Published in final edited form as:

Neurocrit Care. 2017 December ; 27(3): 430–446. doi:10.1007/s12028-017-0408-5.

Medical Management of the Severe Traumatic Brain Injury Patient

Jonathan Marehbian, MD,

Division of Neurocritical Care and Emergency Neurology, Yale School of Medicine, P.O. Box 208018, New Haven, CT 06520, Office: 203-737-8057, Fax: 203-737-4419

Susanne Muehlschlegel, MD, MPH, FNCS, FCCM,

University of Massachusetts Medical School, Depts. of Neurology, Anesthesia/Critical Care, and Surgery, 55 Lake Ave North, S-5, Worcester, MA 01655, Phone: 508-334-4651

Brian L. Edlow, MD,

Massachusetts General Hospital, Division of Neurocritical Care and Emergency Neurology, 55 Fruit Street – Lunder 650 Boston, MA 02114, Office: 617-724-6352

Holly E. Hinson, MD, MCR, and

Oregon Health & Science University, 3181 SW Sam Jackson Park Road, CR-127, Portland, OR 97239, Office/Fax: 503 418-1472

David Y. Hwang, MD

Division of Neurocritical Care and Emergency Neurology, Yale School of Medicine, P.O. Box 208018, New Haven, CT 06520, Office: 203-737-8051, Fax: 203-737-4419

Abstract

Severe traumatic brain injury (sTBI) is a major contributor to long term disability and a leading cause of death worldwide. Medical management of the sTBI patient, beginning with pre-hospital triage, is aimed at preventing secondary brain injury. This review discusses prehospital and emergency department management of severe TBI, as well as aspects of TBI management in the intensive care unit where advances have been made in the past decade. Areas of emphasis include intracranial pressure management, neuromonitoring, management of paroxysmal sympathetic hyperactivity, neuroprotective strategies, prognostication, and communication with families about goals of care. Where appropriate, differences between the third and fourth editions of the Brain Trauma Foundation Guidelines for the Management of Severe Traumatic Brain Injury are highlighted.

Correspondence to: David Y. Hwang.

CONFLICTS OF INTEREST:

Dr. Marehbian has no disclosures or conflicts of interest.

Dr. Muehlschlegel is supported by NIH/NICHD grant 5K23HD080971, which is funding the creation of a goals-of-care decision aid for sTBI patients' families.

Dr. Edlow is supported by NIH/NINDS (K23NS094538) and the James S. McDonnell Foundation. He has no conflicts of interest.

Dr. Hinson consults for Remedy Pharmaceuticals. She has no conflicts of interest.

Dr. Hwang is supported by the American Brain Foundation, the Apple Pickers Foundation (Westerly, RI), the Neurocritical Care Society, and the NIH/NIA Loan Repayment Program. He receives modest royalties for the book *A Guide to Traumatic Brain Injury: The Intensive Care Unit*, published by the Neurocritical Care Society.

Keywords

Brain injuries; traumatic; Critical care; Intracranial pressure; Prognosis; Neuroimaging; Decision making

INTRODUCTION

Traumatic brain injury (TBI) is a common, burdensome health condition disproportionately affecting young adults. In 2010, the CDC estimated that 1.7 million Americans sustain a TBI annually, with TBI contributing to as much as one-third of all injury-related US deaths [1]. In the US, falls are the leading cause of TBI-related emergency department (ED) visits and hospitalizations, with over half a million visits and 60,000 hospitalizations per year [1]. Motor vehicle accidents are responsible for most of the TBI-related deaths among young adults [1]. Similarly, in European countries, falls and motor vehicle accidents are the first and second most prevalent causes of TBI [2]; the inverse is true in Asia, with motor vehicle accidents leading over falls [3].

Classically, clinical classification of TBI severity has been based on a patient's level of consciousness, as assessed by motor, verbal, and eye opening examination findings that comprise the ubiquitous 15-point Glasgow Coma Scale (GCS)[4]. The American Congress of Rehabilitation Medicine defined mild TBI as GCS ≥13 and moderate TBI as a GCS of 9–12 [5]. The contemporary clinical definition of severe TBI (sTBI), adopted from the 1991 Traumatic Coma Data Bank [6], is GCS ≤8 after resuscitation, within 48 hours of injury. Limitations of using GCS alone to define TBI severity include possible confounding by drug intoxication, sedation, and intubation, as well as the inability of the GCS to account for the pathophysiologic heterogeneity of TBI. To address these limitations, The Department of Veterans Affairs has released a Clinical Practice Guideline to further define severity categories of TBI based on criteria including structural imaging, duration of loss/alteration of consciousness, and post traumatic amnesia, in addition to GCS [7].

Two major radiographic scales have been developed to classify TBI based on morphologic characteristics on head CT. Most notable is the Marshall Classification [8], which subcategorizes injury based on the presence of a mass lesion with or without evacuation, basal cistern effacement, and midline shift. The Rotterdam Score also uses basal cistern compression and midline shift in its classification scheme, but with regards to mass lesions only incorporates epidural hematomas into scoring and also includes intraventricular and/or subarachnoid blood as a variable as well [9].

TBI has been defined as "an alteration in brain function, or other evidence of brain pathology, caused by external force[10]." While injury mechanisms are heterogeneous, the pathophysiology of sTBI involves both primary injury (occurring at impact) and secondary injury (occurring after impact). Primary brain injury includes traumatic shearing and tearing of axons, leading to diffuse axonal injury (DAI), and focal injuries, such as intra- and extra-axial hematomas. Secondary brain injury can result from ischemia, cerebral edema, seizures, and oxidative stress; leading to subsequent neuronal, axonal, and glial injury [11]. The aim of intensive care unit (ICU) management of the sTBI patient is to minimize and mitigate all

secondary brain injury. To achieve this, an intensivist must balance multiple considerations for an sTBI patient, including the possibilities of increased intracranial pressure (ICP), decreased cerebral perfusion pressure (CPP), hypoxemia, hypotension and hypertension, impaired cerebral autoregulation, a heightened systemic inflammatory response, and both convulsive and non-convulsive seizures [12]. Close to 90% of sTBI patients also suffer non-neurologic injuries and organ dysfunction that can influence treatment goals and strategies in the ICU [13].

In an effort to standardize care and guide treatment, the Brain Trauma Foundation (BTF; https://www.braintrauma.org) has created evidence-based Guidelines for the Management of Severe TBI. This review focuses on aspects of practical management of sTBI for ICU clinicians and highlights recommendation updates contained in most recent BTF guidelines, now in their 4th iteration [14]. A notable change to this edition was a more stringent approach to the level of evidence necessary for a recommendation to be made, an approach which resulted in downgrading and even omitting some prior recommendations. Moving forward, the BTF is adopting a “living guideline” model, with continual review of the literature and more frequent updates to recommendations.

PREHOSPITAL MANAGEMENT

The BTF’s most recently published Guidelines for Prehospital Management of TBI were updated in 2007 [15]. Recommendations include assessments of GCS and pupillary size in the field, targets of systolic blood pressure (SBP) >90 mmHg and oxygen saturation (SpO_2) > 90%, and rapid triage to a trauma center (Figure 1).

Airway management and blood pressure

The BTF prehospital guidelines call for establishment of a secure airway “by the most appropriate means available” for patients with a GCS <9, an inability to protect their airway, and/or an SpO_2 <90% that is not correctable by supplemental oxygen. Of note, studies examining the impact of prehospital intubation of TBI patients on outcomes have yielded mixed results, with uncertainty regarding “appropriate means.” In a retrospective study of over 1000 TBI patients, 75% of patients with GCS <9 who underwent prehospital intubation survived, compared to 64% of those who did not [16]. In a prospective randomized controlled trial of 312 sTBI patients, prehospital rapid sequence intubation by paramedics resulted in more favorable neurologic outcomes at 6 months compared to intubation upon hospital arrival [17]. Conversely, in a systematic review of over 15,000 TBI patients, no evidence was found in support of prehospital intubation [18]. An expert panel commenting on conflicting findings from prehospital intubation studies noted the inconclusive evidence for rapid sequence intubation in particular [19]. These inconsistent findings may be attributable to the limitations of using the GCS alone to identify intubation candidates, variability in intubation protocols and medications administered, and suboptimal intubation and ventilation techniques with subsequent hypo- or hyperventilation.

With regards to prehospital blood pressure goals, a prospective study of 717 patients from the Traumatic Coma Databank suggested that SBP <90 mmHg is an independent predictor of mortality, with even a single episode of hypotension from the time of injury to

resuscitation doubling mortality and increasing morbidity [20]. The BTF prehospital guidelines recommend treating hypotensive patients with isotonic fluids, with the option of hypertonic fluids for patients with GCS <8 [15]. However, it should be noted that a more recent multicenter cohort study analysis incorporating 5057 patients with significant TBI has suggested that having an admission SBP even below 120 mmHg may increase mortality rates [21].

Triage

The BTF prehospital guidelines recommend that sTBI patients be transported to a hospital with computed tomography (CT) scanning capability and neurosurgical care with ICP monitoring available [15]. In a retrospective study of over 5000 TBI patients, after adjustment for the case mix, risk of death was significantly lower for patients cared for in a major trauma center [22]. Moreover, several studies have observed that care led by dedicated neurointensivists improves outcomes for the general population of brain-injured patients [19–20].

In an analysis of over 51,000 patients from the National Trauma Databank National Sample Program from 2007 to 2009, patients with sTBI who were transferred to a Level I or II trauma center had lower injury severity and lower adjusted mortality rates compared to those who were directly admitted to higher level trauma centers [25], a finding suggesting that clinical severity has indeed been influencing prehospital triage decisions.

Impact of guideline adherence on outcome

While the evidence cited in the BTF prehospital guidelines is limited in by the inclusion of cohort, case control, and database registry studies, guideline adherence has been correlated with higher quality of care and improved outcomes. In a before-after study testing BTF guideline education among emergency providers, data from over 1000 patients revealed that patient rates of hypoxia, hypotension, and mortality were lower in the post-training group. and patients treated post-training had improved 14-day Glasgow Outcome Scores [26].

EMERGENCY DEPARTMENT CONSIDERATIONS

In addition to summarizing prehospital management principles, Figure 1 outlines the standard ED management for sTBI patients. In addition to these general principles, there are special considerations for the prevention of intracranial hemorrhage expansion among sTBI patients.

Tranexamic acid

Tranexamic acid (TXA) is an antifibrinolytic that has been studied in major trauma to prevent excessive blood loss, weighed against the risk of vascular occlusive events such as myocardial infarction, stroke, pulmonary embolism and deep vein thrombosis. The CRASH-2 trial [27] concluded that all-cause mortality was reduced in trauma patients who received TXA, without an increased risk of vascular occlusive events. The nested CRASH-2 intracranial bleeding study suggested that “neither moderate benefits nor moderate harmful effects [of TXA in TBI] can be excluded [28].” Another randomized controlled trial did not

find a benefit of TXA in reducing intracranial hemorrhage expansion [29]. In one systematic review and meta-analysis of TBI patients who received TXA, pooled results demonstrated a statistically significant reduction in intracranial hemorrhage progression and a trend towards improved clinical outcome [30]. Finally, a Cochrane review concluded that TXA reduces mortality in trauma patients, but its use later than three hours post-injury may be harmful, with its efficacy in TBI remaining uncertain [31]. The CRASH-3 trial, still underway, plans to enroll 10,000 adult sTBI patients in order to assess the effects of TXA on in-hospital mortality [32].

Coagulopathy management

When coagulopathy is present, rapid reversal should be a high priority in the ED to prevent hemorrhage expansion leading to secondary injury. In a review of 253 TBI patients requiring serial head imaging, 85% of patients who had at least one abnormal coagulation study on admission developed new or worsening lesions (swelling, intracranial hemorrhage, infarction) on follow up CT scans within 72 hours of admission, compared to 31% of patients with a normal coagulation profile on admission [33]. Another study found progression of traumatic intracranial hemorrhage (i.e., intraparenchymal, epidural, subdural, subarachnoid) in 80% of coagulopathic sTBI patients (INR<1.3, PTT>35, platelets<100,000) compared to 36% of non-coagulopathic sTBI patients, with the intracerebral hemorrhage (ICH) progression group having a 5-fold increase in mortality [34]. New oral anticoagulants (NOACs) have made the reversal of coagulopathy more complex. While dabigatran, a direct thrombin inhibitor, now has an available antidote [35], direct Factor Xa inhibitors still present a challenge. Of note, in a retrospective study of 18 TBI patients with either ICH or subarachnoid hemorrhage who were taking either rivaroxaban or apixaban, 4-factor prothrombin complex concentrate was safely used to potentially reduce hematoma expansion [36]. The Neurocritical Care Society (NCS) has recently released guidelines for the rapid reversal of antithrombotics in ICH [37], the principles of which may serve as a guide for sTBI management as well.

NEUROMONITORING IN THE INTENSIVE CARE UNIT

Once an sTBI patient has been stabilized and transferred from the ED to the ICU, various forms of neuromonitoring may inform treatment thresholds to mitigate secondary injury. The BTF Guidelines for the Management of sTBI mention that a multimodal monitoring approach, in addition to traditional ICP and CPP monitoring, may influence medical decision-making in the ICU; however, no firm recommendation is ultimately made regarding this approach. Of note, in a consensus statement on neuromonitoring, the Neurocritical Care Society and the European Society of Intensive Care Medicine assert that the use of multiple monitoring techniques may help supplement the clinical examination, especially in those patients whose examination is confounded by medication or who are in a comatose state [38].

Utility of intracranial pressure and cerebral perfusion pressure monitoring

The 2007 BTF sTBI management guidelines recommended an ICP monitor to be placed specifically in those sTBI patients considered salvageable with an abnormal CT and in those

with a normal CT and 2 or more of the following: age >40, unilateral or bilateral posturing, and SBP <90[39]. While the new guidelines state that management of sTBI patients using ICP monitoring information is recommended, the specific criteria on exactly which sTBI patients to monitor were not formally carried over, on the basis that their supporting evidence did not meet “current standards.” However, these criteria were explicitly restated in the new publication by the authors to “maintain sufficient recognition” of those patients at risk for elevated ICP. While there is otherwise no new guidance on exactly which population of sTBI patients to monitor in the 2016 guidelines, several studies released between the two most recent editions of the guidelines warrant attention, as assumptions regarding traditional ICP-driven management protocols and patient outcomes have been debated [40].

The BEST:TRIP randomized controlled trial compared a treatment protocol for sTBI patients where ICP monitoring was used versus a protocol in which treatment was based solely on clinical exam and imaging. A composite of survival time, follow-up level of consciousness, and follow-up functional status was the primary outcome [41]. The treatment protocol that included an ICP monitor, with the goal of maintaining ICP either below or at 20 mmHg, was not found to be superior to the protocol reliant on imaging and clinical exam.

Several key limitations of BEST: TRIP warrant mention. A common criticism of this study has been the use of 20 mmHg in the ICP monitoring arm as a strict threshold for escalating management, without in-depth consideration of ICP trends among monitored patients. Furthermore, the protocol called for a strict sequence of medical therapy escalation, with intermittent CSF drainage for those in the monitoring group with extraventricular drains (EVDs) only allowed for short periods of time. The study was conducted in Ecuador and Bolivia, where fewer sTBI patients may survive to hospitalization. The overall patient cohort in BEST:TRIP may thus be less severely injured than a similar patient cohort in a country with more resources. Furthermore, none of the study participants received rehabilitation after hospital discharge, which may have caused any protocol-related effects on outcome to be more difficult to detect.

In contrast to BEST:TRIP, evidence in support of an ICP-monitoring-driven treatment protocol being associated with improved outcomes has recently been published. In a retrospective analysis of 2134 patients with TBI who were tracked as part of a New York state initiative to assess compliance with BTF guidelines, those with sTBI whose treatment involved ICP monitoring had significantly lower mortality compared to unmonitored sTBI patients [42]. Furthermore, an observational study that extracted data from the American College of Surgeons Trauma Quality Improvement Program suggested that hospitals with higher rates of ICP monitoring had significantly lower mortality rates [43]. Given this mixed evidence, the new BTF continues to support the use of ICP monitoring information in the management of sTBI patients in the ICU but backs away from formal criteria on exactly which sTBI patients should have a monitor placed.

In addition to monitoring ICP, cerebral perfusion pressure (CPP) monitoring may provide complementary data to be used for clinical decision-making. One study found significantly decreased mortality associated with a guideline-driven protocol based upon ICP and CPP monitoring data[44]. Based on this study, the new BTF guidelines recommend CPP-based

management if an ICP monitor is placed, suggesting that this approach likely decreases mortality.

Mode of ICP and CPP monitoring

The 2016 BTF guidelines do not specify a preferred mode of ICP and CPP monitoring—e.g., an EVD, an intraparenchymal fiberoptic pressure monitor, or other method. In a retrospective study, EVD use was associated with higher in-hospital mortality for those patients with GCS ≥6, but comatose patients with a lower GCS had a trend towards lower mortality with EVD use [45]. Furthermore, in a separate retrospective study of 62 patients, those patients managed with continual CSF drainage had more effective ICP control as compared to those sTBI patients with intermittent drainage [46]. Based on this evidence, the new guidelines recommend that CSF drainage to lower ICP could be used in patients with a low GCS (<6) within 12 hours of injury and that an EVD may be more effective at lowering ICP burden if it drains continually as opposed to intermittently. These new recommendations are both based on Level III evidence.

Treatment thresholds

Whether the care of patients with sTBI should focus primarily on treatment of ICP or optimization of CPP has been debated in the literature[47, 48], with some arguing that priorities should be assigned based on the cerebral autoregulatory status of the patient[49]. As a practical approach, the new guidelines simply discuss treatment thresholds for both parameters.

If an ICP monitor is placed, the BTF guidelines recommend treatment of ICP sustained above 22 mmHg [14]. This recommendation was mainly derived from a single retrospective analysis of a database with 459 TBI patients, with the aim at identifying proper management thresholds for ICP, as well as CPP and pressure reactivity index (PRx) [50]. Of note, PRx is an index derived from changes in ICP in response to arterial blood pressure over time and is meant to approximate cerebral autoregulation; higher values suggest impaired autoregulation [51]. Analysis of the sTBI patients in the aforementioned database revealed reduced mortality associated with an ICP treatment threshold of ICP >22, a CPP maintenance threshold of >60, and PRx maintenance threshold of <0.3 [50]. Of note, another study of 327 patients with sTBI suggested that PRx values can help guide proper individualized ICP thresholds and that these individualized ICP thresholds may be stronger predictors of death as compared to universally accepted thresholds.[52]

While optimizing capillary hydrostatic pressure via blood pressure control has long been suggested as a theoretical mechanism for reducing cerebral edema in sTBI[53, 54], the relationship of cerebral autoregulation and precise CPP thresholds on outcomes in practice has now been further studied [55]. In one study of 58 TBI patients (90% of whom had sTBI), CPP >70 was indeed associated with unfavorable outcomes among patients thought to have impaired cerebral autoregulation based on analysis of ICP and MAP data; interestingly CPP <60 was associated with favorable outcomes in these same impaired patients [55]. As a result of these limited data, the BTF now gives Level IIB recommendations to maintain CPPs between 60 and 70, but with a note that the minimum

threshold may depend on the autoregulatory function of the patient. The guidelines maintain prior Level III recommendations that aggressive treatment to maintain CPP >70 should be avoided.

Advanced neuromonitoring

As mentioned earlier, the BTF provides no new recommendations on multimodal monitoring, which includes extracellular microdialysis and brain tissue oxygenation ($PbtO_2$). The low-level recommendation that use of information from jugular bulb monitoring of arteriovenous oxygen content difference ($AVDO_2$) may be considered to improve mortality and outcomes has been carried over to the new BTF guidelines from the prior edition. However, research is underway to address the utility of these advanced multimodal neuro-monitoring techniques. A microdialysis study recently demonstrated that metabolic crises—characterized by simultaneously low glucose and high lactate-pyruvate ratio in the brain extracellular fluid—occur frequently after TBI despite controlled ICP and may be predictors of poor outcome [56]. Such crises may also be associated with seizures and periodic discharges [57]. With regards to implications of these findings on current clinical practice, it remains to be proven if intervening on these values might improve outcomes.

With regards to $PbtO_2$-guided therapy, the phase 2 Brain Tissue Oxygen Monitoring in Traumatic Brain Injury (BOOST-2) trial aimed to show that placement of a $PbtO_2$ monitor was safe and that a monitor-guided protocol is feasible [58]. The study enrolled over 100 patients, with preliminary data showing non-futility of a protocol incorporating PbO2-directed interventions versus a standard of care algorithm incorporating ICP alone; a trend was seen towards lower mortality and overall improved 6-month functional neurological outcomes in the intervention arm using a protocolled approach to ICP and $PbtO_2$ treatments compared to the control group with treatment guided by ICP alone [59]. A separate systematic review of the literature has suggested that a combined paradigm using $PbtO_2$, ICP, and CPP values to guide treatment is associated with better outcomes, when compared to traditional ICP- and CPP-guided therapy alone [60]. Despite these studies, the current BTF guidelines no longer include specific $PbtO_2$ thresholds to be used in management. The 2007 BTF guidelines suggested a $PbtO_2$ value less than 15 lasting greater than 30 minutes was associated with higher mortality and used this threshold to recommend treatment [61]. However, the recommendations were removed, as literature inconsistency exists with respect to neurologic outcomes and mortality amongst the above mentioned systematic review and 8 other studies reviewed [14].

A full discussion of the extent of continuous electroencephalography (cEEG) as a neuromonitor in sTBI is beyond the scope of this review. Continuous EEG monitoring can be used to “detect [nonconvulsive seizures] and protect [with goal directed treatment]” the already injured and vulnerable brain [62]. An ongoing area of research is effect of nonconvulsive seizures (NCS) on outcomes, as there has been an association made between NCS in TBI to hippocampal atrophy [63]. It should be noted that the use of electrocorticography is an active areas of research in TBI. Electrocorticography is invasive cEEG used to investigate cortical spreading depressions, or propagating waves of astrocyte depolarization, which have been associated with secondary brain injury[56, 57]. A study that

analyzed 53 TBI patients with electrocorticography concluded that spreading depolarizations are associated with worse clinical outcome[64] The study identified depolarizations with isoelectricity or periodic epileptiform discharges, with prolonged depression of spontaneous activity, and with occurrence in temporal clusters as those in particular that portended worse outcomes.

SPECIFIC STRATEGIES FOR MEDICAL MANAGEMENT

Figure 2 highlights recommendations for sTBI medical management in the 2016 BTF guidelines that are unchanged from 2007, while Figure 3 highlights the new recommendations in 2016 [14, 39]. Of note, in addition to revised ICP and CPP thresholds and recommendations on EVD management as discussed, the scope of the new recommendations also covers blood pressure goals, seizure and infection prophylaxis, and proper nutrition. This section of the review highlights additional aspects of clinical management that may be of particular interest to intensivists.

Osmotic therapy

Osmotic agents are useful for reducing both intracranial pressure and cerebral edema [65, 66]. Though the evidence that osmotic agents improve outcomes is limited, the most recent BTF committee maintains that osmotic agents are useful for ICP reduction for sTBI patients. The 2016 guidelines do not recommend a specific osmotic agent but suggest judicious use of hypertonic saline in patients with chronic hyponatremia and avoidance of mannitol in patients with hypotension. In a retrospective study of matched patients, hypertonic saline administered as bolus therapy was more effective than mannitol at lowering ICP burden, with shorter ICU length-of-stay but similar 2-week mortality [66]. Two additional studies have suggested that boluses of hypertonic saline are more effective at reducing ICP compared to mannitol[67, 68]. A meta-analysis has also concluded that hypertonic saline is more effective than mannitol at treating elevated ICP, although the study was limited by small sample size among its component studies [68]. A recent review of hyperosmolar therapy for intracranial hypertension highlighted the current lack of strong evidence to favor continuous, scheduled bolus, and/or as-needed bolus dosing of hypertonic agents [69].

Hypothermia

Hypothermia has been observed to reduce ICP in clinical practice and in studies, but definitive proof that either prophylactic hypothermia or hypothermia as a treatment for refractory ICP elevation may improve clinical outcomes for sTBI patients is still lacking.

Clifton et al. examined the role of prophylactic mild hypothermia (≤35.0°C) by following patients who were hypothermic on admission and either kept hypothermic or allowed to passively rewarm. Outcomes were compared to those of patients who were normothermic on admission [70]. Six-month outcomes appeared to be improved when hypothermia was maintained, but it was unclear whether this benefit was attributable to neuroprotective effects of early hypothermia versus the adverse effects of early rewarming. In a follow-up trial, sTBI patients ≤45 years old were randomized to either prophylactic mild hypothermia for 48 hours or normothermia [71]. The study was stopped early due to futility after enrolling 232

patients, as an interim analysis showed a non-significant trend towards worse 6-month outcomes and increased mortality in the hypothermia group. Based on these results, the current BTF guidelines do not recommend prophylactic hypothermia. This recommendation is now Level II B, a stronger evidence level than in the prior edition. Of note, the planned POLAR study will further address the effect of prophylactic moderate hypothermia (33°C) on sTBI outcomes, by enrolling older patients (up to age 60) and maintaining hypothermia for a longer duration (72 hours) [72].

The recently published Eurotherm trial examined the use of therapeutic hypothermia for refractory ICP elevations in sTBI patients [73]. Patients were randomized to either standard critical care or standard critical care plus hypothermia (32 to 35°C). Patients in the hypothermia group were allowed to receive osmotherapy only if hypothermia did not control refractory elevations in ICP, defined as ICP >20 mmHg. After enrolling 347 patients, the trial was suspended early due to futility with worse outcomes and higher mortality among patients in the treatment arm, despite hypothermia effectively reducing ICP.

Decompressive craniectomy

A full discussion of the range of intensivist and neurosurgical opinions surrounding decompressive craniectomy for diffuse cerebral edema in sTBI is beyond the scope of this medical management review. Nevertheless, a brief exploration is warranted, in context of the BTF statement that bifrontal decompressive craniectomy is not recommended to improve outcomes at 6 months in sTBI patients without a mass lesion (e.g., epidural hemorrhages, etc.) having refractory ICPs.

Data that influenced this recommendation were derived from the Decompressive Craniectomy in Diffuse Traumatic Brain Injury (DECRA) trial, which randomized 155 patients with sTBI and ICP elevations refractory to first-tier interventions to bifrontal surgical decompression versus continued medical management. The study found unfavorable outcomes in patients with bifrontal decompression, even though surgery effectively reduced ICP [74]. Criticisms were raised over inequity of patient population, with more bilaterally unreactive pupils in the surgical arm, and minimal elevations in ICP leading up to surgery, with the mean only around 20 mmHg. Bifrontal craniectomy also may not have been the optimal surgical approach to reduce ICP, especially with hemispheric lesions. Furthermore, there was an 18% crossover rate to the surgical arm from those randomized to the medical arm.

Importantly, the more recent RESCUEicp trial was published shortly after the release of the new BTF guidelines [75]. Patients in RESCUEicp were randomized to either a surgical or medical arm if, after aggressive medical management, ICP was sustained >25 mmHg for 1–12 hours. This study found that patients in the decompressive craniectomy arm had decreased mortality but were more likely to survive in a vegetative state or with severe disability [75]. Notably, a subset of patients with severe disability regained functional independence by 6 months. Unlike the DECRA study, the RESCUEicp trial defined refractory elevated ICP as that over 25 mmHg (lasting for 1 to 12 hours) as compared to 20 mmHg (for 15 minutes within a one-hour period). RESCUEicp also allowed for both bifrontal craniectomy (63% of craniectomies) and hemicraniectomy (37% of craniectomies),

while DECRA only allowed for bifrontal craniectomy. How the RESCUEicp results might affect clinical practice and future revisions of the BTF guidelines remains unknown, but the study provides important data regarding surgical outcomes that can be used to inform ICU decision-making[76].

If a decision is made to proceed with decompressive craniectomy for an sTBI patient, BTF guidelines favor a large versus a small frontotemporoparietal decompressive craniectomy to reduce mortality and outcomes, based on a prospective study of 486 patients [77].

Paroxysmal sympathetic hyperactivity

A complication of sTBI that received little attention in the BTF guidelines is paroxysmal sympathetic hyperactivity (PSH), also commonly referred to as “dysautonomia” or “sympathetic storming”. This syndrome is characterized by a constellation of adrenergic symptoms, including agitation, diaphoresis, hyperthermia, hypertension, tachycardia, and tachypnea accompanied by motor symptoms such as hypertonia and extensor posturing [78]. A consensus statement sought to simplify >30 forms of nomenclature for this condition and define diagnostic criteria [79]. The writing group for this statement ultimately arrived at PSH as consensus terminology and also developed a diagnostic tool, the paroxysmal sympathetic hyperactivity measure (PSH-AM). This diagnostic tool was created as a probabilistic system which assigns likelihood to the diagnosis, emphasizing the difficulty in excluding alternative diagnoses such as sepsis and drug withdrawal, which can similarly present as overactive sympathetic activity.

PSH occurs in about 10% of sTBI patients[80–82], and is associated with younger age, more severe injury, early fever [83] and diffuse axonal injury [82, 84]. While recovery from the complication is possible, those with PSH generally have longer hospital and ICU stays, greater costs, and possibly worse outcomes [80, 85]. The exact pathophysiology of PSH remains unclear, but current mechanistic hypotheses involve a loss of inhibitory control, producing unopposed sympathetic activity[78–79].

Treatment of PSH may shorten ICU stays and reduce complications, but this has not been assessed prospectively. The pharmacotherapy of PSH targets the inhibition of sensory afferents, central sympathetic outflow and end organ responses to the sympathetic system, [88] including medications such as gabapentin, bromocriptine, oxycodone, clonidine, and propranolol to blunt the effects on those respective targets. Figure 4 illustrates an original approach to the management of PSH, with features adapted from Baguley et al [79]. Recommendations are based upon expert opinion but not yet evidence based.

Seizure Prophylaxis

Early post traumatic seizures (PTS), defined as those that occur within one week of injury, can occur in as high as 16.9% of TBI patients [89]. Ten percent of those patients are at risk of status epilepticus [90]. In a double-blinded randomized controlled trial of 404 patients randomized to either drug or placebo, prophylactic phenytoin was shown to significantly decrease the rate of early PTS [91], prompting a Level II A recommendation on its use for 7 days post injury in the third edition of the BTF guidelines. This recommendation has carried over to the current iteration, given the strength of the data. In a recent prospective study of

813 patients, there were no differences in early PTS rates, adverse drug reactions, or mortality when comparing levetiracetam to phenytoin prophylaxis [92].

PHARMACOLOGIC NEUROPROTECTIVE STRATEGIES

Multiple trials of neuroprotective agents have been conducted with hopes of reducing secondary neuronal necrosis and apoptosis in the injured brain [93]. Pharmacologic therapies that have been tested in sTBI clinical trials or that are currently in development are summarized below.

Corticosteroids

The most notable study regarding corticosteroids for sTBI patients is the CRASH trial, which randomized patients to 48 hours of methylprednisolone treatment versus placebo, with the primary outcomes being death from all causes at 2 weeks and death or severe disability at 6 months [94]. The study was stopped early after 5 years, based on higher risk of death at 2 weeks as well as increased death or severe disability at 6 months. Based largely on this trial, the BTF has adopted a strong Level I recommendation that corticosteroid use among sTBI patients for neuroprotective purposes is contraindicated.

Progesterone

Animal models of TBI suggested a benefit of progesterone administration on the regulation of cytokines, excitotoxicity, apoptosis, and vasogenic edema[95]. Several small, early-stage clinical trials [84–85] also suggested that acute progesterone administration may improve neurologic outcomes patients with sTBI [98]. Based on these findings, the efficacy of progesterone was recently studied in two Phase III trials. The industry-funded SYNAPSE trial enrolled 1195 patients with sTBI and randomized administration of progesterone versus placebo. There was no benefit of progesterone on the primary outcome of Glasgow Outcome Scale (GOS) at 6 months, or secondary outcome of death. There was also no difference in the rate of adverse events between groups[99]. The similar NIH-funded PROTECT III trial was stopped early due to futility, after randomizing 882 of the planned 1140 patients to progesterone versus placebo [100]. There were no benefits of progesterone over placebo either regarding 6-month favorable outcome or secondary outcomes of death or disability.

Other neuroprotective strategies

Several other pharmacologic agents have been studied as possible neuroprotectants for sTBI patients, with most of these trials not powered adequately to assess benefits on neurologic outcome and mortality.

In experimental models of sTBI, cyclosporine-A has been shown to preserve mitochondrial integrity by preventing calcium influx, thus preventing secondary neuronal injury [101]. Several studies have shown that cyclosporine-A is safe and tolerable in humans, with at least no negative impact on outcomes or mortality [90–91]. Lulic et al. have reviewed the shortcomings of the cyclosporine-A preclinical and clinical trials, especially with regard to the heterogeneity of timing of administration of the drug, and have offered guidance for future studies, to clarify the role of cyclosporine in sTBI [104].

Several recent studies have examined the neurocytoprotective effects of erythropoietin (EPO) on outcomes. In one study, 200 TBI patients, who were not able to follow commands, were randomized to one of four groups: EPO, placebo, a hemoglobin transfusion threshold of 7g/dL, or a hemoglobin threshold 10g/dL, respectively [105]. Neither administration of EPO nor a transfusion threshold of 10gdL improved outcomes at 6 months. The higher transfusion threshold of 10g/dL group had a higher incidence of thromboembolic events. EPO treatment in the recent EPO-TBI trial, which randomized 606 patients to either EPO or placebo, did not reduce severe neurologic dysfunction or mortality at 6 months nor increase the incidence of DVT [106].

In a phase II study of 86 sTBI patients, administration of dexanabinol, a cannabis derivative, was shown to help achieve better ICP/CPP control without jeopardizing blood pressure, with a trend towards better neurologic outcome [107]. However, a subsequent phase III trial of 846 patients concluded that the drug is safe but not efficacious in improving 6-month neurologic outcome, as compared to placebo [108].

The use of pre-injury statin has been shown to be associated with reduced risk of death and improved functional recovery at 12 months in moderate to sTBI patients over 65 [109]. However, another study of pre-injury statin use showed no detectable difference regarding disability at 3 months [110]. Whether starting a statin after TBI confers neuroprotective benefit is currently unknown.

Continuous magnesium infusion has been studied as a neuroprotective agent in sTBI. However, a randomized controlled trial not only failed to show efficacy but reported trends towards increased mortality, pulmonary edema, and respiratory failure in the magnesium treatment groups [111].

In animal models, pharmacologic modulation of TBI-induced nitric oxide production has been linked to decreased cerebral edema and improved outcomes [112–113]. NOSTRA, a phase III, randomized, double blinded multicenter trial, is currently assessing the efficacy of a nitric oxide synthase inhibitor on 6 month neurologic outcomes[114].

NEUROPROGNOSTICATION

For sTBI patients, there is significant variability among experts in perceptions of neurologic prognosis, approach to neuroprognostication, and on practice of recommendations made to families regarding continuing life-sustaining therapies [115]. Attempts to develop accurate, reliable models for outcome prognostication for sTBI patients date back as far as 1975, with the development of the GCS [101–102]. The admission GCS remains a key predictor in more recently developed models. Such models have utilized large collaborative databases and multivariable regression to attempt to adjust for confounders, but pitfalls pertaining to generalizability and suboptimal fit of observed data to the regression models limit their use in clinical care. There is still ongoing work to refine prognostication tools, and consideration of adding ICU complications, multimodal data, and “ICP therapy intensity levels” as variables in prognostication have been proposed[118–120].

Clinical scales

The IMPACT study analyzed data from 11 studies, in 8,509 patients, with severe or moderate TBI [121]. In this cohort, the strongest predictors associated with 6-month outcome included age, GCS motor score, pupillary reactivity, hypotension and hypoxemia in the field or ED, and the Marshall CT-score for stratifying head CT findings. A publicly available IMPACT score calculator is available at http://www.tbi-impact.org/?p=impact/calc. Limitations of the IMPACT model include the fact that most patients from which the model was derived were treated in the 1980s and 1990s. Moreover, the accuracy of the GCS motor scores in the model may have been confounded by sedation and paralytics, incomplete data, and missing variables. Only variables from admission are included in the model, which does not factor in complications during the commonly lengthy ICU course of these patients.

Models based on trial data from the CRASH study involved over 10,000 enrolled patients. Two prognostic models (basic and CT) have been created, which include patients' characteristics of age, GCS, pupillary reactivity, and extracranial injury with or without CT characteristics [122]. The inclusion of patients from high and low-middle income countries in the study has the advantage of making the results generalizable to resource poor settings, but the large discrepancies in outcome based on country and income status is a limitation of the model. The publicly available CRASH model risk calculator (http://www.crash2.lshtm.ac.uk/Risk%20calculator/) includes "country" as a variable.

For patients with penetrating brain injury, a recent prognostic score, the SPIN score, was developed to identify predictors associated with survival [123]. Derived from a cohort of 413 penetrating TBI patients from two centers in the U.S., the SPIN score identified motor GCS, pupillary reactivity, self-inflicted injury, transfer from another hospital, sex, injury severity score, and admission INR as independent predictors of survival. This score has not yet been validated.

Limitations of clinical scales

Both the IMPACT and CRASH models have undergone external validation. In one study with 300 consecutively admitted sTBI patients, the two models were shown to be "satisfactory" at predicting outcomes, with good discrimination based on area under the curve (AUC) analysis [124]. However, as with all outcome prediction scales, one should caution their use in individual patients. The self-fulfilling prophecy of early withdrawal of care may be present in observational data on which predictive models are based. One small study of 47 patients formally concluded an overestimation of unfavorable outcome by the CRASH model [125].

These caveats are reflected in the limited use of such scales in clinical practice. A recent qualitative study of 20 attending physicians caring for sTBI patients in the U.S. from all 5 geographic regions in the U.S. and from neurocritical care, neurosurgery, trauma, and palliative care revealed a highly variable knowledge of the IMPACT model and cautionary attitudes towards its use [126]. Of all participants, 75% knew of the IMPACT model, but only 42% used it, and only with great caution. Reasons for hesitation included distrust in the data from which the IMPACT model was derived, heterogeneity of sTBI patients, and the

general concern that outcome scales are derived from populations and are not reliable in individual patients.

Neuroimaging and prognostication

Head CT is the preferred technique for acute neuroimaging of patients with TBI because of its accessibility, speed of acquisition, and ability to detect lesions that require urgent neurosurgical intervention. From the standpoint of prognostication, CT grading systems such as the Marshall CT classification [127] and Rotterdam CT score [9] have been incorporated into the IMPACT and CRASH prediction models [104–105]. Yet despite the widespread use of head CT in the diagnostic and prognostic evaluation of patients with sTBI, multiple studies have shown that MRI provides higher sensitivity for detecting prognostically relevant intracerebral lesions, particularly traumatic axonal injury[128–131]. Accordingly, MRI provides greater prognostic utility than does CT[111–112, 115]. However, MRI is not always feasible in sTBI, given possible metallic injury, inability to lie supine due to elevated ICP, and limited availability of MRI scanners at some hospitals. Moreover, unexpected recovery of functional independence has been reported in MRI studies of patients with severe intracerebral injuries, including brainstem traumatic axonal injury[116–117]. Thus, it is important for intensivists to be aware even MRI has limited specificity for predicting poor outcomes.

Given increasing appreciation for the limitations associated with CT- and MRI-based prognostication, a growing number of studies are testing the prognostic utility of advanced structural and functional imaging techniques [135]. One such advanced technique is diffusion tensor imaging (DTI), which measures the directional diffusion of water along axon bundles [136] and is therefore a potential biomarker of traumatic axonal injury[137]. In the largest DTI prognostic study performed to date in patients with sTBI, DTI measures of white matter injury outperformed the IMPACT score with respect to prognostic accuracy [138]. Diffusor tensor tractography (DTT) can further assess white matter connectivity by creation of 3-dimensional reconstructions of neural tracts using DTI data. Wang and colleagues have shown that DTT data acquired in the acute stage of sTBI may have utility at predicting long-term cognitive function [139].

Functional neuroimaging techniques such as functional MRI (fMRI) and positron emission tomography (PET) have also recently been tested for their prognostic utility, although mostly in the setting of chronic disorders of consciousness (DOC). fMRI uses the blood-oxygen level dependent signal as a marker for cerebral blood flow and, in turn, neuronal activity. In 2010, Monti et al. used stimulus-based fMRI to examine 54 patients with chronic DOC and observed that 5 patients demonstrated fMRI evidence of volitional brain function beyond that detectable on bedside exam [140]. Coleman et al. showed that brain responses detected by fMRI may possibly predict whether a patient with a chronic DOC will go on to recover further behavioral evidence of conscious awareness [141]. These observations raise the possibility that stimulus-based fMRI could have prognostic utility in the acute setting, but no acute studies of stimulus-based fMRI in the acute sTBI population have been performed to date. Stender et al. recently reported that FDG-PET can be used as a complement to the bedside examination to predict recovery from DOC and may provide greater prognostic

accuracy than does fMRI [142]. However, similar to fMRI, FDG-PET has yet to be tested as a prognostic tool in patients with acute sTBI.

FAMILY SUPPORT

The lack of awareness of the general public regarding the impact of sTBI [143] coupled with the shock and stress of an unexpected hospital admission means that many families of sTBI patients are often overwhelmed in the ICU. The unique needs of families of comatose, brain-injured patients in the ICU have been explored in several studies [144–146]. Qualitative investigations have demonstrated that families of sTBI patients in particular specifically emphasize their "need to know"—their need for consistent information, their need for involvement, and their need to make sense of the unexpected ICU experience [144]. The importance of compassionate yet accurate communication of neurologic prognosis and acknowledgement of uncertainty where it may exist have also been reported to be first and foremost in the minds of families of sTBI patients [145]. Family needs for sTBI patients also change significantly over the course of a patient's hospitalization [146]. At the time of survivors' discharge from the hospital, families transition to the challenging task of finding the professional and community support necessary to facilitate ongoing rehabilitative care. Finding such care is especially challenging for patients with persistent DOC, whose rehabilitation options may be limited.

Several organizations provide resources for families of sTBI patients. The Neurocritical Care Society published a guidebook specifically geared towards families of acute sTBI patients who are attempting to make sense of the ICU environment while making decisions on behalf of incapacitated patients [147]. The book, available at https://www.pathlms.com/ncs-ondemand/courses/1282, was spearheaded by a family member of an sTBI patient who had an extended ICU experience. The Brain Injury Association of America (http://www.biausa.org/), whose mission is to progress the field of TBI while improving the quality of life for those injured, has local chapters in many states. Its website contains links to patient and family support groups that may be helpful as families prepare to transition out of the ICU.

Approaches to shared decision-making with surrogate decision makers in neuroscience ICUs have been reviewed recently [131–132]. The aforementioned variability in approaches to neuroprognostication for sTBI patients have called attention to a need for evidence-based methods to assist with shared decision making in goals-of-care discussions. An essential goal of these discussions is to focus on perceived patient preferences in the context of available prognostic data [149]. A formal decision aid to assist both ICU clinicians and sTBI patients' families with prognostic and goals-of-care discussions is currently being developed by a team at the University of Massachusetts and will undergo validation testing over the next few years.

SUMMARY

Severe TBI remains a burdensome public health concern worldwide. Preventing secondary injury continues to be the aim of ICU treatments. While the strength of evidence on which

the most recent BTF guidelines are based is a work in progress and presents a challenge to the neurocritical care community, guideline-driven management nevertheless has been shown to improve outcomes in multiple patient cohorts [133–134]. Attention to recommendation changes in the most recent BTF guidelines, awareness of clinical trial results, use of clinical judgment combined with evidence-based tools for prognostication, compassionate attention to families' needs, and insight into patient values are all vital for optimizing sTBI patient care.

References

1. Barlow KM. Traumatic brain injury. Handbook of Clinical Neurology. 2013; 112:891–904. DOI: 10.1016/B978-0-444-52910-7.00011-8 [PubMed: 23622299]
2. Peeters W, van den Brande R, Polinder S, et al. Epidemiology of traumatic brain injury in Europe. Acta Neurochirurgica. 2015; 157:1683–1696. DOI: 10.1007/s00701-015-2512-7 [PubMed: 26269030]
3. Li M, Zhao Z, Yu G, Zhang J. Epidemiology of Traumatic Brain Injury over the World: A Systematic Review. Austin Neurol & Neurosci. 2016; 1:1007–1020. DOI: 10.4172/2327-5146.1000275
4. Teasdale G, Jennett B. ASSESSMENT OF COMA AND IMPAIRED CONSCIOUSNESS. A Practical Scale. The Lancet. 1974; 304:81–84. DOI: 10.1016/S0140-6736(74)91639-0
5. Kay T, Harrington D, Adams R, et al. Definition of mild traumatic brain injury. Journal of Head Trauma Rehabilitation. 1993; 8:86–87. DOI: 10.1097/00001199-199309000-00010
6. Foulkes M, Eisenberg H, Jane J, et al. The Traumatic Coma Data Bank: design, methods, and baseline characteristics. Journal of neurosurgery. 1991; 75:S8–13. DOI: 10.3171/sup.1991.75.1s.00s8
7. Department of Veterans Affairs, Department of Defense. VA/DoD Clinical Practice Guideline for the Management of Concussion-Mild Traumatic Brain Injury. 2016:1–133.
8. Marshall, Lawrence F., Marshall, Sharon Bowers, Klauber, Melville R., et al. A new classification of head injury based on computerized tomography. Journal of Neurosurgery. 1991; 75:S14–S20. DOI: 10.3171/sup.1991.75.1s.0s14
9. 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; 57:1173–82. 82. [PubMed: 16331165]
10. Menon DK, Schwab K, Wright DW, Maas AI. Position statement: Definition of traumatic brain injury. Archives of Physical Medicine and Rehabilitation. 2010; 91:1637–1640. DOI: 10.1016/j.apmr.2010.05.017 [PubMed: 21044706]
11. Saatman KE, Duhaime a C, Bullock R, et al. Classification of traumatic brain injury for targeted therapies. JNeurotrauma. 2008; 25:719–738. DOI: 10.1089/neu.2008.0586 [PubMed: 18627252]
12. Kinoshita K. Traumatic brain injury: pathophysiology for neurocritical care. Journal of intensive care. 2016; 4:1–10. DOI: 10.1186/s40560-016-0138-3 [PubMed: 26734467]
13. Zygun DA, Kortbeek JB, Fick GH, et al. Non-neurologic organ dysfunction in severe traumatic brain injury. Critical Care Medicine. 2005; 33:654–660. DOI: 10.1097/01.CCM.0000155911.01844.54 [PubMed: 15753760]
14. Carney N, Totten AM, O'Reilly C, et al. Guidelines for the Management of Severe Traumatic Brain Injury, Fourth Edition. Neurosurgery. 2016; 24(Suppl 1):S1–106. DOI: 10.1227/NEU.0000000000001432
15. Badjatia N, Carney N, Crocco TJ, et al. Guidelines for prehospital management of traumatic brain injury 2nd edition. Prehospital emergency care: official journal of the National Association of EMS Physicians and the National Association of State EMS Directors. 2008; 12(Suppl 1):S1–S52. DOI: 10.1080/10903120701732052

16. Winchell RJ, Hoyt DB. Endotracheal intubation in the field improves survival in patients with severe head injury. Trauma Research and Education Foundation of San Diego. Archives of surgery (Chicago, Ill: 1960). 1997; 132:592–7.

17. Bernard SA, Nguyen V, Cameron P, et al. Prehospital Rapid Sequence Intubation Improves Functional Outcome for Patients With Severe Traumatic Brain Injury. Ann Surg. 2010; 252:959–965. DOI: 10.1097/SLA.0b013e3181efc15f [PubMed: 21107105]

18. Von Elm E, Schoettker P, Henzi I, et al. Pre-hospital tracheal intubation in patients with traumatic brain injury: Systematic review of current evidence. British Journal of Anaesthesia. 2009; 103:371–386. DOI: 10.1093/bja/aep202 [PubMed: 19648153]

19. Davis DP, Fakhry SM, Wang HE, et al. Paramedic rapid sequence intubation for severe traumatic brain injury: perspectives from an expert panel. Prehospital emergency care. 2007; 11:1–8. DOI: 10.1080/10903120601021093 [PubMed: 17169868]

20. Chesnut RM, Marshall SB, Piek J, et al. Early and Late Systemic Hypotension as a Frequent and Fundamental Source of Cerebral Ischemia Following Severe Brain Injury in the Traumatic Coma Data Bank. Monitoring of Cerebral Blood Flow and Metabolism in Intensive Care. 1993; 59:121–125. DOI: 10.1007/978-3-7091-9302-0_21

21. Fuller G, Hasler RM, Mealing N, et al. The association between admission systolic blood pressure and mortality in significant traumatic brain injury: A multi-centre cohort study. Injury. 2014; 45:612–617. DOI: 10.1016/j.injury.2013.09.008 [PubMed: 24206920]

22. MacKenzie EJ, Rivara FP, Jurkovich GJ, et al. A national evaluation of the effect of trauma-center care on mortality. The New England journal of medicine. 2006; 354:366–378. DOI: 10.1056/NEJMsa052049 [PubMed: 16436768]

23. Suarez JI, Zaidat OO, Suri MF, et al. Length of stay and mortality in neurocritically ill patients: impact of a specialized neurocritical care team. Critical care medicine. 2004; 32:2311–2317. DOI: 10.1097/01.CCM.0000146132.29042.4C [PubMed: 15640647]

24. Varelas PN, Conti MM, Spanaki MV, et al. The impact of a neurointensivist-led team on a semiclosed neurosciences intensive care unit. Critical care medicine. 2004; 32:2191–2198. DOI: 10.1097/01.CCM.0000146131.03578.21 [PubMed: 15640630]

25. Sugerman DE, Xu L, Pearson WS, Faul M. Patients with severe traumatic brain injury transferred to a Level I or II trauma center: United States, 2007 to 2009. The journal of trauma and acute care surgery. 2012; 73:1491–9. DOI: 10.1097/TA.0b013e3182782675 [PubMed: 23188242]

26. Watts DD, Hanfling D, Waller MA, et al. An evaluation of the use of guidelines in prehospital management of brain injury. Prehospital Emergency Care. 2004; 8:254–261. DOI: 10.1016/j.prehos.2004.02.001 [PubMed: 15295724]

27. CRASH-2 trial collaborators. Shakur H, Roberts I, et al. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. The Lancet. 2010; 376:23–32. DOI: 10.1016/S0140-6736(10)60835-5

28. CRASH-2 Collaborators IBS. Effect of tranexamic acid in traumatic brain injury: a nested randomised, placebo controlled trial (CRASH-2 Intracranial Bleeding Study). Bmj. 2011; 343:d3795.doi: 10.1136/bmj.d3795 [PubMed: 21724564]

29. Yutthakasemsunt S, Kittiwattanagul W, Piyavechvirat P, et al. Tranexamic acid for patients with traumatic brain injury: A randomized, double-blinded, placebo-controlled trial. Journal of Neurotrauma. 2011; 28:A55. doi: http://dx.doi.org/10.1089/neu.2011.9945.

30. Zehtabchi S, Abdel Baki SG, Falzon L, Nishijima DK. Tranexamic acid for traumatic brain injury: a systematic review and meta-analysis. Am J Emerg Med. 2014; 32:1503–1509. DOI: 10.1016/j.ajem.2014.09.023 [PubMed: 25447601]

31. Roberts, I., Shakur, H., Ker, K., et al. Antifibrinolytic drugs for acute traumatic injury (Review). In: Roberts, I., editor. Cochrane Database Syst Rev. John Wiley & Sons, Ltd; Chichester, UK: 2012. p. CD004896-CD004896.

32. Dewan Y. CRASH-3 – tranexamic acid for the treatment of significant traumatic brain injury: study protocol for an international randomized, double-blind, placebo-controlled trial. Trials. 2012; 13:87.doi: 10.1186/1745-6215-13-87 [PubMed: 22721545]

33. Stein S, Young G, Talucci R, et al. Delayed Brain Injury after Head Trauma: Significance of Coagulopathy. Neurosurgery. 1992; 30:160–165. [PubMed: 1545882]
34. Allard CB, Scarpelini S, Rhind SG, et al. Abnormal coagulation tests are associated with progression of traumatic intracranial hemorrhage. The Journal of trauma. 2009; 67:959–67. DOI: 10.1097/TA.0b013e3181ad5d37 [PubMed: 19901655]
35. Pollack CV, Reilly PA, Eikelboom J, et al. Idarucizumab for Dabigatran Reversal. The New England journal of medicine. 2015; 373:1–10. DOI: 10.1056/NEJMoa1502000 [PubMed: 26132937]
36. Grandhi R, Newman WC, Zhang X, et al. Administration of 4-factor prothrombin complex concentrate as an antidote for intracranial bleeding in patients taking direct factor Xa inhibitors. World Neurosurgery. 2015; 84:1956–1961. DOI: 10.1016/j.wneu.2015.08.042 [PubMed: 26341438]
37. Frontera JA, Lewin JJ, Rabinstein AA, et al. Guideline for Reversal of Antithrombotics in Intracranial Hemorrhage: A Statement for Healthcare Professionals from the Neurocritical Care Society and Society of Critical Care Medicine. Neurocritical Care. 2016; 24:6–46. DOI: 10.1007/s12028-015-0222-x [PubMed: 26714677]
38. Le Roux P, Menon DK, Citerio G, et al. The International Multidisciplinary Consensus Conference on Multimodality Monitoring in Neurocritical Care: A List of Recommendations and Additional Conclusions: A Statement for Healthcare Professionals From the Neurocritical Care Society and the European. Neurocritical Care. 2014; 21:282–296. DOI: 10.1007/s12028-014-0077-6
39. Bratton SL, Chestnut RM, Ghajar J, et al. VI. Indications for Intracranial Pressure Monitoring. Journal of Neurotrauma. 2007; 24:S-37–S-44. DOI: 10.1089/neu.2007.9990 [PubMed: 17511544]
40. Shafi S, Diaz-Arrastia R, Madden C, Gentilello L. Intracranial Pressure Monitoring in Brain-Injured Patients is Associated With Worsening of Survival. The Journal of Trauma: Injury, Infection, and Critical Care. 2008; 64:335–340. DOI: 10.1097/TA.0b013e31815dd017
41. Chesnut RM, Temkin N, Carney N, et al. A trial of intracranial-pressure monitoring in traumatic brain injury. The New England journal of medicine. 2012; 367:2471–81. DOI: 10.1056/NEJMoa1207363 [PubMed: 23234472]
42. Farahvar A, Gerber LM, Chiu Y-L, et al. Increased mortality in patients with severe traumatic brain injury treated without intracranial pressure monitoring. Journal of Neurosurgery. 2012; 117:729–734. DOI: 10.3171/2012.7.JNS111816 [PubMed: 22900846]
43. Alali AS, Fowler RA, Mainprize TG, et al. Intracranial Pressure Monitoring in Severe Traumatic Brain Injury: Results from the American College of Surgeons Trauma Quality Improvement Program. Journal of Neurotrauma. 2013; 30:1737–1746. DOI: 10.1089/neu.2012.2802 [PubMed: 23731257]
44. Gerber LM, Chiu Y-L, Carney N, et al. Marked reduction in mortality in patients with severe traumatic brain injury. Journal of neurosurgery. 2013; 119:1583–90. DOI: 10.3171/2013.8.JNS13276 [PubMed: 24098983]
45. Griesdale D, McEwen J, Kurth T, et al. External Ventricular Drains and Mortality in Patients with Severe Traumatic Brain Injury. The Canadian journal of neurological sciences Le journal canadien des sciences neurologiques. 2010; 37:43–8. [PubMed: 20169772]
46. Nwachuku EL, Puccio AM, Fetzick A, et al. Intermittent Versus Continuous Cerebrospinal Fluid Drainage Management in Adult Severe Traumatic Brain Injury: Assessment of Intracranial Pressure Burden. Neurocritical Care. 2014; 20:49–53. DOI: 10.1007/s12028-013-9885-3 [PubMed: 23943318]
47. Robertson CS, Valadka AB, Hannay HJ, et al. Prevention of secondary ischemic insults after severe head injury. Critical care medicine. 1999; 27:2086–95. [PubMed: 10548187]
48. Prabhakar H, Sandhu K, Bhagat H, et al. Current concepts of optimal cerebral perfusion pressure in traumatic brain injury. Journal of anaesthesiology, clinical pharmacology. 2014; 30:318–27. DOI: 10.4103/0970-9185.137260
49. Howells T, Elf K, Jones PA, et al. Pressure reactivity as a guide in the treatment of cerebral perfusion pressure in patients with brain trauma. Journal of Neurosurgery. 2005; 102:311–317. DOI: 10.3171/jns.2005.102.2.0311

50. Sorrentino E, Diedler J, Kasprowicz M, et al. Critical thresholds for cerebrovascular reactivity after traumatic brain injury. Neurocritical Care. 2012; 16:258–266. DOI: 10.1007/s12028-011-9630-8 [PubMed: 21964774]
51. Zweifel C, Lavinio A, Steiner LA, et al. Continuous monitoring of cerebrovascular pressure reactivity in patients with head injury. Neurosurgical focus. 2008; 25:E2.doi: 10.3171/FOC.2008.25.10.E2
52. Lazaridis C, DeSantis SM, Smielewski P, et al. Patient-specific thresholds of intracranial pressure in severe traumatic brain injury. Journal of neurosurgery. 2014; 120:893–900. DOI: 10.3171/2014.1.JNS131292 [PubMed: 24506248]
53. Asgeirsson B, Grände PO, Nordström CH. A new therapy of post-trauma brain oedema based on haemodynamic principles for brain volume regulation. Intensive care medicine. 1994; 20:260–7. [PubMed: 8046119]
54. Eker C, Asgeirsson B, Grände PO, et al. Improved outcome after severe head injury with a new therapy based on principles for brain volume regulation and preserved microcirculation. Critical care medicine. 1998; 26:1881–6. [PubMed: 9824083]
55. Johnson U, Nilsson P, Ronne-Engström E, et al. Favorable outcome in traumatic brain injury patients with impaired cerebral pressure autoregulation when treated at low cerebral perfusion pressure levels. Neurosurgery. 2011; 68:714–721. DOI: 10.1227/NEU.0b013e3182077313 [PubMed: 21311298]
56. Stein NR, McArthur DL, Etchepare M, Vespa PM. Early cerebral metabolic crisis after TBI influences outcome despite adequate hemodynamic resuscitation. Neurocritical Care. 2012; 17:49–57. DOI: 10.1007/s12028-012-9708-y [PubMed: 22528283]
57. Vespa P, Tubi M, Claassen J, et al. Metabolic crisis occurs with seizures and periodic discharges after brain trauma. Annals of Neurology. 2016; 79:579–590. DOI: 10.1002/ana.24606 [PubMed: 26814699]
58. Diaz-Arrastia R. Brain Tissue Oxygen Monitoring in Traumatic Brain Injury (TBI) (BOOST 2). Clinicaltrials.Gov Seattle. 2015 NCT00974259.
59. Shutter L for B-2 investigators. Preliminary results of BOOST-2. Oral presentation of breaking clinical trial abstracts. Neurocritical Care Society Annual Meeting Oral Prese. 2014
60. 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. Neurocritical Care. 2012; 17:131–138. DOI: 10.1007/s12028-011-9621-9 [PubMed: 21845489]
61. Bratton SL, Chestnut RM, Ghajar J, et al. Brain Oxygen Monitoring and Thresholds. Journal of neurotrauma. 2007; 24(Suppl 1):65–70. DOI: 10.1089/neu.2007.9986
62. Vespa P. Continuous EEG monitoring for the detection of seizures in traumatic brain injury, infarction, and intracerebral hemorrhage: “to detect and protect”. Journal of clinical neurophysiology: official publication of the American Electroencephalographic Society. 2005; 22:99–106. DOI: 10.1097/01.WNP.0000154919.54202.E0 [PubMed: 15805809]
63. Vespa PM, Xu Y, Hovda D. Nonconvulsive seizures after traumatic brain injury are associated with hippocampal atrophy. 2010
64. Hartings JA, Watanabe T, Bullock MR, et al. Spreading depolarizations have prolonged direct current shifts and are associated with poor outcome in brain trauma. Brain. 2011; 134:1529–1540. DOI: 10.1093/brain/awr048 [PubMed: 21478187]
65. Becker DP, Vries JK. The alleviation of increased intracranial pressure by the chronic administration of osmotic agents. Intracranial Pressure. 1972:309–315.
66. Mangat HS, Chiu Y-L, Gerber LM, et al. Hypertonic saline reduces cumulative and daily intracranial pressure burdens after severe traumatic brain injury. Journal of neurosurgery. 2015; 122:202–10. DOI: 10.3171/2014.10.JNS132545 [PubMed: 25380107]
67. Vialet R, Albanèse J, Thomachot L, et al. Isovolume hypertonic solutes (sodium chloride or mannitol) in the treatment of refractory posttraumatic intracranial hypertension: 2 mL/kg 7.5% saline is more effective than 2 mL/kg 20% mannitol. Critical care medicine. 2003; 31:1683–1687. DOI: 10.1097/01.CCM.0000063268.91710.DF [PubMed: 12794404]

68. Kamel H, Navi BB, Nakagawa K, et al. Hypertonic saline versus mannitol for the treatment of elevated intracranial pressure – A meta-analysis of randomized clinical trials. Crit Care Med. 2011; 39:554–9. DOI: 10.1097/CCM.0b013e318206b9be [PubMed: 21242790]
69. Torre-Healy A, Marko NF, Weil RJ. Hyperosmolar therapy for intracranial hypertension. Neurocritical Care. 2012; 17:117–130. DOI: 10.1007/s12028-011-9649-x [PubMed: 22090171]
70. Clifton GL, Miller ER, Choi SC, et al. Hypothermia on admission in patients with severe brain injury. Journal of neurotrauma. 2002; 19:293–301. DOI: 10.1089/089771502753594864 [PubMed: 11939497]
71. 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. The Lancet Neurology. 2011; 10:131–139. DOI: 10.1016/S1474-4422(10)70300-8 [PubMed: 21169065]
72. Nichol A, Gantner D, Presneill J, et al. Protocol for a multicentre randomised controlled trial of early and sustained prophylactic hypothermia in the management of traumatic brain injury. Critical care and resuscitation: journal of the Australasian Academy of Critical Care Medicine. 2015; 17:92–100. [PubMed: 26017126]
73. Andrews PJD, Sinclair HL, Rodriguez A, et al. Hypothermia for Intracranial Hypertension after Traumatic Brain Injury. New England Journal of Medicine. 2015; 151007070032002. doi: 10.1056/NEJMoa1507581
74. Cooper DJ, Rosenfeld JV, Murray L, Arabi YM. Decompressive Craniectomy in Diffuse Traumatic Brain Injury. New England Journal Medicine. 2011; 364:1493–1502. DOI: 10.1056/NEJMoa1102077
75. Hutchinson PJ, Kolias AG, Timofeev IS, et al. Trial of Decompressive Craniectomy for Traumatic Intracranial Hypertension. New England Journal of Medicine. 2016; NEJMoa1605215. doi: 10.1056/NEJMoa1605215
76. Shutter LA, Timmons SD. Intracranial Pressure Rescued by Decompressive Surgery after Traumatic Brain Injury. New England Journal of Medicine. 2016; 375:1183–1184. DOI: 10.1056/NEJMe1609722 [PubMed: 27604048]
77. Jiang J, Xu W, Li W, et al. Efficacy of Standard Trauma Craniectomy for Refractory Intracranial Hypertension with Severe Traumatic Brain Injury: A Multicentre, Prospective, Randomized Controlled Study. Journal of neurotrauma. 2005; 22:623–628. DOI: 10.1089/neu.2005.22.623 [PubMed: 15941372]
78. Blackman JA, Patrick PD, Buck ML, Rust RS. Paroxysmal autonomic instability with dystonia after brain injury. Archives of neurology. 2004; 61:321–8. DOI: 10.1001/archneur.61.3.321 [PubMed: 15023807]
79. Baguley IJ, Perkes IE, Fernandez-Ortega J-F, et al. Paroxysmal sympathetic hyperactivity after acquired brain injury: consensus on conceptual definition, nomenclature, and diagnostic criteria. Journal of neurotrauma. 2014; 31:1515–20. DOI: 10.1089/neu.2013.3301 [PubMed: 24731076]
80. Fernandez-Ortega JF, Prieto-Palomino MA, Garcia-Caballero M, et al. Paroxysmal sympathetic hyperactivity after traumatic brain injury: clinical and prognostic implications. J Neurotrauma. 2012; 29:1364–1370. DOI: 10.1089/neu.2011.2033 [PubMed: 22150061]
81. Hendricks HT, Heeren AH, Vos PE. Dysautonomia after severe traumatic brain injury. European Journal of Neurology. 2010; 17:1172–1177. DOI: 10.1111/j.1468-1331.2010.02989.x [PubMed: 20298427]
82. Rabinstein AA. Paroxysmal sympathetic hyperactivity in the neurological intensive care unit. Neurological research. 2007; 29:680–682. DOI: 10.1179/016164107X240071 [PubMed: 18173907]
83. Hinson HE, Schreiber MA, Laurie AL, et al. Early Fever As a Predictor of Paroxysmal Sympathetic Hyperactivity in Traumatic Brain Injury. The Journal of head trauma rehabilitation. 2017; 1doi: 10.1097/HTR.0000000000000271
84. Lv L-Q, Hou L-J, Yu M-K, et al. Risk factors related to dysautonomia after severe traumatic brain injury. The Journal of trauma. 2011; 71:538–42. DOI: 10.1097/TA.0b013e31820ebee1 [PubMed: 21427610]

85. Baguley IJ, Slewa-Younan S, Heriseanu RE, et al. The incidence of dysautonomia and its relationship with autonomic arousal following traumatic brain injury. Brain injury: [BI]. 2007; 21:1175–1181. DOI: 10.1080/02699050701687375

86. Baguley IJ. The excitatory:inhibitory ratio model (EIR model): An integrative explanation of acute autonomic overactivity syndromes. Medical Hypotheses. 2008; 70:26–35. DOI: 10.1016/j.mehy.2007.04.037 [PubMed: 17583440]

87. Meyer KS. Understanding paroxysmal sympathetic hyperactivity after traumatic brain injury. Surgical neurology international. 2014; 5:S490–2. DOI: 10.4103/2152-7806.144632 [PubMed: 25506508]

88. Lump D, Moyer M. Paroxysmal sympathetic hyperactivity after severe brain injury. Current neurology and neuroscience reports. 2014; 14:494.doi: 10.1007/s11910-014-0494-0 [PubMed: 25220846]

89. Frey LC. Epidemiology of posttraumatic epilepsy: a critical review. Epilepsia. 2003; 44(Suppl 1): 11–17. DOI: 10.1046/j.1528-1157.44.s10.4.x

90. Jennett B. Epilepsy after Non-Missile Head Injuries. Scottish Medical Journal. 1973; 18:8–13. DOI: 10.1177/003693307301800103 [PubMed: 4197932]

91. Temkin NR, Dikmen SS, Wilensky AJ, et al. A Randomized, Double-Blind Study of Phenytoin for the Prevention of Post-Traumatic Seizures. New England Journal of Medicine. 1990; 323:497–502. DOI: 10.1056/NEJM199008233230801 [PubMed: 2115976]

92. Inaba K, Menaker J, Branco BC, et al. A prospective multicenter comparison of levetiracetam versus phenytoin for early posttraumatic seizure prophylaxis. Journal of Trauma and Acute Care Surgery. 2013; 74:766–773. DOI: 10.1097/TA.0b013e3182826e84 [PubMed: 23425733]

93. Formigli L, Papucci L, Tani A, et al. Aponecrosis: morphological and biochemical exploration of a syncretic process of cell death sharing apoptosis and necrosis. Journal of cellular physiology. 2000; 182:41–9. DOI: 10.1002/(SICI)1097-4652(200001)182:1<41::AID-JCP5>3.0.CO;2-7 [PubMed: 10567915]

94. Baigent C, Bracken M, Chadwick D, et al. Final results of MRC CRASH, a randomised placebo-controlled trial of intravenous corticosteroid in adults with head injury – outcomes at 6 months. The Lancet. 2005; 365:1957–1959. DOI: 10.1016/S0140-6736(05)66552-X

95. Djebaili M, Guo Q, Pettus EH, et al. The neurosteroids progesterone and allopregnanolone reduce cell death, gliosis, and functional deficits after traumatic brain injury in rats. Journal of neurotrauma. 2005; 22:106–118. DOI: 10.1089/neu.2005.22.106 [PubMed: 15665606]

96. Xiao G, Wei J, Yan W, et al. Improved outcomes from the administration of progesterone for patients with acute severe traumatic brain injury: a randomized controlled trial. Critical care (London, England). 2008; 12:R61.doi: 10.1186/cc6887

97. Shakeri M, Boustani MR, Pak N, et al. Effect of progesterone administration on prognosis of patients with diffuse axonal injury due to severe head trauma. Clinical Neurology and Neurosurgery. 2013; 115:2019–2022. DOI: 10.1016/j.clineuro.2013.06.013 [PubMed: 23871679]

98. Junpeng, M., Huang, S., Qin, S. Progesterone for acute traumatic brain injury. In: Huang, S., editor. The Cochrane database of systematic reviews. John Wiley & Sons, Ltd; Chichester, UK: 2011. p. CD008409

99. Skolnick BE, Maas a I, Narayan RK, et al. A clinical trial of progesterone for severe traumatic brain injury. N Engl J Med. 2014; 371:2467–76. DOI: 10.1056/NEJMoa1411090 [PubMed: 25493978]

100. Wright DW, Yeatts SD, Silbergleit R, et al. Very early administration of progesterone for acute traumatic brain injury. N Engl J Med. 2014; 371:2457–2466. DOI: 10.1056/NEJMoa1404304 [PubMed: 25493974]

101. Okonkwo DO, Büki A, Siman R, Povlishock JT. Cyclosporin A limits calcium-induced axonal damage following traumatic brain injury. Neuroreport. 1999; 10:353–8. [PubMed: 10203334]

102. Mazzeo AT, Brophy GM, Gilman CB, et al. Safety and tolerability of cyclosporin a in severe traumatic brain injury patients: Results from a prospective randomized trial. Journal of Neurotrauma. 2009; 26:2195–2206. DOI: 10.1089/neu.2009.1012 [PubMed: 19621985]

103. Hatton J, Rosbolt B, Empey P, et al. Dosing and safety of cyclosporine in patients with severe brain injury. Journal of neurosurgery. 2008; 109:699–707. DOI: 10.3171/JNS/2008/109/10/0699 [PubMed: 18826358]
104. Lulic D, Burns J, Bae EC, et al. A review of laboratory and clinical data supporting the safety and efficacy of cyclosporin a in traumatic brain injury. Neurosurgery. 2011; 68:1172–1185. DOI: 10.1227/NEU.0b013e31820c6cdc [PubMed: 21307793]
105. Robertson CS, Hannay HJ, Yamal J-M, et al. Effect of erythropoietin and transfusion threshold on neurological recovery after traumatic brain injury: a randomized clinical trial. JAMA: the journal of the American Medical Association. 2014; 312:36–47. DOI: 10.1001/jama.2014.6490 [PubMed: 25058216]
106. Nichol A, French C, Little L, et al. Erythropoietin in traumatic brain injury (EPO-TBI): A double-blind randomised controlled trial. The Lancet. 2015; 386:2499–2506. DOI: 10.1016/S0140-6736(15)00386-4
107. Knoller N, Levi L, Shoshan I, et al. Dexanabinol (HU-211) in the treatment of severe closed head injury: a randomized, placebo-controlled, phase II clinical trial. Critical Care Medicine. 2002; 30:548–554. DOI: 10.1097/00003246-200203000-00009 [PubMed: 11990913]
108. Maas AIR, Murray G, Henney H, et al. Efficacy and safety of dexanabinol in severe traumatic brain injury: Results of a phase III randomised, placebo-controlled, clinical trial. Lancet Neurology. 2006; 5:38–45. DOI: 10.1016/S1474-4422(05)70253-2 [PubMed: 16361021]
109. Schneider EB, Efron DT, MacKenzie EJ, et al. Premorbid statin use is associated with improved survival and functional outcomes in older head-injured individuals. The Journal of trauma. 2011; 71:815–9. DOI: 10.1097/TA.0b013e3182319de5 [PubMed: 21986733]
110. Tapia-Perez JH, Sanchez-Aguilar M, Torres-Corzo JG, et al. Effect of rosuvastatin on amnesia and disorientation after traumatic brain injury (NCT003229758). Journal of neurotrauma. 2008; 25:1011–7. DOI: 10.1089/neu.2008.0554 [PubMed: 18690806]
111. Temkin NR, Anderson GD, Winn HR, et al. Magnesium sulfate for neuroprotection after traumatic brain injury: a randomised controlled trial. Lancet Neurology. 2007; 6:29–38. DOI: 10.1016/S1474-4422(06)70630-5 [PubMed: 17166799]
112. Gahm C, Holmin S, Wiklund PN, et al. Neuroprotection by selective inhibition of inducible nitric oxide synthase after experimental brain contusion. Journal of neurotrauma. 2006; 23:1343–54. DOI: 10.1089/neu.2006.23.1343 [PubMed: 16958586]
113. Terpolilli NA, Zweckberger K, Trabold R, et al. The novel nitric oxide synthase inhibitor 4-amino-tetrahydro-L-biopterine prevents brain edema formation and intracranial hypertension following traumatic brain injury in mice. Journal of neurotrauma. 2009; 26:1963–75. DOI: 10.1089/neu.2008.0853 [PubMed: 19514849]
114. Stover JF, Belli A, Boret H, et al. Nitric Oxide Synthase Inhibition with the Antipterin VAS203 Improves Outcome in Moderate and Severe Traumatic Brain Injury: A Placebo-Controlled Randomized Phase IIa Trial (NOSTRA). Journal of Neurotrauma. 2014; 31:1599–1606. DOI: 10.1089/neu.2014.3344 [PubMed: 24831445]
115. Turgeon AF, Lauzier F, Burns KEA, et al. Determination of Neurological Prognosis and Clinical Decision Making in Adult Patients With Severe Traumatic Brain Injury: A Survey of Canadian Intensivists, Neurosurgeons, and Neurologists. Critical care medicine. 2013; 41:1–8. DOI: 10.1097/CCM.0b013e318275d046 [PubMed: 23222269]
116. Jennett B, Teasdale G, Braakman R, et al. Predicting outcome in individual patients after severe head injury. Lancet. 1976; 1:1031–1034. DOI: 10.1016/0306-4530(76)90018-4 [PubMed: 57446]
117. Jennett B, Bond M. ASSESSMENT OF OUTCOME AFTER SEVERE BRAIN DAMAGE. A Practical Scale. The Lancet. 1975; 305:480–484. DOI: 10.1016/S0140-6736(75)92830-5
118. Muehlschlegel S, Carandang R, Ouillette C, et al. Frequency and impact of intensive care unit complications on moderate-severe traumatic brain injury: Early results of the outcome prognostication in traumatic brain injury (OPTIMISM) study. Neurocritical Care. 2013; 18:318–331. DOI: 10.1007/s12028-013-9817-2 [PubMed: 23377884]
119. Spiotta AM, Stiefel MF, Gracias VH, et al. Brain tissue oxygen–directed management and outcome in patients with severe traumatic brain injury. Journal of Neurosurgery. 2010; 113:571–580. DOI: 10.3171/2010.1.JNS09506 [PubMed: 20415526]

120. Weiner GM, Lacey MR, Mackenzie L, et al. Decompressive Craniectomy for Elevated Intracranial Pressure and Its Effect on the Cumulative Ischemic Burden and Therapeutic Intensity Levels After Severe Traumatic Brain Injury. Neurosurgery. 2010; 66:1111–1119. DOI: 10.1227/01.NEU.0000369607.71913.3E [PubMed: 20386136]

121. 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 Medicine. 2008; 5:1251–1261. DOI: 10.1371/journal.pmed.0050165

122. Perel P, Arango M, Clayton T, et al. Predicting outcome after traumatic brain injury: practical prognostic models based on large cohort of international patients. BMJ (Clinical research ed). 2008; 336:425–429. DOI: 10.1136/bmj.39461.643438.25

123. Muehlschlegel S, Ayturk D, Ahlawat A, et al. Predicting survival after acute civilian penetrating brain injuries: The SPIN score. Neurology. 2016; 87:2244–2253. DOI: 10.1212/WNL.0000000000003355 [PubMed: 27784772]

124. Han J, King NKK, Neilson SJ, et al. External Validation of the CRASH and IMPACT Prognostic Models in Severe Traumatic Brain Injury. Journal of neurotrauma. 2014; 7:1–7. DOI: 10.1089/neu.2013.3003

125. Olivecrona M, Olivecrona Z. Use of the CRASH study prognosis calculator in patients with severe traumatic brain injury treated with an intracranial pressure-targeted therapy. Journal of Clinical Neuroscience. 2013; 20:996–1001. DOI: 10.1016/j.jocn.2012.09.015 [PubMed: 23702375]

126. Moskowitz, Jesse E., Quinn, Thomas T., Shutter, Lori A., Goldberg, Robert R., Col, Nananda N., Mazor SSM, Kathleen K. Variable knowledge, use and perceptions of the IMPACT model among physicians during prognostication meetings for critically-ill TBl patients. Neurocritical Care Society 2016 Meeting Abstract P43. 2016:25. S76.

127. Marshall, Lawrence F., Marshall, Sharon Bowers, Klauber, Melville R., et al. A new classification of head injury based on computerized tomography. Journal of Neurosurgery. 1991; 75:S14–S20. DOI: 10.3171/sup.1991.75.1s.0s14

128. Firsching R, Woischneck D, Diedrich M, et al. Early magnetic resonance imaging of brainstem lesions after severe head injury. Journal of neurosurgery. 1998; 89:707–12. DOI: 10.3171/jns.1998.89.5.0707 [PubMed: 9817405]

129. Lagares A, Ramos A, Pérez-Nuñez A, et al. The role of MR imaging in assessing prognosis after severe and moderate head injury. Acta Neurochirurgica. 2009; 151:341–356. DOI: 10.1007/s00701-009-0194-8 [PubMed: 19224121]

130. Moen KG, Brezova V, Skandsen T, et al. Traumatic Axonal Injury: The Prognostic Value of Lesion Load in Corpus Callosum, Brain Stem, and Thalamus in Different Magnetic Resonance Imaging Sequences. Journal of neurotrauma. 2014; 11:1–11. DOI: 10.1089/neu.2013.3258

131. Paterakis K, Karantanas AH, Komnos A, Volikas Z. Outcome of patients with diffuse axonal injury: the significance and prognostic value of MRI in the acute phase. J Trauma. 2000; 49:1071–1075. DOI: 10.1097/00005373-200012000-00016 [PubMed: 11130491]

132. Skandsen T, Kvistad KA, Solheim O, et al. Prognostic value of magnetic resonance imaging in moderate and severe head injury: a prospective study of early MRI findings and one-year outcome. Journal of Neurotrauma. 2011; 28:691–699. DOI: 10.1089/neu.2010.1590 [PubMed: 21401308]

133. Edlow BL, Giacino JT, Hirschberg RE, et al. Unexpected recovery of function after severe traumatic brain injury: The limits of early neuroimaging-based outcome prediction. Neurocritical Care. 2013; 19:364–375. DOI: 10.1007/s12028-013-9870-x [PubMed: 23860665]

134. McNab JA, Edlow BL, Witzel T, et al. The Human Connectome Project and beyond: Initial applications of 300mT/m gradients. NeuroImage. 2013; 80:234–245. DOI: 10.1016/j.neuroimage.2013.05.074 [PubMed: 23711537]

135. Edlow BL, Wu O. Advanced neuroimaging in traumatic brain injury. Seminars in Neurology. 2012; 32:374–400. DOI: 10.1055/s-0032-1331810 [PubMed: 23361483]

136. Pierpaoli C, Jezzard P, Basser PJ, et al. Diffusion tensor MR imaging of the human brain. Radiology. 1996; 201:637–48. DOI: 10.1148/radiology.201.3.8939209 [PubMed: 8939209]

137. Betz J, Zhuo J, Roy A, et al. Prognostic Value of Diffusion Tensor Imaging Parameters in Severe Traumatic Brain Injury. Journal of Neurotrauma. 2012; 29:1292–1305. DOI: 10.1089/neu.2011.2215 [PubMed: 22364596]
138. Galanaud D, Perlbarg V, Gupta R, et al. Assessment of white matter injury and outcome in severe brain trauma: a prospective multicenter cohort. Anesthesiology. 2012; 117:1300–10. DOI: 10.1097/ALN.0b013e3182755558 [PubMed: 23135261]
139. Wang JY, Bakhadirov K, Devous MD, et al. Diffusion tensor tractography of traumatic diffuse axonal injury. Arch Neurol. 2008; 65:619–26. DOI: 10.1001/archneur.65.5.619 [PubMed: 18474737]
140. Monti MM, Vanhaudenhuyse A, Coleman MR, et al. Willful Modulation of Brain Activity in Disorders of Consciousness. New England Journal of Medicine. 2010; 362:579–589. DOI: 10.1056/NEJMoa0905370 [PubMed: 20130250]
141. Coleman MR, Davis MH, Rodd JM, et al. Towards the routine use of brain imaging to aid the clinical diagnosis of disorders of consciousness. Brain. 2009; 132:2541–2552. DOI: 10.1093/brain/awp183 [PubMed: 19710182]
142. Stender J, Gosseries O, Bruno MA, et al. Diagnostic precision of PET imaging and functional MRI in disorders of consciousness: A clinical validation study. The Lancet. 2014; 384:514–522. DOI: 10.1016/S0140-6736(14)60042-8
143. Langlois JA, Marr A, Mitchko J, Johnson RL. Tracking the Silent Epidemic and Educating the Public: CDC ' s Traumatic Brain Injury – Associated Activities Under the TBI Act of 1996 and the Children ' s Health Act of 2000. Journal of Head Trauma Rehabilitation. 2005; 20:196–204. [PubMed: 15908820]
144. Bond AE, Rae C, Draeger L. Needs of Family Members of Patients With Severe Traumatic Brain Injury. 2003; 23:63–72.
145. Engli M, Kirsivali-Farmer K. Needs of family members of critically ill patients with and without acute brain injury. The Journal of neuroscience nursing: journal of the American Association of Neuroscience Nurses. 1993; 25:78–85. [PubMed: 8478558]
146. Keenan A, Joseph L. The needs of family members of severe traumatic brain injured patients during critical and acute care: a qualitative study. Canadian journal of neuroscience nursing. 2010; 32:25–35. [PubMed: 20865832]
147. David Y, Hwang M, Dayla Maisey Bs. A Guide To Traumatic Brain Injury: The Intensive Care Unit. 2015:1.
148. Cai X, Robinson J, Muehlschlegel S, et al. Patient Preferences and Surrogate Decision Making in Neuroscience Intensive Care Units. Neurocritical Care. 2015; 23:131–141. DOI: 10.1007/s12028-015-0149-2 [PubMed: 25990137]
149. Muehlschlegel S, Shutter L, Col N, Goldberg R. Decision Aids and Shared Decision-Making in Neurocritical Care: An Unmet Need in Our NeuroICUs. Neurocritical Care. 2015; 23:127–130. DOI: 10.1007/s12028-014-0097-2 [PubMed: 25561435]
150. Gerber LM, Chiu Y-L, Carney N, et al. Marked reduction in mortality in patients with severe traumatic brain injury. Journal of Neurosurgery. 2013; 119:1583–1590. DOI: 10.3171/2013.8.JNS13276 [PubMed: 24098983]
151. Talving P, Karamanos E, Teixeira PG, et al. Intracranial pressure monitoring in severe head injury: compliance with Brain Trauma Foundation guidelines and effect on outcomes: a prospective study. Journal of neurosurgery. 2013; 119:1248–54. DOI: 10.3171/2013.7.JNS122255 [PubMed: 23971954]

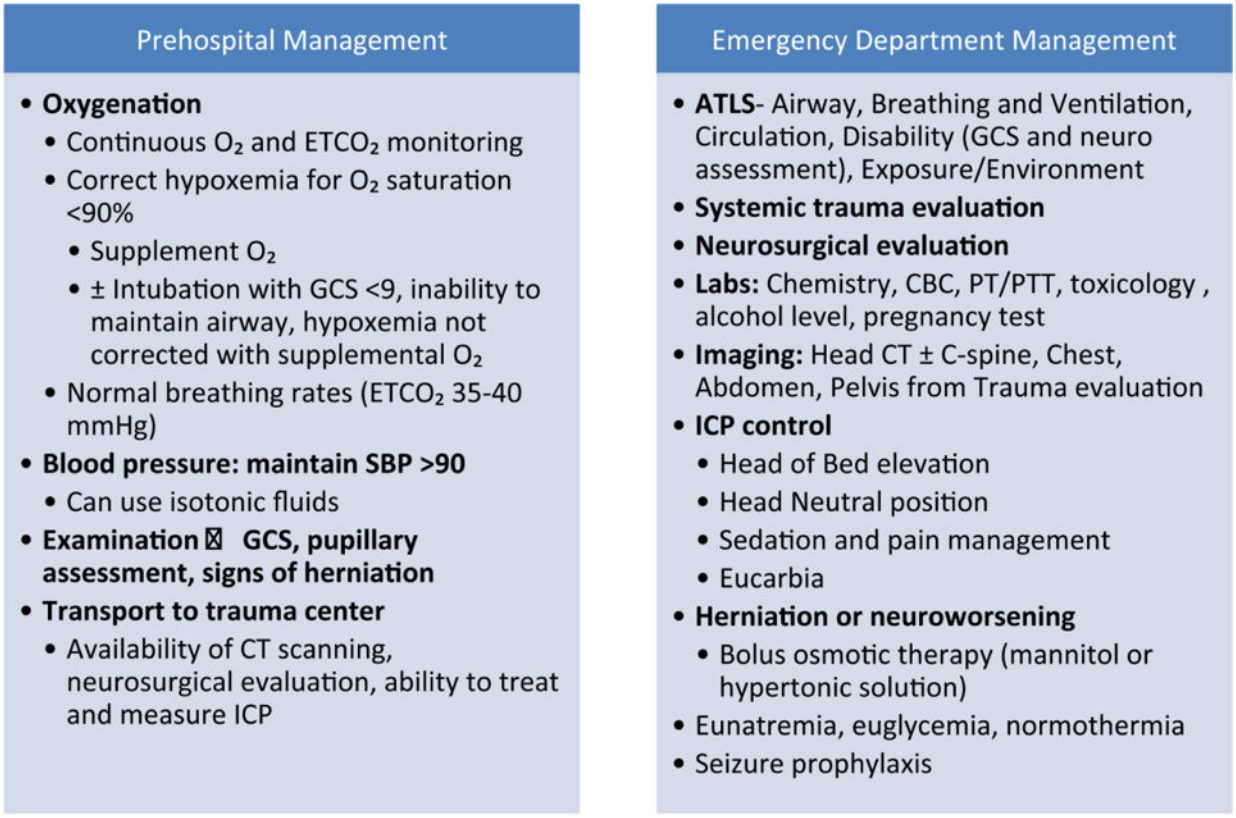

Figure 1.

Initial severe traumatic brain injury management based in part on Brain Trauma Foundation guidelines. O_2 – oxygen, $ETCO_2$ – end-tidal CO_2, SBP – systolic blood pressure, GCS – Glasgow Coma Scale, BPM – breaths per minute, ICP – intracranial pressure, ATLS – Advanced Trauma Life Support, CBC – complete blood count.

Unchanged BTF Guideline Recommendations

Topic	Recommendation
Hyperosmolar therapy	• Mannitol can be used to control elevated ICP but avoid hypotension (SBP<90 mmHg)* • Can use with signs of transtentorial herniation or progressive neuroworsening if no ICP monitor*
Hyperventilation	• Avoid prolonged ppx hyperventilation, and within the first 24 hours • Hyperventilation can be used as a temporizing measure for elevated ICP* • If hyperventilation used monitor O_2 deliver with SjO2 or $BtpO_2$*
Anesthetics	• Avoid ppx use of barbiturates for intracranial hypertension • Can use barbiturates if ICP refractory to max standard medical and surgical means • Propofol can be used for ICP but not for improvement in mortality and 6 mouths outcomes
Steroids	• Not recommended for ICP control or outcome benefit • High dose methylprednisolone is contraindicated due to increased mortality
Infection prophylaxis	• Early tracheostomy can be considered
DVT prophylaxis	• Pharmacologic prophylaxis may be used but there is increased risk of ICH expansion, especially if benefit>risk • No recommendation of preferred agent or timing of initiation
Seizure prophylaxis	• PHT or VPA not recommended for LATE (<7 days) PTS • PHT recommended for early PTS when benefit>risk, though seizures not shown to be associated with worse outcomes
ICP monitoring and threshold	• Monitor salvageable patients (GCS3-8 after resuscitation) + abnormal CT* • Monitor with normal CT + ≥2 of the following: age>40, unilateral/bilateral posturing, SBP<90 mmHg* • ICP values + CT findings may be used to make decisions regarding treatment
Advanced monitoring and threshold	• Jugular bulb monitoring of $AVDO_2$ may be considered • $AVDO_2$ <50% may be a threshold to avoid
CPP threshold	• Avoid fluids and vasopressors to maintain CPP>70, given risk of respiratory failure

Figure 2.

Unchanged BTF guideline recommendations. ICP – intracranial pressure, ppx- prophylaxis, O_2 – oxygen, SjO_2 – jugular bulb venous oxygen saturation, $BtpO_2$ – cerebral tissue oxygenation, ICH – intracerebral hemorrhage, PHT – phenytoin, VPA – valproate, PTS- post traumatic seizures, AVDO2 -arteriovenous oxygen difference, CPP – cerebral perfusion pressure. *Recommendations from the prior (third) BTF guidelines not supported by evidence meeting current standards.

New BTF Guideline Recommendations

Topic	Recommendation
Decompressive craniectomy	• Bifrontal craniectomy is not recommended without a mass lesion, ICP>20 for more than 15 min within 1 hour, refractory to medical therapy*. • A large frontotemporoparietal DC >small frontotemporoparietal DC
Prophylactic hypothermia	• Early (within 2.5 hours) short term (48 hours) prophylactic hypothermia is not recommended
Cerebrospinal fluid drainage	• Continuous EVD drainage may be more effective at lowering ICP burden than intermittent use • Consider CSF drainage to lower ICP in patients with initial GCS<6 within first 12 hours of injury
Nutrition	• Feed patients by the 5th and at most the 7th day
Infection prophylaxis	• PI oral care is not recommended to reduce VAP • Consider an antimicrobial impregnated EVD
Seizure prophylaxis	• Cannot recommend levetiracetam over PHT for early PTS ppx
ICP monitoring and threshold	• Management using information from ICP monitor is recommended • Treat ICP>22 mmHg
CPP monitoring and threshold	• Management using information from CPP monitor is recommended • Target CPP is 60-70 mmHg, but minimum CPP is unclear and may depend on autoregulation status
Blood Pressure Threshold	• Maintain SBP ≥100mmHg for patients 50-69 years old or ≥110mmHg for patients 15-49 or >70 years old

Figure 3.

New BTF guideline recommendations. DC – decompressive craniectomy, ICP – intracranial pressure, EVD – external ventricular drain, ppx – prophylaxis, PI -povidone-iodine, VAP – ventilator associated pneumonia, PHT – phenytoin, PTS – post traumatic seizures, CPP – cerebral perfusion pressure. *Has been shown to reduce ICP and minimize ICU days.

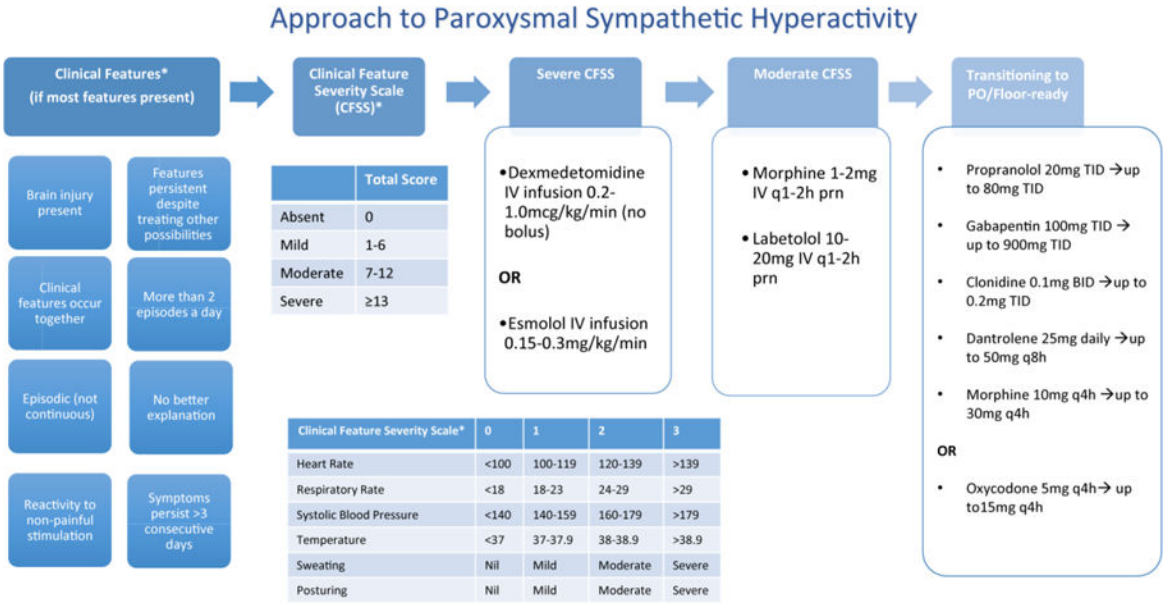

Figure 4.

Suggested approach to paroxsysmal sympathetic hyperactivity. Recommendations are based upon expert opinion but not yet evidence based. *Clinical features adopted from the “Diagnosis Likelihood Tool” and “Clinical Feature Severity Scale (CFSS)” from Baguley et al 2014 [79].