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Management of Traumatic Brain Injury in the Intensive Care Unit

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1. Introduction

Traumatic brain injury (TBI) is a major source of death and severe disability worldwide. In the USA alone, this type of injury causes 290, 000 hospital admissions, 51, 000 deaths, and 80, 000 permanently disabled survivors [1, 2]. TBI occurs in two phases, primary and secondary brain injury. The primary injury results from the direct physical impact to the brain parenchyma resulting in structural and shearing injury of neurons, injury to vessels, and interruption of neurochemical processes. This leads to hemorrhage, edema, compression of intracranial structures. Primary injury is unalterable after the time of the trauma.The secondary injury, on the other hand, is characterized by a cascade of events that starts within minutes of the primary injury. As in ischemia –reperfusion injuries, the acute post-injury period in TBI is characterized by several pathophysiologic processes that start in the minutes to hours following injury and may last for hours to days. These result in further neuronal injury and are termed the secondary injury. The causes of the secondary injury can be evaluated by those that occur of the systemic or extracerebral level and those that occur on the cellular level. On the systemic level contributing factors include hypoxia, hypotension, hypercapnia, acidosis and hyperglycemia [3, 4].While the cellular mechanisms of secondary injury include all of the following: apoptosis, mitochondrial dysfunction, excitotoxicity, disruption in ATP metabolism, disruption in calcium homeostasis, increase in inflammatory mediators and cells, free radical formation, DNA damage, blood-brain barrier disruption, brain glucose utilization disruption, microcirculatory dysfunction and microvascular thrombosis [5-8]. All this leads to development of cerebral edema, blood-brain barrier disruption, vasospasm, increase in volume of bleeding and contusions, and intracranial hypertension.TBI patients, like other patients with brain injury, need multidisciplinary approach

(neurointensivists, neurologists, neurosurgeons, and specialized nurses, respiratory therapists, physical therapists, nutritionists, etc.) for improved outcomes. Mortality and functional outcomes in all brain injured patients, including TBI patients improve when monitored and managed in neuroICUs and by neurointensivists [9-12]. This chapter will focus on the management of TBI patients in the intensive care unit.

2. Neurological assessment

The most widely used and most studied coma scale to date is the Glasgow coma scale (GCS) (Figure 1), first described by Teasdale and Jennett in 1974 and revised in 1976 with the addition of a sixth point in the motor response subscale for ''withdrawal from painful stimulus'' [13, 14]. The GCS was initially intended to assess level of consciousness after TBI in a Neurosurgical Intensive Care Unit (Neuro-ICU) [13].The GCS was broadly accepted as an instrument to classify the severity of TBI because it was easy to use and reproducible. It was used to classify the severity of TBI as mild (GCS 13-15), moderate (GCS 9-12), and severe (GCS 8 and below) [15, 16]. Since then it has become the gold standard against which newer scales are compared. As a result, the GCS was incorporated into several scoring systems, including the APACHE II [17], the Simplified Acute Physiology Score (SAPS) and SAPSII [18], the Revised Trauma Score (RTS) [19], the Circulation, Respiration, Abdomen, Motor, Speech scale (CRAMS) [20], the Traumatic Injury Scoring System (TRISS) [21], and A Severity Characterization of Trauma (ASCOT) scale [22], all of which are used to score the severity and predict outcome of TBI. However, the reliability of GCS in predicting patient outcomes is unsatisfactory, especially with regard to the verbal component. As a result, Widjicks et al. published a new scoring system in 2005, the Full Outline of UnResponsiveness (FOUR) score (Figure 2), a newer scale, developed to provide a more comprehensive assessment [23]. The FOUR score includes additional information not assessed by the GCS like brainstem reflexes, visual tracking, breathing patterns, and respiratory drive [23] (Figure 2). It is also more practical for evaluating critically ill intubated patients, as it does not depend on an evaluation of the verbal response. It has already been validated in various populations of comatose patients, including TBI patients [24-30]. While GCS lacks the ability to identify subtle changes in alteration of consciousness, the FOUR score assesses four variables: eye response, motor response, brainstem reflexes, and respiration pattern (Figure 2). The acronym also reflects the number of categories and the maximum number of potential points in each category, making it fairly simple to use and remember. In addition, the FOUR score can account for the intubated patient and can also differentiate between a locked-in state and a vegetative state, via the addition of testing eye tracking, thus incorporating midbrain and pontine functions, effectively allowing the examiner to localize lesions. Another advantage for the FOUR score is that is gives all components equal weight, making it linear which is ideal for a coma scale compared to the GCS score is weighted toward motor responses. The GCS scale does offer the benefit of rapid evaluation in the emergency department, it is readily reproducible by multiple personal, from nursing staff to trauma surgeons, and gives a rapid assessment of the severity of injury. This is likely attributable to its long standing applica-

tion in the field, which makes it second nature for many to communicate the information. More studies are needed to favor one over the other. For now, using either GCS or FOUR score for initial neurological assessment as well as follow up neurologic checks is acceptable.

Best eye response (E)	Spontaneous--open with blinking at baseline	4
	Opens to verbal command, speech, or shout	3
	Opens to pain, not applied to face	2
	None	1
Best verbal response (V)	Oriented	5
	Confused conversation, but able to answer questions	4
	Inappropriate responses, words discernible	3
	Incomprehensible speech	2
	None	1
Best motor response (M)	Obeys commands for movement	6
	Purposeful movement to painful stimulus	5
	Withdraws from pain	4
	Abnormal (spastic) flexion, decorticate posture	3
	Extensor (rigid) response, decerebrate posture	2
	None	1

Figure 1. Glasgow Coma Scale

3. Intracranial pressure monitoring

Intracranial hypertension develops commonly in acute brain injury related to trauma [31, 32]. Raised Intracranial pressure (ICP) is an important predictor of mortality in patients with severe TBI, and aggressive treatment of elevated ICP has been shown to reduce mortality and improve outcome (32-39). Guidelines for the Management of Severe TBI, published in the Journal of Neurotrauma in 2007 [4] make a Level II recommendation that ICP should be monitored in all salvageable patients with a severe TBI (Glasgow Coma Scale [GCS] score of 3–8 after resuscitation) and an abnormal computed tomography (CT) scan. ICP monitoring is also recommended in patients with severe TBI and a normal CT scan if two or more of the following features are noted at admission: age over 40 years, unilateral or bilateral motor posturing, or systolic blood pressure < 90 mm Hg (Level III recommendation). In comatose TBI patients with an abnormal CT scan, the incidence of ICH was 53–63% [40]. Patients with a normal CT scan at admission, on the other hand, had a relatively low incidence of intracranial hypertension (13%). However, within the normal CT group, if patients demonstrated at least two of three adverse features (age over 40 years, unilateral or bilateral motor posturing,
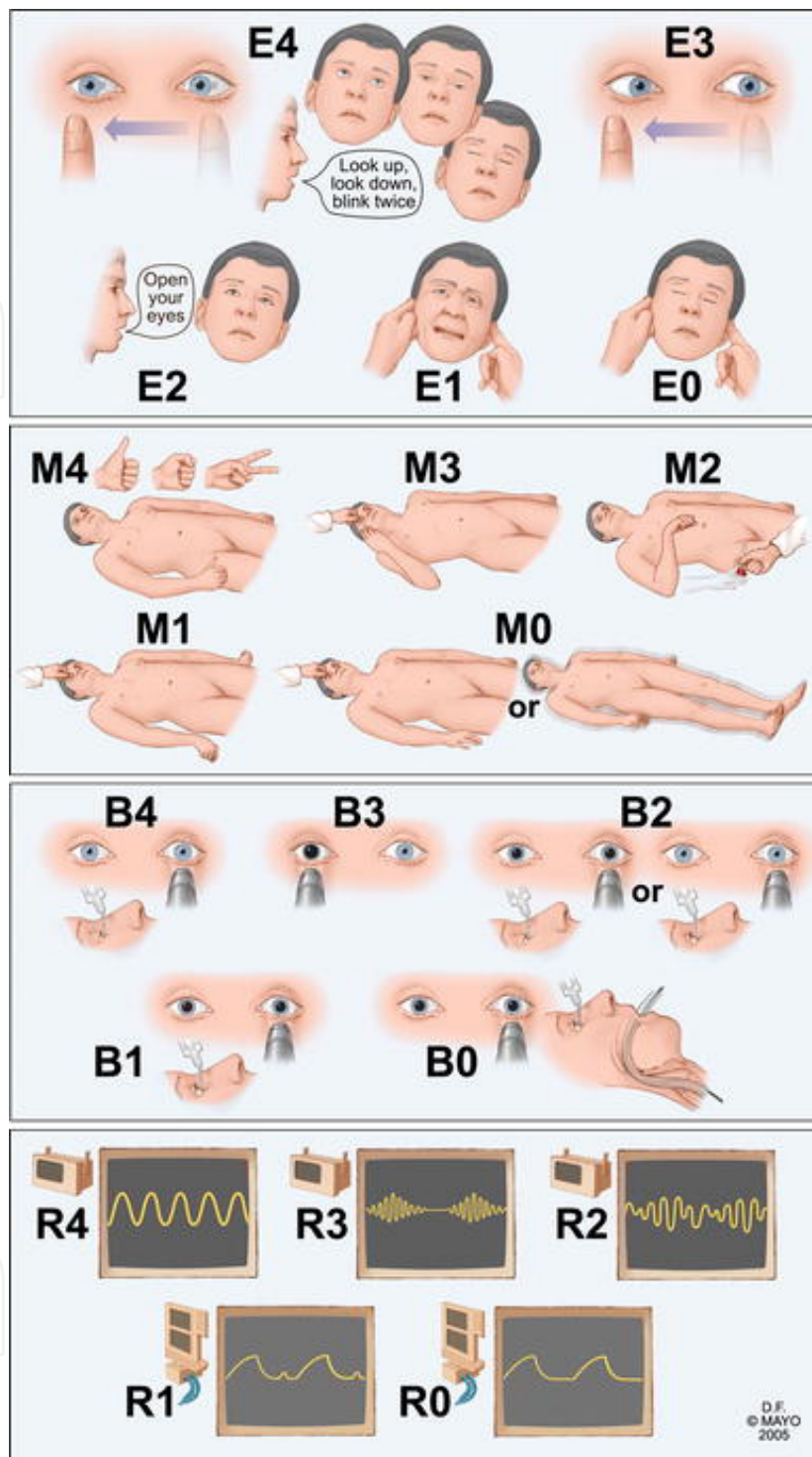
Figure 2. Full Outline of UnResponsiveness (FOUR) score. Eye response: E4 eyelids open or opened, tracking, or blinking to command; E3 eyelids open but not tracking; E2 eyelids closed but open to loud voice; E1 eyelids closed but open to pain; and E0 eyelids remain closed with pain. Motor response: M4 thumbs-up, fist, or peace sign; M3 localizing to pain; M2 flexion response to pain; M1 extension response to pain; and M0 no response to pain or generalized myoclonus status. Brainstem reflexes: B4 pupil and corneal reflexes present; B3 one pupil wide and fixed; B2 pupil or corneal reflexes absent; B1 pupil and corneal reflexes absent; and B0 absent pupil, corneal, and cough reflex. Respiration pattern: R4 not intubated, regular breathing pattern; R3 not intubated, Cheyne-Stokes breathing pattern; R2 not intubated, irregular breathing; R1 breathes above ventilatory rate; and R0 breathes at ventilator rate or apnea.
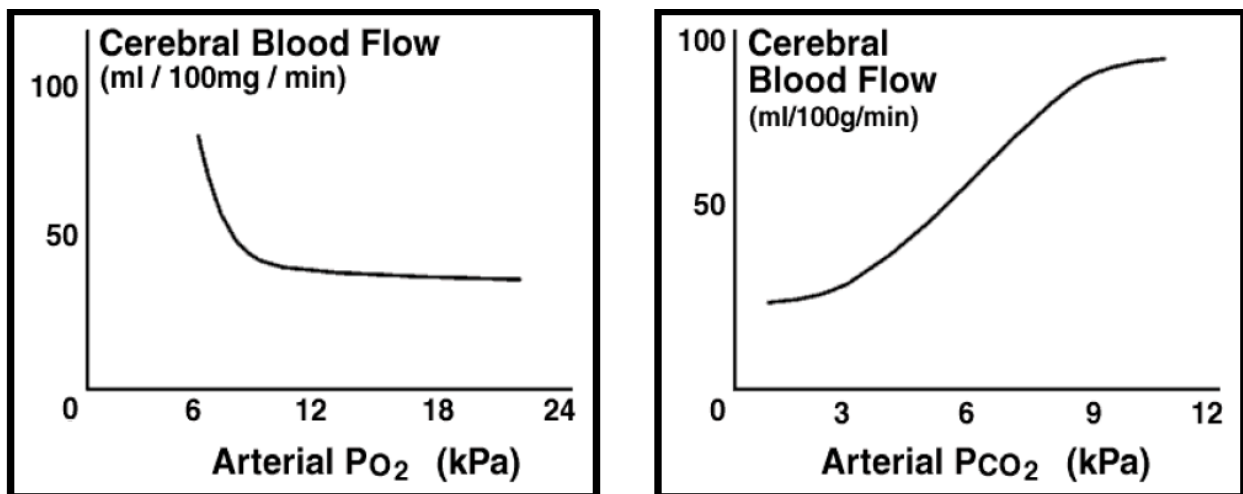
Figure 3. Oxygen tension and carbon dioxide effects on Cerebral Blood flow

or systolic BP < 90 mm Hg), their risk of intracranial hypertension was similar to that of patients with abnormal CT scans [4]. ICP is a strong predictor of outcome from severe TBI [33, 34, 36, 41-43]. Because of this, ethically a randomized trial of ICP monitoring with and without treatment is unlikely to be carried out. Similarly, a trial for treating or not treating systemic hypotension is not likely. Both hypotension and raised ICP are the leading causes of death in severe TBI. Furthermore, several studies have shown that patients who do not have intracranial hypertension or who respond to ICP-lowering therapies have a lower mortality than those who do not respond to therapy [5-12, 44-47]. As a result, Guidelines for the Management of Severe TBI recommend that treatment should be initiated with ICP thresholds above 20 mm Hg (level II) as well as target a cerebral perfusion pressure (CPP) within the range of 50-70 (level III) [4]. Prevention and/or treatment of intracranial hypertension is commonly accomplished by employing a progression of therapeutic approaches that are efficacious in controlling ICP and uniformly believed to be easily applied with minimal or rare negative side effects. These measures include(but are not limited to): elevation of the head of the bed, avoiding hypotension, hypoxia, and hypercapnea or prolonged hypocapnea, intravenous sedation and analgesia, administration of hyperosmolar agents (mannitol, hypertonic saline), and CSF drainage [4].

4. Oxygenation and ventilation

Hypoxia (PaO2 < 60 mmHg or O2 saturation < 90%) worsens secondary brain injury and thus significantly worsens outcome in patients with TBI [48, 49]. In addition, duration of hypoxemia (median duration ranging from 11.5 to 20 min) was found to be an independent predictor of mortality [50]. Elevated Carbon dioxide dilates the cerebral blood vessels, increasing the volume of blood in the intracranial vault and therefore increasing ICP [51]. On the other hand, hyperventilation leads to cerebral vasoconstriction, and thus can result in cerebral ischemia, despite possible improvements in CPP and ICP [52]. Thus, hyperventila-

tion is recommended only as a temporizing measure to reduce an elevated ICP, preferably not below 30 mmHG unless absolutely necessary and only for few minutes while determining an etiology of the intracranial hypertension and initiating other treatment options or surgical intervention. The ventilator settings should be adjusted to maintain normoxia with a pulse oximetry (SpO2) around 95% or PaO2 around 80 mm Hg and eucapnia with PaCO2 of 35 to 40 mm Hg (in patients with chronic CO2 retention, such as COPD patients, CO2 should be maintained close to their baseline CO2 and normal pH). (Figure 3) At this point it is worth mentioning acute lung injury (ALI) and acute respiratory distress syndrome (ARDS). The incidence of ALI/ARDS in TBI is reported between 10 % and 30 % [53, 54]. ALI/ARDS could develop secondary to aspiration, pneumonia, pulmonary contusion, massive blood transfusion, transfusion-related ALI (TRALI), sepsis, or neurogenic pulmonary edema. Management of ALI/ARDS entails low tidal volumes, higher positive end expiratory pressure, and permissive hypercapnea [55]. However, as mentioned above, hypercapnea (> 40 mmHG) is contraindicated in TBI patients with intracranial hypertension. One needs to balance need for low tidal volume and CO2 levels, and thus frequent ABG measurements is warranted.

5. Blood pressure and cerebral perfusion

Hypotension (SBP < 90 mm Hg) can worsen secondary injury in TBI and is associated with worsening mortality and neurologic outcomes [56, 57]. In TBI patients from the Trauma Coma Data Bank, early hypotension occurred in 34.6% of patients with severe traumatic brain injury and was shown to double the mortality rate (55% versus 27%). Late hypotension (in the ICU) occurred in 32% of patients. For patients whose only hypotensive episode occurred in the ICU, 66% died or were vegetative survivors compared with 17% of patients who never had a hypotensive episode [56]. We recommend IVF resuscitation to maintain euvolemia, using either invasive (e.g. CVP or pulmonary capillary wedge pressure) or noninvasive methods (e.g. Echocardiogram or NICOM-noninvasive cardiac output monitoring) to measure either static (CVP) or dynamic (Stroke volume index variation) surrogates of intravascular volume and hemodynamics. Hypotonic, hyponatremic, and sugar containing fluids should be avoided. If patient is euvolemic and remains hypotensive, then vasopressors should be started to maintain adequate blood pressure. Cerebral perfusion pressure is defined as mean arterial pressure (MAP) minus ICP (CPP = MAP – ICP). CPP < 60 mm HG should be avoided since it is associated with poor outcomes in patients with TBI [58]. Both 60 mmHg and 70 mm Hg are cited in the literature as the threshold above which CPP should be maintained. However, as reported earlier, the Guidelines for the Management of Severe Traumatic Brain injury recommend maintaining CPP between 50-70 mmHg [4]. In our patients, when the neurologic status is stable with a normal ICP, aggressive measures do not need to be taken as long as CPP >50 mmHg. Conversely, in patient's where exam is poor or ICP has been elevated/required treatment, then would recommend CPP >60 mmHg since the risk of secondary injury developing is more imminent in these patients. In the ab-

sence of cerebral ischemia, aggressive attempts to maintain CPP above 70 mmHg with fluids and vasopressors should be avoided because of the risk of ARDS [59].

6. Hyperosmolar therapy

Brain parenchyma is 80% water, and thus brain volume is very responsive to changes in water content. A hyperosmolar agent creates a gradient for water to move from brain parenchyma to the intravascular space across the blood-brain barrier (BBB). As a result, the effectiveness of a hyperosmolar agent depends on the extent it is prevented from crossing the BBB. Both mannitol and hypertonic saline posses this property and will be discussed in this section. Mannitol is given in a 20% or 25 % solution in boluses of 0.25 to 1.0 g per kilogram of body weight at intervals of 2, 4, 6, or more hours. In addition to the osmotic properties of mannitol, , it also lowers blood viscosity which leads to increase cerebral blood flow resulting in cerebral vasoconstriction (autoregulation), which in turn reduces cerebral blood volume and thus intracranial pressure [60]. In patients with impaired cerebral autoregulation, aggressive use of mannitol could result in increased ICP. As this implies, for mannitol to be fully effective, the blood brain barrier must be intact. In patients where the BBB is not intact, mannitol crosses the BBB and can draw fluid into brain resulting in an increase in ICP [61, 62], hence concentrations of mannitol should be assessed before each dose. Instead of measuring actual mannitol, an easier and more practical way is to measure serum osmolarity or osmolar gap (measured – calculated serum osmolarity) before infusing mannitol. Because of the above as well as to minimize risk of acute kidney injury, Mannitol should thus not be given if serum osmolarity is more than 320 mOsm/Kg H_2O or osmolar gap > 10. Side effects of mannitol include hypotension, hypovolemia, hypokalemia, hyperkalemia, and acute kidney injury [63, 64]. Mannitol is contraindicated in patients with renal failure. Hypertonic saline increases serum osmolarity directly rather than by inducing osmotic dieresis, as well as by viscosity-related cerebral vasoconstriction [65]. It is used in a 3% solution infusion or in boluses of approximately 150 ml, in a 7.5% solution in 75-ml boluses, or in a 23.4% solution in 30-ml boluses every 2, 4, 6, or more hours. Serum osmolarity and serum sodium should be checked before dosing hypertonic saline. Hypertonic saline should not be given if serum Na is more than 160 mmol/liter. Side effects of hypertonic saline include fluid overload secondary to intravascular volume expansion, acidosis, hypokalemia, and hyperchloremia. There is a potential for development of central pontine myelinolysis with rapid increase in serum Na concentration, however, this phenomenon has not been documented in this scenario of management of intracranial hypertension. The question remains as to which one, mannitol or hypertonic saline, is superior? Recent evidence including two metanalysis, suggest that hypertonic saline may be more effective than mannitol in reducing ICP [66-69], however, high quality studies comparing the agents, while accounting for side effects and contraindications are lacking. Furthermore, it is very important to take into consideration patient characteristics, such as volume status, renal function, hemodynamic status, sodium levels, etc.., when choosing the appropriate hyperosmolar agent. Hyperosmolar therapy should be weaned gradually rather than stopped abruptly in the days to follow.

7. Refractory intracranial hypertension: Therapeutic hypothermia and barbiturate coma

Refractory intracranial hypertension (RICH) is defined as intracranial pressures that exceed 25 mm Hg for 30 minutes, 30 mm Hg for 15 minutes, or 40 mm Hg for 1 minute despite tier 1 and tier 2 therapies [70]. Tier 1 therapies include head of patient's bed at or more than 30 degrees, adequate sedation and analgesia, and adequate CSF draining if ICP is monitored by ventriculostomy. Tier 2 therapies include adequate hyperosmolar therapy (mannitol or hypertonic saline or both), mild hyperventilation (pCO_2 goal of 30 – 35 mmHg), and neuromascular blockade. RICH occurs in approximately 15% of patients with traumatic brain injury [70]. If it is not aggressively treated, RICH can result in cerebral herniation and death.High-dose barbiturate administration is recommended to control elevated ICP refractory to maximum standard medical and surgical treatment (level II) [3]. High-dose barbiturates have been scarcely studied for this indication. In 2004, the Cochrane Injuries Group performed a systematic review of the barbiturate RCTs. In the only two studies examining the effect on ICP, the relative risk for refractory ICP with barbiturate therapy was 0.81 (95% CI 0.62–1.06). Concerning this indication, the Cochrane group concluded: "There is no evidence that barbiturate therapy in patients with acute severe head injury improves outcome. Barbiturate therapy results in a fall in blood pressure in one of four treated patients. The hypotensive effect of barbiturate therapy will offset any ICP lowering effect on cerebral perfusion pressure" [71]. Significant side effects of barbiturates include hypotension, arrhythmias, immunosuppression, hepatotoxicity, fever and injection site reactions. The Guidelines for the Management of Severe TBI recommend that more studies are needed to identify alternative agents for this indication - "elevated ICP refractory to standard therapy" [3]. Albeit small, there are more RCT evaluating the effect of therapeutic hypothermia on ICH in severe TBI (13 studies) than for barbiturates; all consistently demonstrating that hypothermia is effective in controlling ICP (This is reviewed in more detail elsewhere : Farid Sadaka, Christopher Veremakis, Rekha Lakshmanan and Ashok Palagiri (2013). Therapeutic Hypothermia in Traumatic Brain Injury, Therapeutic Hypothermia in Brain Injury, Dr. Farid Sadaka (Ed.), ISBN: 978-953-51-0960-0, InTech, DOI: 10.5772/48818. Available from: http://www.intechopen.com/books/therapeutic-hypothermia-in-brain-injury/therapeutic-hypothermia-in-traumatic-brain-injury). Complications from hypothermia include electrolyte imbalances, increase in incidence of infections, thrombocytopenia, coagulopathy, arrhythmias (especially bradycardia), pancreatitis, and rebound ICH (during re-warming). In one extensive review [72], Povlishock et al showed that posttraumatic hypothermia followed by slow rewarming appeared to provide maximal protection in terms of traumatically induced axonal damage, microvascular damage and dysfunction, contusional expansion, intracranial hypertension, and neurocognitive recovery. In contrast, hypothermia followed by rapid rewarming not only reversed the protective effects associated with hypothermic intervention, but exacerbated the traumatically induced pathology and its neurologic consequences. Povlishock's review concluded that the rate of posthypothermic rewarming is an important variable in assuring maximal efficacy following the use of hypothermic intervention. The most challenging issue appears to be rebound ICP during re-warming. We suggest that re-warming

only be considered if the patient's ICP is stable and <20mmHg for at least 48 hours, and, thereafter implemented at a rate not faster than 0.1 -0.25°C per hour. Surgical management of TBI patients such as Decompressive hemi-craniectomy or bilateral craniectomy are discussed in more detail in chapter http://www.intechopen.com/books/traumatic-brain-injury/surgical-treatment-of-severe-traumatic-brain-injury. Please refer to figure 4 for protocolized step-wise approach to ICP management.
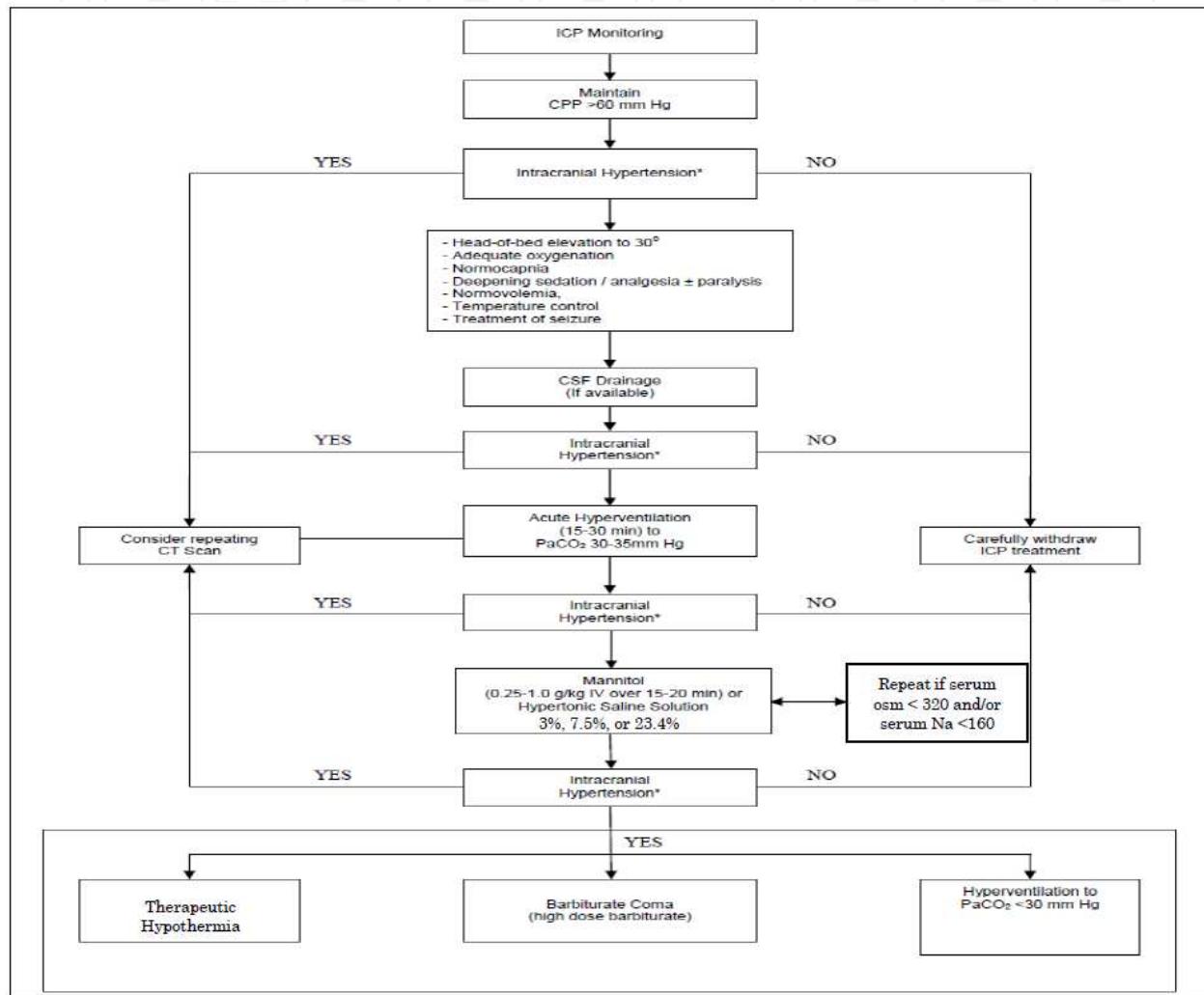

Figure 4. Stepwise approach to management of intracranial hypertension.

8. Temperature modulation and normothermia

Aside from role of hypothermia in ICP control in patients with refractory intracranial hypertension, therapeutic hypothermia has also been studied as a primary neuroprotectant in patients with severe TBI, based on the fact that early administration of TH could halt the secondary injury processes discussed above, and thus possibly improve outcome. This topic

is reviewed in more detail elsewhere : Farid Sadaka, Christopher Veremakis, Rekha Laksh-manan and Ashok Palagiri (2013). Therapeutic Hypothermia in Traumatic Brain Injury, Therapeutic Hypothermia in Brain Injury, Dr. Farid Sadaka (Ed.), ISBN: 978-953-51-0960-0, InTech, DOI: 10.5772/48818. Available from: http://www.intechopen.com/books/therapeutic-hypothermia-in-brain-injury/therapeutic-hypothermia-in-traumatic-brain-injury. In short, although single-center studies were encouraging, multicenter trials with early administra-tion of hypothermia for a defined period of time irrespective of ICP have almost uniformly been negative except maybe for patients undergoing craniotomy for hematoma evacuations. However, hypothermia was maintained for a fixed duration of only 48 hrs, and ICP eleva-tions mainly occurred during and after rewarming. These results suggest that a period of 48 hours of hypothermia may be too short to have a beneficial effect on outcome. A standar-dized one size fit all may be inappropriate. The rate of rewarming plays an important role as well as pointed above.The rebound increase in ICP during and after rewarming in these studies and the encouraging outcomes from the randomized studies that induced hypother-mia early and continued it throughout the period of intracranial hypertension point to the realization that individualizing the duration of hypothermia to fit a patient's ICP in future trials may be a better strategy than a predetermined period of hypothermia regardless of ICP. As for now, therapeutic hypothermia cannot be recommended for TBI patients aside from control of refractory ICP discussed above.All of the mechanisms of secondary brain in-jury in TBI discussed above (apoptosis, mitochondrial dysfunction, excitotoxicity, disruption in ATP metabolism, disruption in calcium homeostasis, increase in inflammatory mediators and cells, free radical formation, DNA damage, blood-brain barrier disruption, brain glu-cose utilization disruption, microcirculatory dysfunction and microvascular thrombosis) are temperature dependant. They are all stimulated and exacerbated by fever [73]. In addition, fever occurs with high frequency in this patient population, with up to 68% of patients expe-riencing at least one fever during their intensive care unit stay [74]. Fever in the TBI popula-tion may result from multiple causes and for reasons other than infection and has proven difficult to control. Disruption of the hypothalamic set point, tissue ischemia/infarction, sur-gery, medications, and blood product transfusions may all induce hyperthermia. Early hy-perthermia following TBI is associated with a longer ICU length of stay and worsened neurologic outcomes [75-77]. Thereby, temperature should be controlled, fever should be ag-gressively treated, and normothermia should be maintained in patients with TBI.

9. Nutrition and glucose control

TBI, especially severe TBI, can cause increase metabolism and can create a hypercatabolic state that results in rapid depletion of nutrition reserves, as well as worsening immune func-tion and morbidity [78, 79]. In TBI patients, adequate nutrition that is started early after in-jury is associated with enhanced immunity, decreased infectious morbidity, shortened length of hospitalization, improved neurological recovery and reduced mortality [80, 81]. Brain trauma foundation recommends that patients should be fed to attain full caloric re-placement by day 7 post-injury [3]. American Society for Parenteral and Enteral Nutrition

(ASPEN) for nutrition support in critically-ill adult patients suggest that enteral nutrition should be started within the first 24–48 h following admission, as long as patients are hemodynamically stable [82]. The European Society for Parenteral and Enteral Nutrition (ESPEN) recommends initiating enteral nutrition within 24 h if possible [83]. Despite popular belief, recent evidence reiterates that bowel sounds and passing flatus or stool are not required for the initiation of enteral nutrition[82]. In circumstances when early enteral nutrition cannot be initiated, parenteral nutrition should be strongly considered.There is no question that hyperglycemia is associated with worse outcome in brain injured patients [84, 85]. Hypoglycemia leads to deprivation of the brain of its fuel which can lead to compromised brain energy metabolism and worsen the already existent brain injury, especially during the increase in glucose utilization and brain energy demand observed after TBI [86, 87]. However, the optimal target for systemic glucose control is not known. In patients with severe brain injury, tight systemic glucose control (80–120 mg/dL) was associated with reduced cerebral extracellular glucose availability and increased prevalence of brain energy crisis, which in turn correlates with increased mortality [88]. Intensive insulin therapy may thus impair cerebral glucose metabolism after severe brain injury. Based on the existing low quality evidence, the most recent guidelines from the Society of Critical Care Medicine (SCCM) suggest that blood glucose (BG) ≥ 150 mg/dL should trigger initiation of insulin therapy for most patients admitted to an ICU with the diagnosis of TBI, titrated to achieve BG values absolutely < 180 mg/dL, to minimize the adverse effects of hyperglycemia [89]. The guidelines also suggest that BG < 100 mg/dL be avoided during insulin infusion for patients with brain injury [89].

10. Anemia and transfusion

Hypoxia and hypotension worsen secondary brain injury and are important determinants of outcome in TBI patients. They both are associated with worse outcomes as discussed above. This could be the reason why many patients with TBI are still transfused to a hemoglobin threshold of 10 g/dl. Although red blood cells are an essential requirement for the transport of oxygen to the tissues, several problems are documented with red blood cells (RBC) transfusions such as infection, pulmonary complications such as transfusion-related acute lung injury (TRALI) and transfusion-associated circulatory overload (TACO), transfusion-related immunomodulation (TRIM) and multiorgan failure, and increased mortality [90]. Besides, there is no clear correlation between anemia and hypoxia or hypotension in TBI patients. In one retrospective study, linear regression showed that more days with hematocrit < 30% was associated with improved neurologic outcomes. In addition, transfusion of RBCs was significantly associated with worse outcomes [91]. In a subgroup analysis of a multicenter randomized controlled clinical trial involving 67 critically ill patients from the Transfusion Requirements in the Critical Care trial who sustained a closed head injury, patients were randomized to a restrictive RBC transfusion strategy (Hb 7.0 g/dL and maintained between 7.0 and 9.0 g/dL) or a liberal strategy (Hb 10.0 g/dL and maintained between 10.0 and 12.0 g/dL). This study was unable to detect significant improvements in mortality with a liberal as compared with a restrictive transfusion strategy in critically ill trauma patients with moder-

ate-to severe TBI [92]. Guidelines for transfusion developed by EAST (Eastern Association for Surgery of Trauma) and the American College of Critical Care Medicine (ACCM) of the Society of Critical Care Medicine (SCCM) state that there is no benefit of a "liberal" transfusion strategy (transfusion when Hb is <10 g/dL) in patients with moderate-to-severe TBI [93]. Large multicenter prospective studies are needed to evaluate the effects of anemia and RBC transfusion in patients with TBI.

11. Deep venous thrombosis

The application of chemical venous thrombo-embolism (VTE) prophylaxis traumatic brain injury patients has been long been guided by the dogma of physicians practicing under assumptions rather than evidenced based guidelines. This has resulted in the blanket denial of the use of any chemical DVT prophylaxis up until more recent years, despite the common knowledge that trauma patient are at high risk for development of venous thromboembolic events. The overwhelming fear associated with propagating the intracranial injury has also limited the number of studies until recently. Most of the data that is currently applied to support the safety of chemical prophylaxis has been extrapolated from studies that were performed looking that the risks of post-operative hemorrhage in elective craniotomy patients. In 1998 Agnelli et. al. compared the use of enoxaparin combined with compression stockings to patients treated with compression stockings alone and found a significant reduction in the number of VTE without any increase in hemorrhage after elective neurosurgery [94]. This study and others like it opened the door for further application and research in the area of traumatic brain injury. The current formal recommendation by the Guidelines for the Management of Severe Traumatic Brain Injury 2007 state that the use of low-molecular weight heparin or low dose unfractionated heparin should be used in combination with mechanical prophylaxis, but there is an increased risk for expansion of intracranial hemorrhage. There is insufficient evidence to support recommendations regarding the preferred agent, dose, or timing [4].The lack of guidelines to follow has prompted many institutions to develop their own guidelines based on extrapolated data and to record and report their experiences. In 2010, clinicians at McGill University published their findings, which showed an acceptable VTE control rate without increased risk of expanding intracranial hemorrhage [95]. The general principles that predominate in the use of chemical VTE prophylaxis are the following: 1) patients not expected to go to the operating room in the next 24 hours for intracranial procedure 2) no evidence of systemic coagulopathy 3) 2 stable CT scans. All guidelines should be applied with the consideration of the injuries of the specific patient in question and altered as seen appropriate for the situation. The first phase of a randomized, double-blind study involving the early use of enoxaparin in trauma patients was just published in 2012 [96]. The study found at 2.3% higher rate of progression in the patients treated with enoxaparin over placebo, however, none were clinically significant. DEEP-II is intended to evaluate the efficacy of this VTE prevention and DEEP-III will apply to moderate-risk patients. A recently published systematic review and meta-analysis of the use of early chemical VTE prophylaxis in TBI patients found that it reduced the risk of VTE without progres-

sion of intracranial hemorrhage [97]. While there is certainly the need for more studies to quantify the risk associated with the early use of chemical VTE prophylaxis, there is evidence that supports the appropriate application in traumatic brain injury patients at high risk for developing DVT. Although we cannot not provide official recommendations, dosage, or timing of administration, it is used in our institution.

12. Conclusion

TBI is a devastating injury and often these patients would require monitoring and treatment in intensive care unit. Management of TBI patients requires multidisciplinary approach, frequent close monitoring and judicious use of multiple treatments to lessen secondary brain injury and improve outcomes. There is a lot of opportunity for further research in TBI, including but not limited to multimodal monitoring, and therapeutics to further improve outcomes in this very common mechanism of brain injury.

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