whom the ICP remains refractory to maximal medical intervention. Traditionally, this is achieved using high-dose barbiturates with the aim of achieving an EEG burst-suppression pattern; propofol infusion is another reasonable alternative. Regardless of the agent chosen, patient selection is crucial and should include patients who have failed other ICP therapies, have intact autoregulation, are hemodynamically stable (have adequate cardiac reserve), and do not have diffuse injury.[33,34]

Therapeutic hypothermia is another measure for reducing ICP refractory to first-line therapies. Mild hypothermia to 35° C for between 48 hours to 5 days effectively reduces ICP, and improves outcomes in such patients.[35,36] Hypothermia may cause shivering, which raises the metabolic rate and should be avoided. Control of the rewarming phase is crucial to avoid rebound ICP and temperature overshooting and should not exceed 0.25°C per hour.[37]

Removal of CSF may also reduce ICP, particularly in the setting of hydrocephalus. An external ventricular drain (EVD) has the advantage of being used for ICP measurement once connected to an external transducer set-up.

Brain edema reduction in cerebral white matter is best managed by osmotherapy. The most commonly used agents are mannitol and hypertonic saline. Mannitol is to be used in the setting of raised ICP or herniation because prophylactic therapy is of little benefit and is associated with adverse effects such as hypotension and hypovolemia.[6] Hypertonic saline is the other commonly used osmolar agent. Its effects typically last for hours; hence, it provides more sustained ICP control than mannitol.

The use of steroids is not recommended for ICP management in patients with TBI, even though steroids are commonly used in treating increased ICP due to vasogenic edema from mass lesions in non-TBI patients.[16]

Decompressive craniectomy (DC) is another measure that was formerly more often employed in the management of raised ICP in TBI. It is still performed, but less frequently and as an adjunct to evacuation of mass lesions (usually hematomas) for management of malignant cerebral edema and intracranial hypertension (ICH).[38] However, DC performed for management of ICH alone is more controversial in light of the DECRA trial (Decompressive Craniectomy in Diffuse TBI), which concluded that while early bifrontotemporal-parietal decompressive craniectomy decreased ICP and length of ICU stay in severe diffuse TBI, it was associated with more unfavorable outcomes.[39] The results of

the RESCUE ICP trial (Randomized Evaluation of Surgery with Craniectomy for Uncontrollable Elevation of ICP), which is currently nearing completion, are eagerly awaited.

Therapies to Optimize Cerebral Perfusion Pressure

Optimizing CPP can be achieved by decreasing ICP and/or increasing the MAP (see Equation 1). Intravenous fluids should be administered judiciously, aiming for a systolic blood pressure of at least 90 mm Hg per the Brain Trauma Foundation guidelines.[40] Aggressive fluid resuscitation and use of hypotonic or dextrose containing solutions is counterproductive in TBI. In addition the use of colloids may actually worsen outcomes.[41] Vasopressors are used if the CPP fails to respond to IV fluids resuscitation. Noradrenaline has a more predictable and efficient augmentation of CPP and CBF as estimated by transcranial Doppler,[42] and improves brain tissue oxygenation as compared with dopamine in TBI patients.[43]

Therapies to Increase Cerebral Oxygenation

The role of lung protective ventilation strategies with lower tidal volumes and lower PaO_2/FiO_2 ratios cannot be over-emphasized in the prevention of acute lung injury (ALI),[44] which in turn is an independent risk factor for compromised $PbtO_2$ in TBI patients.

Management of Complications and Other Neurocritical Care Issues

Fever

Both the degree and duration of early posttrauma hyperthermia are closely correlated with the outcomes of acute TBI.[45] However, conclusive evidence linking prevention of hyperthermia with improved outcomes in TBI patients is lacking.[46] In addition, the role of early hypothermia as a neuroprotective strategy could not be demonstrated in a randomized trial.[47] This may in part be due to the suboptimal effectiveness of existing cooling methods; newer cooling devices may allow this issue to be readdressed. Regardless, strict fever control is recommended despite the lack of definitive evidence linking it with improved outcomes. Of note, therapeutic hypothermia for refractory ICP management is relatively well established.[35]

Seizures

The incidence of posttraumatic seizures (PTS) in the first 2 years after severe TBI ranges from 21%[48] to almost 50% after penetrating war-related TBI.[49] Posttraumatic seizures are classified as either early or late; those occurring before 7 days are early PTS. Seizures exacerbate secondary brain injury by increasing ICP, worsening cerebral hypoxia, and increasing metabolic demand. Nonconvulsive electrographic seizures also occur, and can lead to cerebral metabolic crisis, a delayed increase in ICP, and worse clinical outcomes.[29] Current evidence supports the use of antiepileptic drugs (AEDs) to prevent early PTS, but not late PTS.[48,50,51] Risk factors for developing early PTS include penetrating TBI, depressed skull fractures, cortical contusions, and subdural and epidural hematomas. At risk patients should be managed with AEDs for seizure prophylaxis for 7 days.[51] Phenytoin, carbamazepine, and valproate have all been studied for PTS, but none of these reduced the

incidence of late posttraumatic seizures. [50] Although there is no data to clearly establish the efficacy and tolerability of intravenous levetiracetam over phenytoin, the former is emerging as a favorable alternative in cases where there is risk of significant drug-drug interaction and drug toxicity; however, further studies are needed.[52] Age, development of early PTS, and EEG findings may assist in predicting the risk of late PTS.[53]

Coagulopathy

One out of three patients suffering from TBI displays signs of a coagulopathy.[54] Functional assays such as viscoelastic tests may better phenotype the coagulopathy of TBI and guide targeted therapy.[55] The prophylactic use of FFP in severe TBI patients was associated with adverse effects, including delayed intracranial hematomas and an increase in mortality.[56] Although blood and blood product transfusions may be necessary in patients with active bleeding, they carry with them certain risks that need to be carefully weighed against benefits, especially if the hematologic derangements are only mild to moderate.[57]

Hyperglycemia

Deranged glucose metabolism is both a complication of severe TBI as well as an independent marker associated with increased mortality and long-term poor outcomes.[58] However, correcting these levels with early and aggressive insulin therapy does not necessarily translate into better outcomes.[58,59] In addition, strict glycemic control (< 110 mg/dL) is associated with increased episodes of cerebral hypoglycemia as determined by cerebral microdialysis.[60] Therefore, although reasonably tight glucose control is still recommended in moderate to severe TBI, care must be taken to avoid hypoglycemic episodes, which are potentially quite injurious to the brain even in the nontraumatic state.

Nutrition

After severe TBI, patients experience a systemic and cerebral hypermetabolic state. Patients given early nutrition have a lower mortality rate and significantly lower rates of infection. Current guidelines recommend nutrition at 140% of resting requirements in nonparalyzed patients, and at 100% in paralyzed patients.[6]

Endocrine Derangements

Traumatic brain injury can be complicated by neuroendocrine abnormalities, most commonly hypopituitarism, which was detected in 21% of patients in one study.[61] This can manifest as increased vasopressor requirements or cerebral salt wasting. In the acute phase, adrenal glucocorticoid insufficiency is managed with replacement-dose hydrocortisone. Diabetes insipidus should be managed aggressively to prevent severe hypernatremia, but once present, the serum sodium should be lowered gradually to avoid malignant rebound cerebral edema.[6] Recently, neuroendocrine immune dysfunction (involving cortisol dysregulation) has been described in TBI, and is associated with poor outcomes.[62]

Posttraumatic Vasospasm

Posttraumatic vasospasm (PTV) has an estimated incidence of between 10 to 15%, and typically develops between 12 hours to 5 days.[63] Risk factors for the development of PTV

include parenchymal contusions and fever.[64] Vasospasm can be screened for using TCD, CT angiography, or digital subtraction angiography. Posttraumatic vasospasm is particularly a problem after blast TBI, and is associated with the presence of pseudoaneurysms. Therapy is not well established, but open surgical treatment was associated with neurologic improvement, and microballoon angioplasty significantly lowered middle cerebral artery and basilar blood flow velocities in one study.[65]

Paroxysmal Sympathetic Hyperactivity

Paroxysmal sympathetic hyperactivity (PSH) is defined as "a syndrome, recognized in a subgroup of survivors of severe acquired brain injury, of simultaneous, paroxysmal transient increases in sympathetic [elevated heart rate, blood pressure, respiratory rate, temperature, sweating] and motor [posturing] activity."[66] Its incidence varies between 8 to 33% in different series.[67,68] Overresponsiveness to afferent stimuli is a recently described hallmark of PSH, and may assist the clinical diagnosis.[69] Young age and diffuse axonal injury are risk factors for developing PSH.[70] There are no specific guidelines for managing PSH. The evidence for drug therapy is limited to case reports or case series, and includes opiates, GABA agonists, α- and β-blockers, and dopamine agonists with varying effectiveness.

Prognosis

The most important predictors of outcome after severe TBI include GCS after full resuscitation, age, pupillary reactivity, CT findings, and the presence of major extracranial injury.[71] Though the GCS has been traditionally used for prognostication and has a 70% predictive value,[6] it has certain limitations that can be addressed using the full outline of unresponsiveness (FOUR) score. The latter was shown to be superior in predicting in-hospital mortality in TBI patients.[11] Chemical biomarkers, though used in research, are not routinely applied in clinical prognostication. Neuroimaging is an important tool in prognostication after TBI. Computed tomography findings associated with poor outcomes include compressed or absent basal cisterns, traumatic SAH, midline shift, and intracranial lesions.[72] Magnetic resonance imaging has added significantly to the accuracy of long-term outcome prediction, especially by the use of quantitative diffusion tensor imaging (DTI) for white matter assessment[73]; this, however, is not widely available for clinical use yet. Various outcome prediction models have been developed; two such models, referred to as the IMPACT and CRASH models, have been reciprocally validated and were shown to provide adequate discrimination between patients with good and poor 6-month outcomes after TBI using baseline characteristics, especially if CT and laboratory findings (glucose, platelets, hemoglobin) were considered in addition to traditional predictors.[74] The largest amount of prognostic information was contained in a core set of three predictors: age, motor score, and pupillary reactivity at admission.[74] There are no guidelines as to the optimum timing for prognostication. Not surprisingly, in a recent study withdrawal of care was the most important predictor of in-hospital mortality post-TBI, thus forming the basis of self-fulfilling prophecies.[75] More research is needed in this regard, not only for clinical purposes, but also to enable more objective assessment of the efficacy of neuroprotective therapies under research. Finally, adherence to evidence-based guidelines has been shown to improve outcomes after TBI and decrease hospital expenses.[76]

Acknowledgments

We would like to thank Sakina Ramji for her assistance with typesetting the manuscript.

References

1. Maas AIR, Stocchetti N, Bullock R. Moderate and severe traumatic brain injury in adults. Lancet Neurol. 2008; 7(8):728–741. [PubMed: 18635021]
2. Ling GSF, Marshall SA, Moore DF. Diagnosis and management of traumatic brain injury. Continuum (Minneap Minn). 2010; 16 (6):27–40. Traumatic Brain Injury. [PubMed: 22810712]
3. Frattalone AR, Ling GSF. Moderate and severe traumatic brain injury: pathophysiology and management. Neurosurg Clin N Am. 2013; 24(3):309–319. [PubMed: 23809027]
4. Teasdale G, Jennett B. Assessment of coma and impaired consciousness. A practical scale. Lancet. 1974; 2(7872):81–84. [PubMed: 4136544]
5. Andriessen TMJC, Jacobs B, Vos PE. Clinical characteristics and pathophysiological mechanisms of focal and diffuse traumatic brain injury. J Cell Mol Med. 2010; 14(10):2381–2392. [PubMed: 20738443]
6. Mangat HS. Severe traumatic brain injury. Continuum (Minneap Minn). 2012; 18(3):532–546. [PubMed: 22810247]
7. Jennett B, Teasdale G, Braakman R, Minderhoud J, Knill-Jones R. Predicting outcome in individual patients after severe head injury. Lancet. 1976; 1(7968):1031–1034. [PubMed: 57446]
8. Huisman TAGM, Schwamm LH, Schaefer PW, et al. Diffusion tensor imaging as potential biomarker of white matter injury in diffuse axonal injury. AJNR Am J Neuroradiol. 2004; 25(3): 370–376. [PubMed: 15037457]
9. Le Roux P. Physiological monitoring of the severe traumatic brain injury patient in the intensive care unit. Curr Neurol Neurosci Rep. 2013; 13(3):331. [PubMed: 23328942]
10. Wijdicks EFM, Rabinstein AA, Bamlet WR, Mandrekar JN. FOUR score and Glasgow Coma Scale in predicting outcome of comatose patients: a pooled analysis. Neurology. 2011; 77(1):84–85. [PubMed: 21562252]
11. Okasha AS, Fayed AM, Saleh AS. The FOUR score predicts mortality, endotracheal intubation and ICU length of stay after traumatic brain injury. Neurocrit Care. 2014; 21(3):496–504. [PubMed: 24865273]
12. Marmarou A, Anderson RL, Ward JD, et al. Impact of ICP instability and hypotension on outcome in patients with severe head trauma. J Neurosurg. 1991; 75(1s):S59–S66.
13. Hawthorne C, Piper I. Monitoring of intracranial pressure in patients with traumatic brain injury. Front Neurol. 2014; 5:121. [PubMed: 25076934]
14. Chesnut RM, Temkin N, Carney N, et al. Global Neurotrauma Research Group. A trial of intracranial-pressure monitoring in traumatic brain injury. N Engl J Med. 2012; 367(26):2471–2481. [PubMed: 23234472]
15. Oddo M, Gasche Y. Update on the management of severe traumatic brain injury. Rev Med Suisse. 2009; 5(229):2506–2510. [PubMed: 20084870]
16. Bratton SL, Chestnut RM, Ghajar J, et al. Brain Trauma Foundation; American Association of Neurological Surgeons; Congress of Neurological Surgeons; Joint Section on Neurotrauma and Critical Care, AANS/CNS. Guidelines for the management of severe traumatic brain injury. VI. Indications for intracranial pressure monitoring. J Neurotrauma. 2007; 24(Suppl 1):S37–S44. [PubMed: 17511544]
17. Eisenberg HM, Gary HE Jr, Aldrich EF, et al. Initial CT findings in 753 patients with severe head injury. A report from the NIH Traumatic Coma Data Bank. J Neurosurg. 1990; 73(5):688–698. [PubMed: 2213158]
18. Narayan RK, Kishore PR, Becker DP, et al. Intracranial pressure: to monitor or not to monitor? A review of our experience with severe head injury. J Neurosurg. 1982; 56(5):650–659. [PubMed: 7069477]

19. Stocchetti N, Picetti E, Berardino M, et al. Clinical applications of intracranial pressure monitoring in traumatic brain injury : report of the Milan consensus conference. Acta Neurochir (Wien). 2014; 156(8):1615–1622. [PubMed: 24849391]
20. Rosner MJ, Rosner SD, Johnson AH. Cerebral perfusion pressure: management protocol and clinical results. J Neurosurg. 1995; 83(6):949–962. [PubMed: 7490638]
21. Aries MJH, Czosnyka M, Budohoski KP, et al. Continuous determination of optimal cerebral perfusion pressure in traumatic brain injury. Crit Care Med. 2012; 40(8):2456–2463. [PubMed: 22622398]
22. Maloney-Wilensky E, Gracias V, Itkin A, et al. Brain tissue oxygen and outcome after severe traumatic brain injury: a systematic review. Crit Care Med. 2009; 37(6):2057–2063. [PubMed: 19384213]
23. Narotam PK, Morrison JF, Nathoo N. Brain tissue oxygen monitoring in traumatic brain injury and major trauma: outcome analysis of a brain tissue oxygen-directed therapy. J Neurosurg. 2009; 111(4):672–682. [PubMed: 19463048]
24. Nangunoori R, Maloney-Wilensky E, Stiefel M, et al. Brain tissue oxygen-based therapy and outcome after severe traumatic brain injury: a systematic literature review. Neurocrit Care. 2012; 17(1):131–138. [PubMed: 21845489]
25. Martini RP, Deem S, Yanez ND, et al. Management guided by brain tissue oxygen monitoring and outcome following severe traumatic brain injury. J Neurosurg. 2009; 111(4):644–649. [PubMed: 19392603]
26. Purins K, Lewén A, Hillered L, Howells T, Enblad P. Brain tissue oxygenation and cerebral metabolic patterns in focal and diffuse traumatic brain injury. Front Neurol. 2014; 5:64. [PubMed: 24817863]
27. Adamides AA, Rosenfeldt FL, Winter CD, et al. Brain tissue lactate elevations predict episodes of intracranial hypertension in patients with traumatic brain injury. J Am Coll Surg. 2009; 209(4): 531–539. [PubMed: 19801326]
28. Belli A, Sen J, Petzold A, Russo S, Kitchen N, Smith M. Metabolic failure precedes intracranial pressure rises in traumatic brain injury: a microdialysis study. Acta Neurochir (Wien). 2008; 150(5):461–469. discussion 470. [PubMed: 18421408]
29. Vespa PM, Miller C, McArthur D, et al. Nonconvulsive electrographic seizures after traumatic brain injury result in a delayed, prolonged increase in intracranial pressure and metabolic crisis. Crit Care Med. 2007; 35(12):2830–2836. [PubMed: 18074483]
30. Ronne-Engstrom E, Winkler T. Continuous EEG monitoring in patients with traumatic brain injury reveals a high incidence of epileptiform activity. Acta Neurol Scand. 2006; 114(1):47–53. [PubMed: 16774627]
31. Diaz-Arrastia R, Baxter VK. Genetic factors in outcome after traumatic brain injury: what the human genome project can teach us about brain trauma. J Head Trauma Rehabil. 2006; 21(4):361–374. [PubMed: 16915011]
32. Muizelaar JP, Marmarou A, Ward JD, et al. Adverse effects of prolonged hyperventilation in patients with severe head injury: a randomized clinical trial. J Neurosurg. 1991; 75(5):731–739. [PubMed: 1919695]
33. Lobato RD, Sarabia R, Cordobes F, et al. Posttraumatic cerebral hemispheric swelling. Analysis of 55 cases studied with computerized tomography. J Neurosurg. 1988; 68(3):417–423. [PubMed: 3343614]
34. Nordström CH, Messeter K, Sundbärg G, Schalén W, Werner M, Ryding E. Cerebral blood flow, vasoreactivity, and oxygen consumption during barbiturate therapy in severe traumatic brain lesions. J Neurosurg. 1988; 68(3):424–431. [PubMed: 3125310]
35. Jiang J-Y, Xu W, Li W-P, et al. Effect of long-term mild hypothermia or short-term mild hypothermia on outcome of patients with severe traumatic brain injury. J Cereb Blood Flow Metab. 2006; 26(6):771–776. [PubMed: 16306933]
36. Bouzat P, Francony G, Oddo M, Payen J-F. Therapeutic hypothermia for severe traumatic brain injury. Ann Fr Anesth Reanim. 2013; 32(11):787–791. [PubMed: 24138767]

37. Sadaka F, Veremakis C. Therapeutic hypothermia for the management of intracranial hypertension in severe traumatic brain injury: a systematic review. Brain Inj. 2012; 26(7–8):899–908. [PubMed: 22448655]
38. Bohman L-E, Schuster JM. Decompressive craniectomy for management of traumatic brain injury: an update. Curr Neurol Neurosci Rep. 2013; 13(11):392. [PubMed: 24101348]
39. Cooper DJ, Rosenfeld JV, Murray L, et al. DECRA Trial Investigators; Australian and New Zealand Intensive Care Society Clinical Trials Group. Decompressive craniectomy in diffuse traumatic brain injury. N Engl J Med. 2011; 364(16):1493–1502. [PubMed: 21434843]
40. Bratton SL, Chestnut RM, Ghajar J, et al. Brain Trauma Foundation; American Association of Neurological Surgeons; Congress of Neurological Surgeons; Joint Section on Neurotrauma and Critical Care, AANS/CNS. Guidelines for the management of severe traumatic brain injury. I. Blood pressure and oxygenation. J Neurotrauma. 2007; 24(Suppl 1):S7–S13. [PubMed: 17511549]
41. Myburgh J, Cooper DJ, Finfer S, et al. SAFE Study Investigators; Australian and New Zealand Intensive Care Society Clinical Trials Group; Australian Red Cross Blood Service; George Institute for International Health. Saline or albumin for fluid resuscitation in patients with traumatic brain injury. N Engl J Med. 2007; 357(9):874–884. [PubMed: 17761591]
42. Steiner LA, Johnston AJ, Czosnyka M, et al. Direct comparison of cerebrovascular effects of norepinephrine and dopamine in head-injured patients. Crit Care Med. 2004; 32(4):1049–1054. [PubMed: 15071400]
43. Johnston AJ, Steiner LA, Chatfield DA, et al. Effect of cerebral perfusion pressure augmentation with dopamine and norepinephrine on global and focal brain oxygenation after traumatic brain injury. Intensive Care Med. 2004; 30(5):791–797. [PubMed: 15048550]
44. Mascia L, Zavala E, Bosma K, et al. Brain IT group. High tidal volume is associated with the development of acute lung injury after severe brain injury: an international observational study. Crit Care Med. 2007; 35(8):1815–1820. [PubMed: 17568331]
45. Li J, Jiang JY. Chinese Head Trauma Data Bank: effect of hyperthermia on the outcome of acute head trauma patients. J Neurotrauma. 2012; 29(1):96–100. [PubMed: 22026424]
46. Aiyagari V, Diringer MN. Fever control and its impact on outcomes: what is the evidence? J Neurol Sci. 2007; 261(1–2):39–46. [PubMed: 17537459]
47. Clifton GL, Valadka A, Zygun D, et al. Very early hypothermia induction in patients with severe brain injury (the National Acute Brain Injury Study: hypothermia II): a randomised trial. Lancet Neurol. 2011; 10(2):131–139. [PubMed: 21169065]
48. Temkin NR, Dikmen SS, Wilensky AJ, Keihm J, Chabal S, Winn HR. A randomized, double-blind study of phenytoin for the prevention of post-traumatic seizures. N Engl J Med. 1990; 323(8):497–502. [PubMed: 2115976]
49. Salazar AM, Jabbari B, Vance SC, Grafman J, Amin D, Dillon JD. Epilepsy after penetrating head injury. I. Clinical correlates: a report of the Vietnam Head Injury Study. Neurology. 1985; 35(10): 1406–1414. [PubMed: 3929158]
50. Temkin NR. Antiepileptogenesis and seizure prevention trials with antiepileptic drugs: meta-analysis of controlled trials. Epilepsia. 2001; 42(4):515–524. [PubMed: 11440347]
51. Chang BS, Lowenstein DH. Quality Standards Subcommittee of the American Academy of Neurology. Practice parameter: antiepileptic drug prophylaxis in severe traumatic brain injury: report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 2003; 60(1):10–16. [PubMed: 12525711]
52. Kirmani BF, Mungall D, Ling G. Role of intravenous levetiracetam in seizure prophylaxis of severe traumatic brain injury patients. Front Neurol. 2013; 4:170. [PubMed: 24198810]
53. Nakamura A, Ohira T, Ishihara M, et al. Cooperative multicentric study on posttraumatic epilepsy. No To Shinkei. 1995; 47(12):1170–1176. [PubMed: 8534554]
54. Harhangi BS, Kompanje EJO, Leebeek FWG, Maas AIR. Coagulation disorders after traumatic brain injury. Acta Neurochir (Wien). 2008; 150(2):165–175. discussion 175. [PubMed: 18166989]
55. Maegele M. Coagulopathy after traumatic brain injury: incidence, pathogenesis, and treatment options. Transfusion. 2013; 53 (Suppl 1):28S–37S. [PubMed: 23301970]

56. Etemadrezaie H, Baharvahdat H, Shariati Z, Lari SM, Shakeri MT, Ganjeifar B. The effect of fresh frozen plasma in severe closed head injury. Clin Neurol Neurosurg. 2007; 109(2):166–171. [PubMed: 17029771]
57. Anglin CO, Spence JS, Warner MA, et al. Effects of platelet and plasma transfusion on outcome in traumatic brain injury patients with moderate bleeding diatheses. J Neurosurg. 2013; 118(3):676–686. [PubMed: 23259827]
58. Salim A, Hadjizacharia P, Dubose J, et al. Persistent hyperglycemia in severe traumatic brain injury: an independent predictor of outcome. Am Surg. 2009; 75(1):25–29. [PubMed: 19213392]
59. Coester A, Neumann CR, Schmidt MI. Intensive insulin therapy in severe traumatic brain injury: a randomized trial. J Trauma. 2010; 68(4):904–911. [PubMed: 20032790]
60. Oddo M, Schmidt JM, Carrera E, et al. Impact of tight glycemic control on cerebral glucose metabolism after severe brain injury: a microdialysis study. Crit Care Med. 2008; 36(12):3233–3238. [PubMed: 18936695]
61. Krahulik D, Zapletalova J, Frysak Z, Vaverka M. Dysfunction of hypothalamic-hypophysial axis after traumatic brain injury in adults. J Neurosurg. 2010; 113(3):581–584. [PubMed: 19929195]
62. Santarsieri M, Kumar RG, Kochanek PM, Berga S, Wagner AK. Variable neuroendocrine-immune dysfunction in individuals with unfavorable outcome after severe traumatic brain injury. Brain Behav Immun. 2014 ePub ahead of print.
63. Shahlaie K, Boggan JE, Latchaw RE, Ji C, Muizelaar JP. Posttraumatic vasospasm detected by continuous brain tissue oxygen monitoring: treatment with intraarterial verapamil and balloon angioplasty. Neurocrit Care. 2009; 10(1):61–69. [PubMed: 18807219]
64. Shahlaie K, Keachie K, Hutchins IM, et al. Risk factors for posttraumatic vasospasm. J Neurosurg. 2011; 115(3):602–611. [PubMed: 21663415]
65. Armonda RA, Bell RS, Vo AH, et al. Wartime traumatic cerebral vasospasm: recent review of combat casualties. Neurosurgery. 2006; 59(6):1215–1225. discussion 1225. [PubMed: 17277684]
66. Baguley IJ, Perkes IE, Fernandez-Ortega J-F, Rabinstein AA, Dolce G, Hendricks HT. Paroxysmal sympathetic hyperactivity after acquired brain injury: consensus on conceptual definition, nomenclature, and diagnostic criteria. J Neurotrauma. 2014; 31(17):1515–1520. [PubMed: 24731076]
67. Baguley IJ, Slewa-Younan S, Heriseanu RE, Nott MT, Mudaliar Y, Nayyar V. The incidence of dysautonomia and its relationship with autonomic arousal following traumatic brain injury. Brain Inj. 2007; 21(11):1175–1181. [PubMed: 17952716]
68. Perkes I, Baguley IJ, Nott MT, Menon DK. A review of paroxysmal sympathetic hyperactivity after acquired brain injury. Ann Neurol. 2010; 68(2):126–135. [PubMed: 20695005]
69. Baguley IJ, Nott MT, Slewa-Younan S, Heriseanu RE, Perkes IE. Diagnosing dysautonomia after acute traumatic brain injury: evidence for overresponsiveness to afferent stimuli. Arch Phys Med Rehabil. 2009; 90(4):580–586. [PubMed: 19345772]
70. Lv L-Q, Hou L-J, Yu M-K, et al. Risk factors related to dysautonomia after severe traumatic brain injury. J Trauma. 2011; 71(3):538–542. [PubMed: 21427610]
71. Perel P, Arango M, Clayton T, et al. MRC CRASH Trial Collaborators. Predicting outcome after traumatic brain injury: practical prognostic models based on large cohort of international patients. BMJ. 2008; 336(7641):425–429. [PubMed: 18270239]
72. Maas AIR, Hukkelhoven CWPM, Marshall LF, Steyerberg EW. Prediction of outcome in traumatic brain injury with computed tomographic characteristics: a comparison between the computed tomographic classification and combinations of computed tomographic predictors. Neurosurgery. 2005; 57(6):1173–1182. discussion 1173–1182. [PubMed: 16331165]
73. Galanaud D, Perlbarg V, Gupta R, et al. Neuro Imaging for Coma Emergence and Recovery Consortium. Assessment of white matter injury and outcome in severe brain trauma: a prospective multicenter cohort. Anesthesiology. 2012; 117(6):1300–1310. [PubMed: 23135261]
74. Steyerberg EW, Mushkudiani N, Perel P, et al. Predicting outcome after traumatic brain injury: development and international validation of prognostic scores based on admission characteristics. PLoS Med. 2008; 5(8):e165. discussion e165. [PubMed: 18684008]

75. Izzy S, Compton R, Carandang R, Hall W, Muehlschlegel S. Selffulfilling prophecies through withdrawal of care: do they exist in traumatic brain injury, too? Neurocrit Care. 2013; 19(3):347–363. [PubMed: 24132565]

76. Fakhry SM, Trask AL, Waller MA, Watts DD. IRTC Neurotrauma Task Force. Management of brain-injured patients by an evidence-based medicine protocol improves outcomes and decreases hospital charges. J Trauma. 2004; 56(3):492–499. discussion 499–500. [PubMed: 15128118]