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Traumatic Brain Injury Management

Evidence Based Medicine Guideline

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Traumatic brain injury (TBI) is a major cause of death in all age groups in the United States, contributing to over 30% of all trauma-related deaths. TBI has been classified into mild (Glasgow Coma Scale, or GCS, 13-15), moderate (GCS 9-12), and severe (post-resuscitation GCS ≤ 8). Protocolized management of severe TBI improves patient outcomes. Primary endpoints in the management of severe TBI include minimizing cerebral edema and intracranial pressure(ICP) while simultaneously optimizing cerebral perfusion pressure (CPP) and tissue oxygenation to reduce secondary ischemic injury. Management of severe TBI patients using guideline-based recommendations is recommended to decrease mortality.

RECOMMENDATIONS

SIBICC guidelines for TBI treatment now allow jumping between tiers to achieve patient treatment goals

<u>All Patients with Traumatic Brain Injury (TBI) – Mild Moderate, or Severe</u>

- **Perform Head CT to define extent of TBI**
- **Reverse anticoagulation (see recommendations below)**
- **Elevate head of bed 30-45 degrees at all times**
- **Protect the patient's airway and intubate if GCS ≤ 8**
- **Maintain systolic blood pressure > 100 mmHg and SpO2 >94%**
- **Avoid core body temperature above 38°C; consider early antipyretics and cooling blankets for temperatures above 38° C**
- **Provide judicious sedation/analgesia to control pain and agitation**
- **Perform serial evaluations of neurological status in a neuromonitoring capable unit**
- **Obtain a repeat Head CT six hours after initial imaging and repeat as appropriate until stable**

<u>Management of Severe TBI (GCS ≤ 8) and Intracranial Hypertension</u>

- **TIER ZERO (*considered to be basic ICU interventions)***
  - **Admission to the ICU for neurological monitoring**
  - **Serial neurological exams to include pupillary reactivity**
  - **Elevate the head of the bed 30-45°**
  - **Ensure good venous return from the head by keeping the head midline and confirming the cervical collar (if present) is not too tight**
  - **Protect the patient's airway with intubation and mechanical ventilation**
  - **Provide adequate sedation/analgesia for signs of pain, agitation, and ventilator asynchrony**
  - **Insert an intracranial pressure (ICP) and/or brain tissue oxygenation ($PbtO_2$) monitoring device in salvageable patients within 24 hours of resuscitation with initial goals of ICP ≤ 22 mmHg, $PbtO_2$ ≥ 20 mmHg, and CPP ≥ 60 mmHg**
  - **Maintain SpO2 ≥ 94%**
  - **Target core temperature of 36.0-37.9° C; treat temperatures above 38° C with antipyretics and cooling blankets**
  - **Maintain hemoglobin > 7 g/dL**
  - **Insert an arterial line for continuous blood pressure monitoring with goal systolic blood pressure (SBP) of 100-160 mmHg**
  - **Avoid hyponatremia (serum Na goal 135-145 mEg/L)**
  - **Initiate seizure prophylaxis for first seven days post-injury with levetiracetam 1000 mg BID (see text for exemptions)**

RECOMMENDATIONS (continued)

- **TIER ONE**
  - **Maintain CPP 60-70 mmHg**
  - **Utilize sedation and analgesia to lower and achieve ICP goals**
  - **Maintain $PaCO_2$ 35-38 mmHg**
  - **Administer hypertonic saline by intermittent bolus (see protocol recommendations)**
  - **Administer mannitol by intermittent bolus (0.25-1.0 g/kg) (see protocol recommendations)**
  - **Consider placement of extraventricular drain (EVD) to allow drainage of CSF**
  - **Obtain electroencephalography (EEG) monitoring (spot vs. continuous)**

- **TIER TWO**
  - **Maintain $PaCO_2$ 32-35 mmHg (mild hypocapnia) if ICP goals unmet**
  - **Consider neuromuscular paralysis to lower ICP (see protocol recommendations)**
  - **Perform mean arterial pressure (MAP) challenge (see protocol recommendations) to evaluate autoregulation; adjust MAP according to protocol outcome/recommendations**

- **TIER THREE**
  - **Administer pentobarbital or sodium thiopentone; titrate to ICP if found to be effective in lowering ICP (see protocol below)**
  - **Consider secondary craniotomy**
  - **Maintain mild hypothermia (35-36°C) using active cooling measures**

- Inter-Tier Recommendations
  - **Repeat and review imaging, physiological parameters, and physical examinations**
  - **Re-evaluate the patient for other potential sources of ICP elevation (i.e. intra-abdominal hypertension or elevated intrathoracic pressure)**
  - **Consider surgical options including repeat surgical therapy**
  - **Consider transfer to a tertiary referral center**

<u>Surgical Management of TBI</u>

- Evacuating epidural hematoma (EDH) and subdural hematoma (SDH)
  - **Perform urgent evacuation of large hematomas (>25 mL) for comatose patients with a meaningful chance of recovery**
  - **Evacuate large traumatic hematomas before neurological deterioration (even in patients with a high GCS)**
  - **Maintain a low threshold for surgery in patients with posterior fossa lesions**
  - **Promptly evacuate delayed or enlarging bleeds found on repeat imaging**

- Decompressive Craniectomy
  - **Initial/Primary - after mass lesion (i.e. acute SDH) evacuated and swelling ensues**
  - **Secondary - recommended for persistently raised ICPs refractory to other interventions**

RECOMMENDATIONS ALGORITHM

Patient with Severe TBI (GCS ≤ 8)

TIER ZERO (*considered to be basic ICU interventions*)

- Admission to the ICU for serial neurological status monitoring
- Reverse anticoagulation, if applicable (See Appendix 1)
- Serial neurological exams to include pupillary reactivity
- Elevate the head of the bed 30-45°
- Ensure good venous return from the head by keeping the head midline and confirming the cervical collar (if present) is not too tight
- Protect the patient's airway with intubation and mechanical ventilation
- Provide adequate sedation and analgesia for signs / symptoms of pain, agitation, and ventilator asynchrony
- Insert an ICP and/or $PbtO_2$ monitoring device with initial goals of ICP ≤ 22 mmHg, $PbtO_2$ ≥ 20 mmHg, CPP ≥ 60 mmHg in salvageable patients within 24 hours of resuscitation
- Maintain SpO_2 ≥ 94%
- Target core temperature of 36.0-37.9° C; treat temperature above 38° C with antipyretics (acetaminophen / ibuprofen) and cooling blanket; avoid hypothermia < 35°C (See Appendix 2)
- Maintain hemoglobin > 7 g/dL and platelet count > 75,000
- Maintain blood glucose 100-180 mg/dL
- Insert an arterial line for continuous blood pressure monitoring (SBP 100-160 mmHg)
- Avoid hyponatremia (serum Na goal 135-145 mmol/L)
- Initiate seizure prophylaxis; levetiracetam 1000 mg Q12 hrs x 7 days (see text for exemptions / renal dose adjustments)

TIER ONE

- Maintain CPP ≥ 60 mmHg (goal 60-70 mmHg)
- Utilize sedation and analgesia to lower and achieve ICP goals
- $PaCO_2$ to be maintained at low end of normal (35-38 mmHg)
- Administer hypertonic saline by intermittent bolus (see Appendix 3)
- Consider administering mannitol by intermittent bolus (0.25-1.0 g/kg) (see protocol recommendations)
- Consider placement of EVD drain to allow drainage of CSF
- Obtain electroencephalography (EEG) monitoring (spot vs. continuous)

TIER TWO

- Mild hypocapnia (32-35 mmHg)
- Neuromuscular paralysis to lower ICP (see Appendix 3)
- Perform Mean Arterial Pressure (MAP) Challenge (see protocol recommendations) to evaluate autoregulation allowing individualized guide to MAP and CPP goals (see Appendix 4)
- Adjust MAP according to protocol outcome/recommendation

TIER THREE

- Administer pentobarbital (titrate to burst suppression (2-3 bursts/15 second screen) (Do NOT titrate to ICP.) If burst suppression achieved and ICP still > 22 mmHg, contact neurosurgery / managing critical care team. (See Appendix 3)
- Consider secondary decompressive craniotomy
- Maintain mild hypothermia (35-36 ºC) using active cooling measures

INTER-TIER RECOMMENDATIONS

- Repeat and review imaging, physiological parameters, and physical examinations
- Re-evaluate the patient for other potential sources of ICP elevation (i.e. abdominal or thoracic)
- Consider surgical/repeat surgical options
- Seek higher level of care

LITERATURE REVIEW

Introduction

Traumatic Brain Injury (TBI) is a potentially lethal injury with mortality rates as high as 30%. Approximately 2.5 million people sustain TBI annually in the United States resulting in over 50,000 deaths and 500,000 individuals with permanent neurologic sequelae (1). Nearly 85% of TBI-related mortalities occur within the first two weeks of injury, reflecting the early impact of systemic hypotension and intracranial hypertension.

Patient outcomes following severe TBI (defined by a post-resuscitation GCS ≤ 8) are significantly improved when such patients are managed according to a comprehensive neuro-resuscitation protocol such as those recommended by the Brain Trauma Foundation (BTF) (www.braintrauma.org) or Neurocritical Care Society (www.neurocriticalcare.org) (1-8). A database analysis of TBI resuscitation and patient outcome in New York state demonstrated a decrease in mortality from 22% in 2001 to 13% in 2009 ($p<0.0001$) when such guidelines were followed (1). Between these two time periods, guideline adherence increased from 56% to 75% ($p<0.0001$), adherence to the cerebral perfusion pressure (CPP) recommendations increased from 15% to 48% ($p<0.0001$), and the proportion of patients with ICP > 25 mmHg decreased from 42% to 29% ($p<0.0001$). This was confirmed by a similar study at Lancaster General Hospital, a Level II Trauma Center, that showed a decrease in mortality from 55% to 15% when compliance improved from <55% to 55-75% (2).

The following guideline outlines an evidence-based medicine approach to the management of patients with severe TBI based upon the current medical literature and published consensus statements. The guidelines consist of three tiers of progressively escalating therapies targeted at controlling ICP. The importance of frequent and open communication between intensive care providers and the neurosurgery team cannot be overemphasized. Please note that patients with stroke, ruptured intracranial aneurysms, and those undergoing ICP monitoring for other neurological conditions should not be managed according to these TBI guidelines unless otherwise determined by the consulting neurosurgeon.

Pathophysiology

Based on the Monroe-Kellie Doctrine, the intracranial volume [brain 80%, cerebral spinal fluid (CSF) 10%, and cerebral blood volume 10%] is fixed within the confines of the cranial vault and cannot expand. Since brain tissue has minimal compensatory capacity in the presence of cerebral edema or space-occupying lesions, CSF and blood volume must decrease to regulate ICP. CSF may drain through the lumbar plexus and blood volume is tightly autoregulated by both $PaCO_2$ and PaO_2. This allows cerebral blood volume to decrease, reducing ICP, while at the same time maintaining adequate CPP.

The goal of ICP monitoring and control in the TBI patient is to maintain an appropriate CPP defined as mean arterial pressure (MAP) minus ICP] through either increasing MAP or decreasing ICP. A variety of therapies may be applied to lower ICP and reduce cerebral edema to maintain sufficient CPP to provide adequate oxygen delivery to avoid secondary cerebral injury due to ischemia. There is a delicate balance between increasing cerebral perfusion and keeping ICP and cerebral edema minimized.

Initial Evaluation

All patients who present with suspected TBI should undergo rapid primary and secondary surveys with thorough evaluation of their airway, breathing, and circulation. Airway patency and adequate oxygenation and ventilation are paramount to avoiding secondary brain injury (8). The patient’s cervical spine should be immobilized until cervical spine injury is ruled out. Urgent intubation to secure the patient’s airway should be considered in any patient who presents with a GCS < 8 or in those who are unable to protect their airway. Intravenous access should be rapidly established. Bedside glucose testing should be performed in all unconscious patients and hypoglycemia rapidly treated if present. Thiamine (100 mg) should be administered in patients at risk for nutritional deficiency. If opioid toxicity is suspected (e.g., history of illicit drug use, apnea, bradypnea, small pupils), naloxone 0.4 mg IV should be administered and repeated as necessary, up to a total of 4 mg. Appropriate laboratory tests [serum electrolytes, CBC with platelets, coagulation studies, arterial blood gas, urinalysis, and urine toxicology / alcohol level (as appropriate)] should be performed. If definitive neurosurgical care cannot be provided at the initial presenting institution, transfer to a higher level of care should be facilitated in a rapid fashion to preserve the “Golden Hour” and optimize the patient's outcome. Certain key resuscitative interventions should be initiated at the referring facility, such as reversal of preexisting anticoagulation, to minimize secondary cerebral injury (5,8) (Appendix 1).

Hypotension / Hypertension Management

Prehospital and in-hospital systemic hypotension independently increases morbidity and mortality following TBI (3). Systolic hypotension leads to cerebral ischemia and secondary brain injury. New literature suggests that maintaining a higher systolic blood pressure (SBP) in a severe TBI patient may lead to decreased mortality and improved outcomes. The current recommendations is to maintain a SBP of 110-160 mmHg (3,4). The relationship between SBP, MAP, and CPP should always be considered when interpreting these values. In the hypotensive patient with GCS < 8, SBP should be maintained using judicious isotonic intravenous fluids (without dextrose) until an ICP monitor is available. The goal should be to always maintain CPP > 60 mmHg (3,4,7). As the brain is very sensitive to anoxia, this will serve to improve oxygen delivery and further avoid secondary brain injury. If the patient's SBP cannot be maintained above 110 mmHg (or CPP > 60 mmHg if ICP monitoring is available) with intravenous fluid alone, low-dose norepinephrine should be initiated (3,4,7).

While hypotension should be avoided, there is growing evidence that the catecholamine surge after TBI and associated hypertension can have significant negative effects on both cardiovascular and neurologic function. Specific neurological issues include worsening cerebral edema and intracranial hypertension (9). Despite the known effects of catecholamine-induced hypertension, optimal management of elevated blood pressure has not been established in the literature (10). Currently, the BTF provides no recommendations for acceptable upper limit of SBP, treatment of hypertension, or optimal antihypertensive agents. Current expert opinion is to maintain SBP < 160 mmHg. Use of beta-blockers was found to have significantly lower mortality in the beta-blocker group compared to the non- beta-blocker group (18.6% vs. 4.4%, p=0.012) (11).

Cerebral Perfusion Pressure (CPP)

CPP, defined as MAP minus ICP, is an important resuscitative parameter in the treatment of patients with TBI. The BTF recommends a CPP range of 60-70 mmHg. A minimal optimal target of 60 versus 70 mmHg may depend on the individual patient's autoregulatory status (3,4). Measurements of cerebral blood flow, cerebral oxygenation [either jugular venous saturation ($SjvO_2$) > 50% or brain tissue oxygen tension (PbO_2) > 15 mmHg] and metabolism are considered complimentary tools in the management of TBI when available (3). Aggressive maintenance of CPP > 70 mmHg should be avoided due to an increased risk of over-resuscitation and acute respiratory distress syndrome (ARDS). CPP < 60 mmHg should be avoided due to the risk of low cerebral blood flow, cerebral hypoxia, and secondary brain injury (4).

Head of Bed Elevation

All patients with TBI should have their head of bed elevated 30 degrees to reduce cerebral edema and augment venous drainage from the cranial vault. Elevation of the head may also lower ICP without adverse impact upon either cerebral blood flow or CPP (12). In patients with suspected or documented spine injury, this is best achieved by placing the patient's bed in the reverse Trendelenburg position. Elevation of the head of bed greater than 30 degrees has not been demonstrated to be beneficial.

Normothermia

Elevated body temperature / fever has a significant deleterious impact upon the brain. While fever is typically defined as a core body temperature greater than 38.3°C, temperatures above 37°C can significantly impact the already impaired brain parenchyma. Elevated body temperature increases the patient's inflammatory response by elevating levels of pro-inflammatory cytokines and neutrophils. This can increase sympathetic tone, resting energy expenditure, oxygen consumption, heart rate, and minute ventilation. While fever occurs in 30-45% of the non-neurologically injured, it may be seen in up to 70% of those with TBI. In these patients, an infectious etiology is present less than 50% of the time, with the remainder being classified as "central fever." Central fever is believed to be due to direct damage to the thermoregulatory centers of the brain, which are found in the preoptic nucleus of the hypothalamus and focal centers of the pons. Severe damage to these centers can result in profound hypothermia, which can result in coagulopathy, cardiac arrhythmias, or decreased immune function (13-15).

Significantly worse outcomes occur in patients with intracerebral hemorrhage who develop a body temperature greater than 37.5°C within the first 72 hours (12). Early fever following TBI has been associated with lower GCS, presence of diffuse axonal injury, cerebral edema, hypotension, hypoglycemia, and leukocytosis (11). Fever within the first week is associated with increased intracranial pressure, neurologic impairment, and prolonged ICU stay (15). Among 846 patients with TBI, fever at any time in the first week was associated with intermediate decline and poor overall long-term outcome (16).

Hypothermia is also associated with worse outcomes in TBI. Among 1,403 ICU patients with TBI, a core temperature less than 35°C was observed in 11% of patients (17). Patients in the hypothermia group were less likely to survive ($p<0.013$) and were more likely to have penetrating injury, Injury Severity Score > 25, and need for exploratory laparotomy. In a multivariate logistic regression model, the Odd's ratio for death among hypothermic patients was 1.7 times greater than that of normothermic patients (18).

Aggressive efforts to control temperature in the TBI patient should be implemented including early intravenous and enteral antipyretic medications, control of room temperature, and cooling blankets or pads. Due to the deleterious effect of fever on the brain parenchyma, therapy should be initiated when patient temperature exceeds 37°C rather than waiting until the traditional definition of fever has been reached with a target temperature of 37°C.

Prophylactic and Therapeutic Hypothermia

Therapeutic hypothermia has not been demonstrated to improve long-term neurologic outcomes in TBI patients. Additionally, therapeutic hypothermia is associated with multiple potential complications including hypotension, electrolyte disturbances, impaired coagulation, shivering, hyperglycemia, and increased risk of infection (7). Both early prophylactic hypothermia and therapeutic hypothermia for refractory intracranial hypertension have been evaluated – neither has been shown to improve clinical outcomes at 3 or 6 months after injury (7,21).

In 2001, 392 TBI patients were randomly assigned to hypothermia (core body temperature of 33°C using ice, cold gastric lavage, and surface cooling for 48 hours) or normothermia. Poor outcomes, defined as severe disability, persistent vegetative state, or death, occurred in 57% of patients in both groups. Mortality was essentially the same (28% vs. 27%) in both groups ($p=0.79$). The authors concluded that therapeutic hypothermia was not effective in improving outcomes in TBI (19). Two additional randomized trials comparing therapeutic hypothermia with normothermia similarly found no benefit in TBI patients (23,24).

In 2011, Clifton et al. conducted a randomized multicenter trial of severe TBI patients. Patients were enrolled in the trial within 2.5 hours of injury and randomized to either hypothermia (target 33°C) or normothermia. The patients in the hypothermia group were maintained at target temperature for 48 hrs and then rewarmed. Patients in the hypothermia group had more episodes of intracranial hypertension ($p=0.003$). There was no difference in mortality or Glasgow Outcome Scale (GOS) at 6 months between the two groups (24).

In 1993, Shiozaki et al. demonstrated that patients with refractory elevations in ICP (ICP > 20 mmHg) despite maximal medical therapy including barbiturate coma might benefit from induced hypothermia (target temperature of 34°C). Patients in the hypothermia group were maintained at 34°C until ICP < 20 mmHg for at least 24 hours. The investigators found that mild hypothermia resulted in significantly lower ICP and higher CPP compared to the normothermia group ($p<0.01$). They also reported a significantly higher survival rate in the hypothermia group (50% vs. 18%, $p<0.05$). There was also a trend towards improved 6-month GOS in the hypothermia group (20).

Since that time, several other studies have been conducted. In 2016, Zhu et al. conducted a meta-analysis of 18 trials involving 2177 TBI patients assessing therapeutic hypothermia vs. normothermia. The study demonstrated no difference in 3-month or 6-month mortality, or unfavorable clinical outcomes (GOS of 3, 4, or 5), Additionally, the therapeutic hypothermia group had a higher risk of developing pneumonia ($p=0.006$) and cardiovascular complications ($p=0.01$) (18). Based on the currently available data, neither prophylactic (within 2.5 to 48 hours after injury) nor therapeutic (treatment for refractory ICP elevation) hypothermia are recommended as therapies to improve outcomes in patients with diffuse TBI (4,21).

Crompton et al. published a meta-analysis on the use of therapeutic hypothermia for adult and pediatric TBI patients. The results of the meta-analysis showed a 35% increase in favorable neurologic outcomes in adults (RR 1.35, 95% CI 1.18-1.54; p<0.00001) and a significant (18%) reduction in mortality (RR 0.82, 95% CI 0.70-0.96, p=0.01). However, there was significant population heterogeneity limiting the validity of these findings. Selective brain cooling to 33°C for 72 hours followed by natural rewarming was determined to be optimal management, but the included studies had very small sample sizes. The combination of barbiturates and therapeutic hypothermia was shown to be less effective at reducing ICP compared to therapeutic hypothermia alone. The published study did not address the direct impact of therapeutic hypothermia on ICP measurements or timing of implementation of therapeutic hypothermia although it was prophylactic in most studies. Patients treated with therapeutic hypothermia were 28% more likely to develop pneumonia (27).

Targeted Temperature Management for Normothermia (Appendix 2)
With the deleterious effects of both fever (hyperthermia) and hypothermia established for TBI patients, maintenance of normothermia is imperative. Many modalities for achieving normothermia have been described (28). Conventional cooling methods include skin exposure, ice, cold packs, infused cold fluid, peritoneal lavage, and antipyretics. There are also many commercially available cooling devices available. The Blanketrol™ (Cincinnati Subzero, Cincinnati, OH) is a water-circulating blanket system that utilizes two large cooling blankets, one beneath and one on top of the patient, to maintain the desired patient temperature. The Arctic Sun™ (Medivance, Jugenheim, Germany) circulates water through gel pads that are applied to the patient's back, abdomen, and thighs, automatically controlled by a rectal thermometer. Several intravascular cooling systems are also commercially available. These systems infuse cold fluids via a closed-loop central venous catheter to maintain the desired body temperature. In a prospective study of ICU patients, Hoedemakers et al. found superior temperature control using water-circulating blankets, gel-pads, and intravascular cooling as compared to conventional cooling techniques and air-circulating blankets (33).

Shivering Control During Targeted Temperature Management (Appendix 3)
When body temperature is lowered, the physiologic response is to prevent further heat loss through vasoconstriction. When vasoconstriction is no longer effective, shivering occurs to counterbalance heat loss. In the context of the use of cooling devices to achieve normothermia, shivering is undesirable because it causes patient discomfort, increases body temperature, increases metabolic / oxygen demand, and increases intraocular and intracranial pressures (25,26). A stepwise approach to the prevention of shivering is appropriate. Pharmacologic options for the control of shivering include benzodiazepines, buspirone, fentanyl, magnesium, meperidine, morphine, propofol, and neuromuscular blockers (26,33). It is important to consider that data on pharmacologic interventions for shivering control are based upon experience with either healthy volunteers or in the postoperative setting (28-31). Therefore, the effect of repetitive dosing and prolonged use of these agents in therapeutic hypothermia is lacking (i.e., central nervous system toxicity associated with meperidine).

Seizure Prophylaxis
Post-traumatic seizures may be classified as early (≤ 7 days post-injury) or late (> 7 days post-injury) (3). Both early and late seizures should be avoided. Anticonvulsant therapy, using either levetiracetam or phenytoin, is indicated to decrease the incidence of early post-traumatic seizures in severe TBI, but not mild or moderate TBI. Levetiracetam does not require blood level monitoring and has fewer drug interactions compared with phenytoin. Additionally, recent studies suggest decreased long-term functional outcome among patients who receive phenytoin prophylaxis (4). Routine prophylaxis of late post-traumatic seizures with any antiepileptic agent is not recommended (see "Seizure Prophylaxis in Patients with Traumatic Brain Injury" guideline on www.surgicalcriticalcare.net) (3,4). Seizure prophylaxis can generally be discontinued after 7 days of therapy in the absence of seizure activity (4,34).

Corticosteroids
Multiple prospective, randomized studies have demonstrated no benefit in lowering ICP or improvement in patient outcome using high-dose corticosteroids in acute TBI. The use of methylprednisolone in patients with moderate to severe TBI has been demonstrated to increase mortality and is contraindicated (3,4).

Hyperventilation
Hypercapnia is a potent cerebral vasodilator and should be avoided in patients with cerebral edema and elevated ICP. Hyperventilation reduces ICP by causing cerebral vasoconstriction and reducing cerebral blood flow. Aggressive hyperventilation has been historically used in the treatment of elevated ICP but has been demonstrated to have a deleterious outcome (13). Prophylactic hyperventilation ($PaCO_2$ < 25 mmHg) is no longer recommended (3,4). A $PaCO_2$ target of 35-40 mmHg is appropriate in the initial resuscitation of the patient with severe TBI. In patients with refractory elevations in ICP, a revised target of 30-34 mmHg may be appropriate. Hyperventilation should be avoided in the first 24 hours post-injury when cerebral blood flow is often critically reduced (4). Hyperventilation may have a role as a temporizing measure in the acute reduction of elevated ICP. When hyperventilation is used for more than a brief period, monitoring of cerebral oxygenation using either jugular venous bulb oximetry ($SjvO_2$) or brain tissue oxygen tension ($PbrO_2$) should be considered (4).

Hyperosmolar Therapy
Hyperosmolar therapy refers to treatment with either hypertonic saline (HTS) or mannitol. In 2020, the Neurocritical Care Society published guidelines for the management of cerebral edema. These guidelines recommend the use of HTS over mannitol for patient with TBI (36). The recommendation of HTS over mannitol comes with several benefits including faster onset of action, more robust and sustainable decrease in ICP, and concurrent elevation of MAP and CPP (36), A meta-analysis published in 2018 by Gu et al. included 12 randomized, controlled trials. Outcomes in this study included more successful ICP control with HTS (38). Finally, a prospective case-control study published in 2020 also demonstrated HTS was superior to mannitol in both lower ICP and raising CPP (35). Regardless of the choice of agent, patients should be closely monitored for hypernatremia with serial serum sodium measurements (and serum osmolality measurements if administering mannitol).

HTS reduces cerebral edema while simultaneously lowering ICP and augmenting CPP by increasing MAP. Concentrations of 3%, 7.5%, and 23.4% HTS have all been studied in severe TBI. Use of 3% saline boluses in volumes of 100-500 mL may be administered as needed to reduce ICP. Hypotensive patients with severe TBI may benefit from 250-500 mL of 3% saline as an acute resuscitative intervention to raise MAP, reduce ICP, and avoid crystalloid over-resuscitation. Wade et al. demonstrated that hypotensive TBI patients resuscitated with HTS were twice as likely to survive compared to those that received normal saline resuscitation ($p < 0.05$) (41). Vasser et al. showed that trauma patients with a GCS ≤ 8 receiving HTS had a significant improvement in survival to discharge compared to either normal saline or Lactated Ringer’s solution (42). Concentrated boluses of 23.4% sodium chloride 30 mL IV over 15 minutes are best used for refractory elevated ICP as it will lower ICP while only raising the serum sodium 1-2 mmol/L.

When utilized, mannitol should be administered in doses of 0.25-1.0 gm/kg every 6 hours as needed to reduce ICP (39,40). Mendelow et al. have shown that mannitol improves MAP, CPP, cerebral blood flow, and ICP (37). Mannitol should not be administered in the absence of ICP monitoring unless the patient is showing signs of transtentorial herniation (3,4). Serum sodium and serum osmolality levels should be obtained at least every 6 hours for patients receiving repeated doses of mannitol for ICP control. The goal is to maintain a serum sodium < 160 mEq/L and an osmolar gap < 20 mOsm/kg (35).

Intracranial Pressure (ICP)
ICP ≥ 15 mmHg has been independently associated with increased mortality following TBI (33). ICP ≤ 22 mmHg has been demonstrated to predict improved outcome (3,4,44). The goal of ICP treatment should be to reduce ICP ≤ 22 mmHg wherever possible, balancing the risks of continued intracranial hypertension against the potential iatrogenic risks of overtreatment. Using information from ICP monitoring for patient management has been shown to reduce in-hospital and 2-week post-injury mortality (3,4).

ICP cannot be predicted by CT scan alone. As a result, ICP monitors should be placed and utilized to guide resuscitative therapy in the following three patient populations (3):

1. Salvageable patients with severe TBI (GCS 3-8 after resuscitation) and an abnormal CT scan (hemorrhage, contusions, swelling, herniation or compressed basal cisterns)
2. Patients with severe TBI and a normal CT scan if two of the following are noted at admission: age > 40 years, unilateral or bilateral posturing, or systolic BP < 90 mmHg
3. Patients with TBI whose GCS cannot be determined for a prolonged period

ICP monitors should not be placed in patients that are deemed to have a non-survivable injury or who will undergo neurosurgical intervention within four hours of the initial injury. Overall, management decisions for treating elevated ICP should include a combination of treating ICP values and clinical and brain CT findings.

Cerebrospinal Fluid Drainage

External ventricular drainage (EVD) systems can allow for continuous monitoring of ICP when closed, and drainage of cerebrospinal fluid (CSF) when open. For patients with an initial GCS < 6 during the first twelve hours after injury, EVD can be considered to drain CSF and therapeutically lower ICP. Evidence suggests that an EVD system with continuous drainage of CSF may lower ICP more effectively than when used intermittently (3,4).

Advanced Cerebral Monitoring

Advanced cerebral monitoring techniques for blood flow and oxygen include transcranial Doppler (TCD)/duplex sonography, differences between arterial and arterio-jugular venous oxygen ($AVDO_2$), and measurements of local tissue oxygen. Jugular bulb monitoring of arteriovenous oxygen content difference ($AVDO_2$), as a source of information for management decisions, may be considered to reduce mortality and improve outcomes at 3- and 6-months post-injury (3).

Brain Tissue Oxygenation Monitoring ($PbtO_2$)

Brain tissue hypoxia can occur even when ICP and CPP are within normal ranges. The Phase II prospective randomized controlled trial (BOOST-II) evaluated the effectiveness of combining brain tissue oxygen ($PbtO_2$) monitoring with standard ICP management. Results showed that patients receiving both ICP and $PbtO_2$-guided treatment experienced a statistically significant reduction in the duration and severity of brain hypoxia (mean hypoxia burden: 0.45 in the ICP-only group vs. 0.16 in the ICP + $PbtO_2$ group; $p < 0.0001$). Additionally, this combined approach was associated with lower mortality rates and improved neurological outcomes at six months.

Hemoglobin Resuscitation

Current evidence-based guidelines for TBI transfusion protocols recommend a restrictive hemoglobin threshold of <7 g/dL. The multicenter randomized controlled HEMOTION trial demonstrated that adults with moderate or severe TBI and anemia receiving transfusion according to a restrictive strategy (transfusions initiated at ≤7 g/dL) had comparable neurologic outcomes to those receiving a liberal strategy (transfusions initiated at ≤10 g/dL) (45). The American College of Surgeons (ACS) has incorporated this evidence into their revised best practice guidelines for managing TBI patients released in October 2024 (46). Systematic reviews and meta-analyses consistently demonstrate that restrictive red blood cell transfusion strategies may be useful in moderate to severe TBI as allogenic transfusion has been associated with poorer neurological outcomes (47,48). Additionally, the recent CENTER-TBI collaborative analysis shows that hemoglobin values and transfusion practices significantly impact long-term outcomes in critically ill patients with TBI (49). This evidence-based shift toward restrictive transfusion practices aligns with broader critical care medicine trends prioritizing patient safety while maintaining adequate cerebral oxygen delivery and reducing transfusion-associated complications in vulnerable TBI populations.

Analgesia and Sedation

Analgesia and sedation in the TBI patient have the advantages of reducing elevated ICP, controlling blood pressure, preventing temperature elevation, and facilitating mechanical ventilation (3). These goals must be balanced against the potential loss of a reliable neurologic examination and iatrogenic reduction in systemic blood pressure and cerebral perfusion.

Analgesia is best obtained using continuous narcotic infusions. Fentanyl has minimal hemodynamic effects and a short half-life (10-20 minutes) allowing rapid titration on and off for neurologic examination. Propofol is a sedative hypnotic agent that has a favorable pharmacokinetic profile and beneficial effects on both cerebral metabolic rate and ICP following TBI. It has a short half-life (9 minutes) making it easy to titrate on and off for neurologic examination. Propofol does depress respiratory drive and must be used in conjunction with mechanical ventilation. It is also a cardiac depressant and directly reduces preload, contractility, and systemic vascular resistance, potentially leading to systemic hypotension if used inappropriately. High dose propofol infusions (>83 mcg/kg/min for greater than 24 hours) have been associated with fatal acidosis, rhabdomyolysis, and refractory arrhythmias (known as "Propofol Infusion Syndrome") (48). In general, doses ≤50 mcg/kg/min are both effective and safe. Short-term infusions of high-dose propofol (>50 mcg/kg/min) may be deemed necessary to control ICP after discussion with both the patient's neurosurgeon and intensivist (7). Despite the utility of propofol for the acute control of elevated ICP, its use did not show improvement in mortality or 6-month outcomes (4).

Neuromuscular paralysis

Pharmacologic neuromuscular paralysis can be beneficial in the control of refractory intracranial hypertension by reducing cerebral metabolic rate. Few studies exist to support this as a routine practice. Prophylactic paralysis is associated with increased pneumonia and ICU stay; therefore, use of neuromuscular blockers should be instituted only after failure to respond to less invasive therapies (49).

Decompressive Craniectomy

Current evidence-based guidelines for decompressive craniectomy (DC) in TBI have undergone significant refinement based on randomized controlled trials and long-term outcome data. The 2024 American College of Surgeons Trauma Quality Improvement Program (ACS-TQIP) revised best practice guidelines incorporate findings from the RESCUEicp trial which demonstrated that DC for refractory intracranial hypertension results in significantly lower mortality (26.9% vs. 48.9%), but higher rates of severe disability compared to standard medical care (46,52). The BTF 2020 updated guidelines recommend that DC should be considered as a last-tier therapy for patients aged 18-65 years with severe TBI and refractory intracranial hypertension (ICP >25 mmHg for >15 minutes) when maximum medical management has failed (53,54). However, the decision must involve comprehensive family discussions regarding the trade-off between reduced mortality and increased risk of severe disability as 24-month follow-up data from RESCUEicp confirmed sustained functional improvements in some patients initially classified as severely disabled (55). In contrast to secondary DC for refractory ICP, the evidence for primary DC remains controversial with the DECRA trial showing worse outcomes when performed early for mild-to-moderate intracranial hypertension (56). Recent multicenter observational studies suggest that when DC is performed as a second or third-tier intervention in carefully selected patients, favorable outcomes (Glasgow Outcome Scale Extended ≥5) can be achieved in approximately 48.6% of cases (57). Secondary craniectomy is now part of the TQIP recommendations for refractory intracranial hypertension (1). The current consensus emphasizes individualized decision-making, considering patient age, injury pattern, pre-injury functional status, and family preferences, while recognizing that DC remains an important life-saving intervention when performed for appropriate indications in specialized neurotrauma centers (58).

Barbiturate Coma

The beneficial effects of high-dose barbiturates in reducing ICP have been known since the 1930s (3). These agents are powerful myocardial depressants, however, and have deleterious effects on other organ systems as well. The prophylactic administration of barbiturates to reduce ICP and induce burst suppression on EEG is not recommended (3). High-dose barbiturates are recommended to control elevated ICP that is refractory to maximal medical and surgical management. When implemented, advanced hemodynamic monitoring may be necessary to ensure hemodynamic stability before and during barbiturate infusion (3,4,7).

Infection Prevention

There has been a strong movement to reduce hospital-acquired infections and minimize their potentially devastating effects on hospital morbidity, mortality, and length of stay. Severe TBI can increase a patient's susceptibility to infection because of necessary mechanical ventilation to prevent airway obstruction, aspiration, and consequential hypoxia, in addition to invasive monitoring. (3) Nosocomial infection is a significant concern in the critically ill. Central line-associated bloodstream infection (CLABSI) and catheter-associated urinary tract infection (CAUTI) should be prevented. Ventilator-associated pneumonia (VAP) should be reduced using VAP bundles and early extubation when appropriate. Early tracheostomy is recommended to reduce ventilator days, however, it has not been shown to reduce the rates of nosocomial pneumonia or overall mortality (3,4). Routine ventricular catheter exchange and prophylactic antibiotic administration has not been demonstrated to reduce the risk of infection (3). The use of povidone-iodine (PI) oral care is not recommended to reduce VAP and may cause an increased risk of ARDS (3).

Deep Vein Thrombosis Prophylaxis

TBI patients are at high risk for developing venous thromboembolism (VTE) due to a combination of factors including prolonged immobilization and focal motor deficits. Low molecular weight heparin or low-dose unfractioned heparin should be used in combination with mechanical prophylaxis – with the increased risk for expansion of intracranial hemorrhage (3,4). Deep venous thrombosis prophylaxis should be initiated within 24-48 hrs after presentation, once active cerebral hemorrhage has ceased or the brain injury is considered stable, or 24 hrs after craniotomy. Low-molecular-weight heparin (LMWH) is preferred over unfractionated heparin (UFH) for prophylaxis in TBI patients (see “Deep Venous Thrombosis Prophylaxis in the Critically Ill” guideline on www.surgicalcriticalcare.net) (59).

Nutrition, Stress Ulcer Prophylaxis & Skin Breakdown Prevention

Appropriate critical care management should be initiated in any patient with TBI. Gastrointestinal stress ulcer prophylaxis should be administered in patients using either an H_2-blocker or proton pump inhibitor (see “Stress Ulcer Prophylaxis” guideline on www.surgicalcriticalcare.net). Early enteral nutritional support should be initiated in all TBI patients to avoid the development of protein-calorie malnutrition. Patients should receive full-caloric replacement by day 5 and at most by day 7 post-injury to decrease mortality. Transgastric jejunal feeding is the recommended route to decrease the incidence of VAP (see “ICU Enteral Feeding Guidelines” on www.surgicalcriticalcare.net for the full recommendations) (4). Skin breakdown and decubitus ulcer formation should be prevented using appropriate pressure-reduction bed surfaces.

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APPENDIX 1: Anticoagulation & Antiplatelet Reversal Recommendations

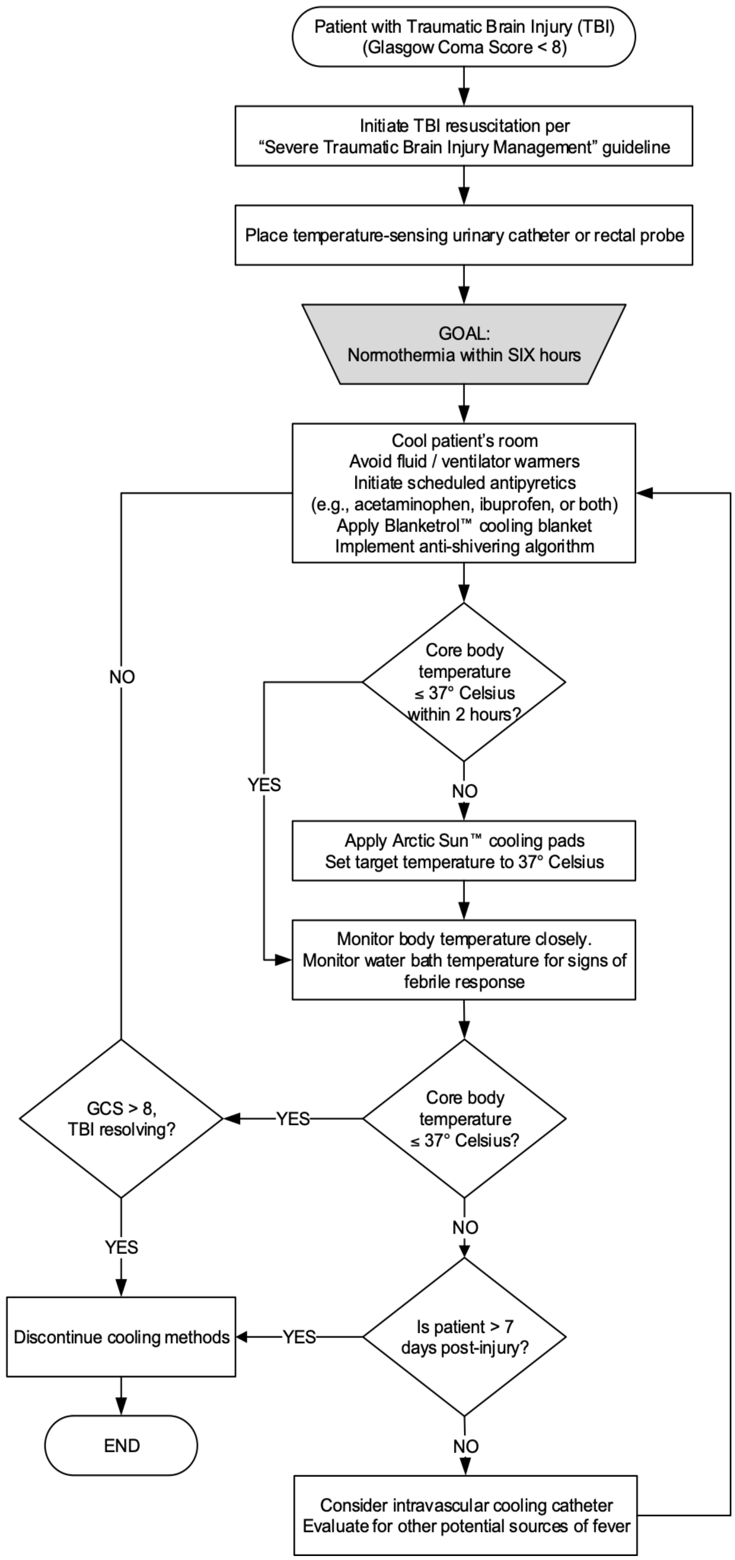
- Time of last dose of anticoagulant (dabigatran, Factor Xa Inhibitors, Fondaparinux, low-molecular weight heparins) should be confirmed – reversal is not recommended if more than 24 hours since last dose.
- Baseline PT / INR should be obtained for warfarin to determine need for reversal.

Anticoagulant	Reversal
Dabigatran (Pradaxa)	Idarucizumab (Praxbind)
Factor Xa Inhibitors (apixaban, edoxaban, rivaroxaban)	aPCC/PCC *Alternative:* Andexanet alfa[1]
Fondaparinux	PCC or formulary alternative
Heparin, unfractionated – therapeutic infusion	Protamine (dose calculated per last 3 hours)
Low-molecular weight heparins	Protamine (dose based on time of last dose)
Warfarin	PCC + phytonadione (Vitamin K)

[1]Andexanet alfa should be used if available on local formulary
aPCC = activated prothrombin complex concentration; PCC = prothrombin complex concentrate

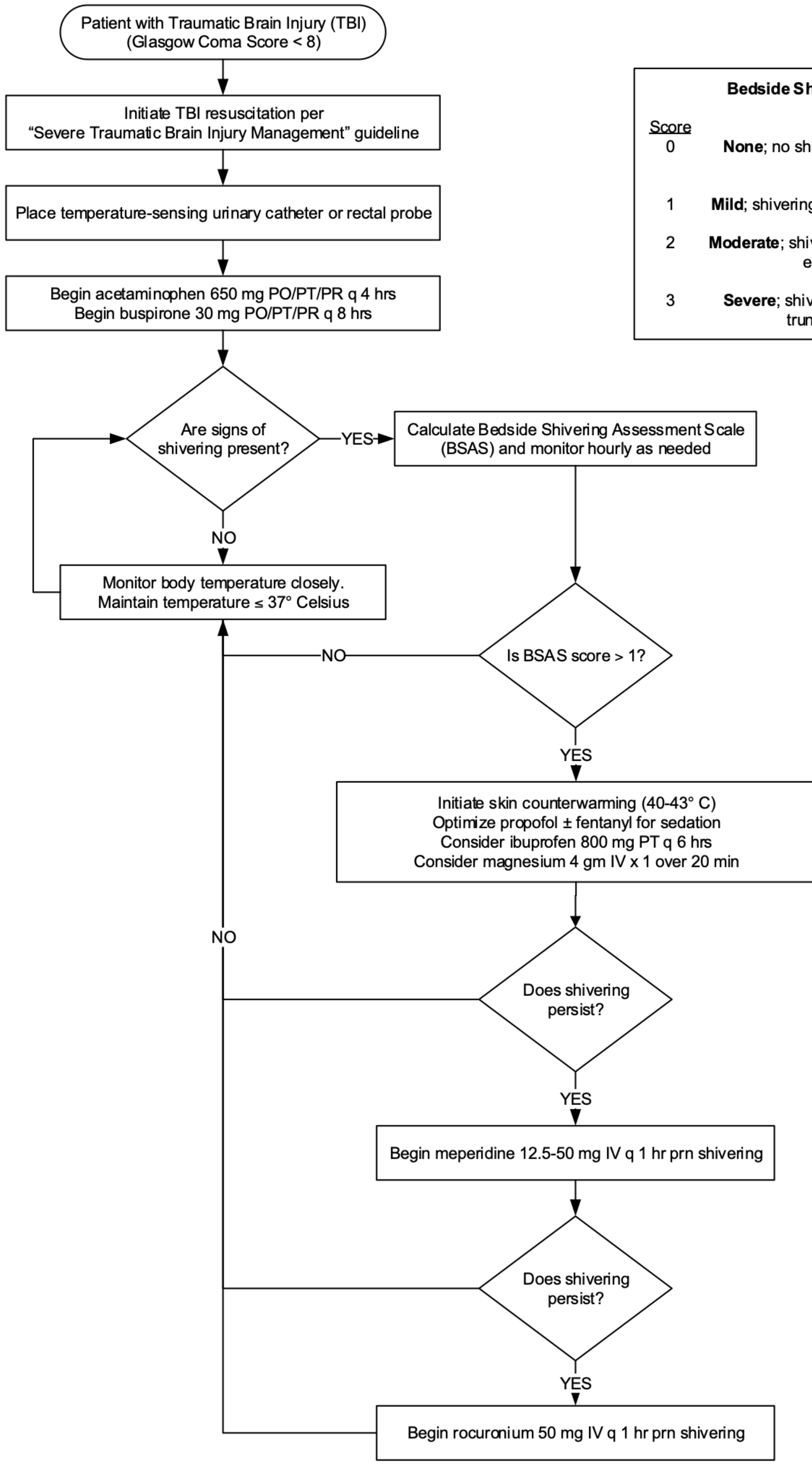
Antiplatelet	Reversal
Aspirin Clopidogrel Prasugrel Ticagrelor	Consider if emergent neurosurgical intervention AND platelet function assay demonstrates activity Desmopressin 0.3 units/kg IV x 1 AND Platelet transfusion (1-2 units)

APPENDIX 2: TARGETED TEMPERATURE MANAGEMENT IN TBI PATIENTS



References 4,10,11,13,17,19

APPENDIX 3: SHIVERING MANAGEMENT IN TBI PATIENTS



Bedside Shivering Assessment Scale

Score	Definition
0	**None**; no shivering noted on palpation of masseter, neck, or chest wall
1	**Mild**; shivering localized to the neck and/or thorax only
2	**Moderate**; shivering involves gross movement of upper extremities, neck, and thorax
3	**Severe**; shivering involves gross movements of the trunk and upper/lower extremities

References 4,25,26,31

APPENDIX 4: MEDICAL MANAGEMENT OF ELEVATED ICP

<u>Hyperosmolar Therapy for ICP > 22 mmHg</u>

- **First line**
  - 3% Sodium Chloride 500 mL IV bolus over 15 min x 1 (500 mL raises serum Na 3-5 mmol/L)
    OR
  - 23.4% Sodium Chloride 30 mL IV bolus over 15 minutes x 1 (30 mL raises serum Na 1-2 mmol/L)
- **Alternative therapy**
  - Mannitol 0.25-1.0 g/kg (nearest 12.5 g) IV-push x 1
- **Monitoring**
  - ICP – continuous
  - Serum sodium every 4 hours
  - Serum osmolality every 4 hours, if using mannitol
- Repeat above osmolar therapy as long serum Na < 160 mEq/L and osmolality < 320 mOsm/L
- Hold hypertonic NaCl therapy for serum Na ≥ 160 mEq/L, mannitol therapy for serum Na ≥ 160 mEq/L and/or serum osmolality > 320 mOsm/L

<u>Neuromuscular Paralysis Protocol Recommendations</u>

- Ensure RASS -5 before initiation of paralytic, obtain baseline Train of Four
- Administer bolus dose of neuromuscular blocker (rocuronium 50 mg IVP x 1 or cisatracurium 0.1 mg/kg IVP x 1) – if ICP does not decrease, use of continuous infusion may be futile
- Start rocuronium (50 mg IVP loading dose, then 4mcg/kg/hr (range 0-20 mcg/kg/hr)) or cisatracurium (0.1 mg/kg bolus, then 2 mcg/kg/min (range 0-10 mcg/kg/min)
- Titrate drip to Train of Four 1 of 4

<u>Barbiturate Coma Protocol Recommendations</u>

- If not a surgical candidate, and refractory to all above interventions, consider pentobarbital coma
- Hemodynamic stability is essential before and during pentobarbital therapy
- **NOTE: Cannot declare brain death for a minimum of 7 days after discontinuation and must obtain levels (send outs, take 7 days to result) to demonstrate clearance. A comprehensive Goals of Care discussion should be held with the patient's family before proceeding with pentobarbital coma.**

Pentobarbital coma

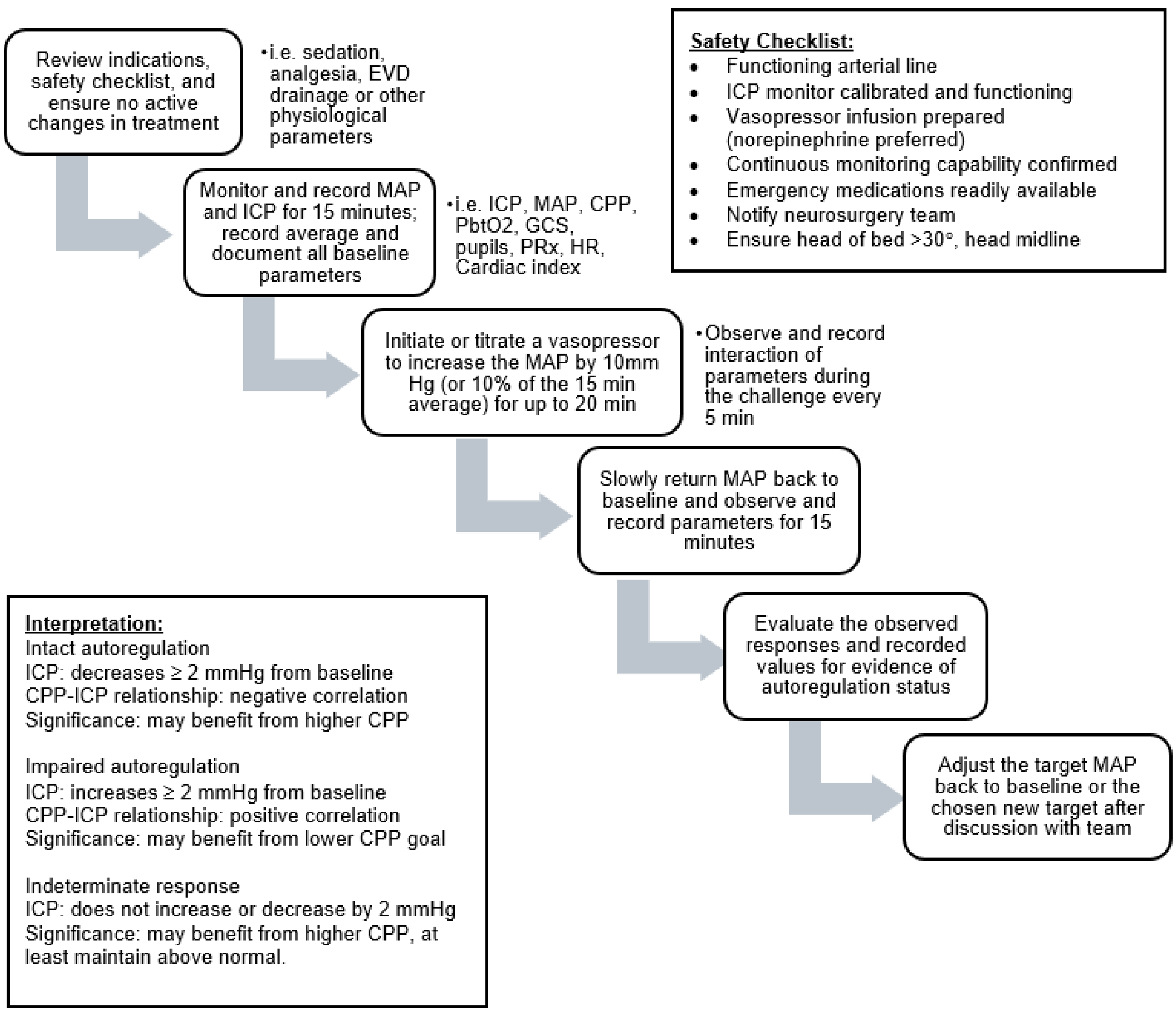
- Pentobarbital 10 mg/kg IV over 10 minutes, then 5 mg/kg/h x 3 hours, then 1 mg/kg/hr IV infusion.
- Titrate pentobarbital to the minimal dose required to achieve EEG burst suppression (2-3 bursts / 15 seconds [usually 1 burst per screen])
- Discontinue all other sedative agents and paralytics after pentobarbital loading doses complete (4 hours), continue non-titratable analgesia (e.g. fentanyl infusion at 50-60% of the recent rate)
- Consider invasive hemodynamic monitoring (such as pulmonary artery catheter) due to the negative ionotropic effects of pentobarbital
- Once ICP ≤ 22 mmHg for 48 hours, wean pentobarbital dose over the next 48-72 hours.
- If unable to maintain ICP ≤ 22 at 72 hours, discussion should ensue regarding discontinuation of therapy.
- Discontinue or decrease tube feeds to trophic rate (10-20 mL/hr)

Appendix 5: MAP Challenge

Purpose: To assess cerebral autoregulation status to guide individual cerebral perfusion pressure (CPP) management. Must be approved by the intensivist or neurosurgeon.

Target population: Severe TBI patients with ICP monitoring requiring CPP optimization

Inclusion Criteria	**Exclusion Criteria**
• Severe TBI (GCS ≤ 8) with ICP monitoring device in place • Age ≥ 18 years old • Hemodynamically stable (no active bleeding/shock) • ≥ 72 hours post injury (Optimal timing) • Baseline CPP 60-80 mmHg • Closed cranium	• Hemodynamic instability requiring prohibitive doses of vasopressors • Active intracranial hemorrhage expansion • Baseline CPP <50 or >90 mmHg • Severe Cardiac dysfunction (EF <30%) • Recent decompressive craniotomy (<48 hours) • Malignant arrythmias



Appendix 6: Intracranial Pressure (ICP) & Brain Tissue Oxygen ($PbtO_2$) Management Algorithm

Begin Tier 1 within 15 minutes of an episode. If interventions are ineffective after 60 minutes, move to next tier.

<table>
<tr><th></th><th>ICP < 20 mmHg</th><th>ICP ≥ 22 mmHg</th></tr>
<tr><td>$PbtO_2 \geq 20$ mmHg</td><td><u>Type A</u>
No interventions
• Continue to monitor</td><td><u>Type B</u>
Interventions to lower ICP
Tier 1:
• Adjust HOB
• Maintain CPP 60-70 mmHg
• Titrate analgesia / sedation
• Maintain $PaCO_2$ at low end of normal (35-45 mmHg)
• Ensure normothermia (goal = 37°C)
• Drain CSF from EVD if present
• Check serum Na^+ and consider hypertonic saline bolus
Tier 2:
• Mild hypocapnia; Adjust $PaCO_2$ to 32-35 mmHg (if $PBtO_2$ tolerates)
• Consider CT Head
• Consider surgical options, decompressive craniectomy
Tier 3:
• Consider Pentobarbital Coma
• Consider Neuromuscular Blockade
• Mild hypothermia (35-36°C) using Arctic Sun cooling blanket</td></tr>
<tr><td>$PbtO_2 < 20$ mmHg</td><td><u>Type C</u>
Interventions to increase $PBt0_2$
Tier 1:
• Adjust head of bed
• Ensure temp < 37°C
• Increase CPP 60-70 mmHg
• Maintain $PaCO_2$ > 35 mmHg
• Increase PaO_2 by increasing FiO_2 to 60%
• Increase PaO_2 by adjusting PEEP (if ICP tolerates)
Tier 2:
• Increase FiO_2 to 100%
• Decrease ICP, drain CSF if EVD present
• Increase sedation to improve mechanical ventilation
• Cautiously increase CPP >70 mmHg, monitor for respiratory complications.
Tier 3:
• Increase $PaCO_2$ to 45-50 mm Hg (if ICP tolerates)
• Transfuse pRBC's to goal Hgb > 10 g/dL if no improvement</td><td><u>Type D</u>
Interventions aimed at lowering ICP and increasing $PBt0_2$
Tier 1:
• Adjust HOB to lower ICP
• Ensure temp < 37°C
• Titrate analgesia/sedation
• Drain CSF from EVD if present
• Increase CPP to a max > 70 mmHg
• Hypertonic saline bolus
• Increase FiO_2 to 60%
• Increase PEEP (avoid additional increase in ICP)
Tier 2:
• Increase PaO_2 by increasing FiO_2 100%
• Cautiously increase CPP > 70 mmHg, monitor for respiratory complications
• Consider CT Head
• Consider surgical options/decompressive craniectomy
• Consider mild hypothermia 35-37°C with Arctic Sun cooling blanket
Tier 3:
• If $PbtO_2$ remains <20 mmHg, transfuse pRBC's to goal Hgb $\geq$ 10 g/dL
• Consider pentobarbital coma
• Consider neuromuscular blockade</td></tr>
</table>