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# SEVERE TRAUMATIC BRAIN INJURY MANAGEMENT

## SUMMARY

Traumatic brain injury (TBI) is a major cause of death for all age groups in the United States, contributing to over 30% of trauma-related deaths. Protocolized management of severe TBI (defined as a post-resuscitation Glasgow Coma Score (GCS)  $\leq 8$ ) has been demonstrated to improve 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) (CPP = MAP – ICP) and tissue oxygenation to reduce secondary ischemic injury.

## RECOMMENDATIONS

- **Level 1**
  - None
- **Level 2**
  - If ICP monitor in place, maintain ICP  $< 22$  mmHg and CPP  $\geq 60$  mmHg
  - Maintain patient temperature 36-37° Celsius; consider early antipyretics and cooling blankets
  - Do not administer high-dose steroids in TBI
  - Protect the patient's airway and intubate if GCS  $\leq 8$
  - Maintain oxygenation (PaO<sub>2</sub> 80-120 mmHg) and normocarbica (PaCO<sub>2</sub> 35-40 mmHg)
  - Elevate head of bed 30 degrees at all times
  - Consider ICP monitor if GCS  $\leq 8$  (after resuscitation) AND concern for elevated ICP on imaging or physical examination
  - Provide judicious sedation and analgesia to control pain and agitation
  - Initiate norepinephrine if CPP  $< 60$  mmHg despite appropriate volume resuscitation
  - If ICP is persistently  $> 22$  mmHg:
    - Administer 7.5% sodium chloride 250mL IVPB x1 over 15 minutes
      - Alternative therapy: Mannitol 0.25-1.0 gm/kg IV x 1
    - Order serum sodium levels every 4 hrs (and serum osmolality if using mannitol)
  - Consider neuromuscular blockade for refractory ICP
  - Initiate seizure prophylaxis for the first 7 days post-injury with Levetiracetam 1000 mg bid x 7 d
  - Consider continuous EEG to rule out non-convulsive status epilepticus
  - Ensure appropriate early nutrition, stress ulcer, and deep venous thrombosis prophylaxis
- **Level 3**
  - Maintain MAP  $\geq 80$  mmHg if an ICP monitor is unavailable
  - Maintain hemoglobin  $> 9$  gm during the patient's critical illness
  - If ICP is sustained  $> 22$  mmHg and patient has been admitted  $> 24$  hours, consider short-term hyperventilation to a PaCO<sub>2</sub> of 30-35 mmHg
  - Consider decompressive craniectomy / craniotomy for patients with a surgical lesion.
  - If the patient is not a surgical candidate, consider pentobarbital coma for refractory ICP

## EVIDENCE DEFINITIONS

- **Class I:** Prospective randomized controlled trial.
- **Class II:** Prospective clinical study or retrospective analysis of reliable data. Includes observational, cohort, prevalence, or case control studies.
- **Class III:** Retrospective study. Includes database or registry reviews, large series of case reports, expert opinion.
- **Technology assessment:** A technology study which does not lend itself to classification in the above-mentioned format. Devices are evaluated in terms of their accuracy, reliability, therapeutic potential, or cost effectiveness.

## LEVEL OF RECOMMENDATION DEFINITIONS

- **Level 1:** Convincingly justifiable based on available scientific information alone. Usually based on Class I data or strong Class II evidence if randomized testing is inappropriate. Conversely, low quality or contradictory Class I data may be insufficient to support a Level I recommendation.
- **Level 2:** Reasonably justifiable based on available scientific evidence and strongly supported by expert opinion. Usually supported by Class II data or a preponderance of Class III evidence.
- **Level 3:** Supported by available data, but scientific evidence is lacking. Generally supported by Class III data. Useful for educational purposes and in guiding future clinical research.

## TRAUMATIC BRAIN INJURY – TIERS OF THERAPY

### TIER ZERO

The following interventions should be implemented in all patients with TBI:

- ❑ Maintain target MAP  $\geq$  80 mmHg if no ICP monitor is in place
- ❑ Administer supplemental oxygen to maintain SpO<sub>2</sub> > 92%
- ❑ Elevate head of bed to 30 degrees
- ❑ Maintain head in neutral position to avoid jugular vein constriction
- ❑ Maintain serum sodium  $\geq$  140 mEq/L with isotonic intravenous fluids (no dextrose)
- ❑ Correct coagulopathy with the appropriate reversal agent in life-threatening bleeds
  - Patient on warfarin AND INR > 2: FEIBA NF 1000 units IV-syringe infusion over 20 minutes
  - Patient on Factor Xa inhibitors:
    - FEIBA NF 2000 units IV-syringe infusion over 20 minutes
    - Tranexamic acid 1g IVPB x 1 over 10 minutes
  - Patient on dabigatran: idarucizumab 2.5 gms IVPB q 10 minutes x 2 doses
- ❑ Consider platelet transfusion in patients requiring neurosurgical intervention and documented platelet dysfunction (positive PFA-Plavix) secondary to ADP-inhibitors (e.g. clopidogrel, prasugrel, ticagrelor or ticlodipine) (see “Antiplatelet Agent Reversal in Adults with Traumatic Intracranial Hemorrhage” guideline)
- ❑ Maintain normothermia (temperature 36-37° Celsius)
  - Acetaminophen 650 mg PO/PT q 4 hrs scheduled if temperature > 37° Celsius
  - Consider Ibuprofen 800 mg PO/PT q 6 hrs (if unable to control with acetaminophen)
  - Consider utilizing the Arctic Sun™ cooling device if unable to maintain normothermia
- ❑ Maintain serum glucose  $\geq$  70 mg/dL and  $\leq$  180 mg/dL
- ❑ Ensure early appropriate nutritional support (within 24 hrs; post-pyloric feeding preferred)
- ❑ Prevent deep venous thrombosis (DVT) – initiate subcutaneous heparin within 24 hours of injury
- ❑ Initiate gastrointestinal stress ulcer prophylaxis in mechanically ventilated patients
- ❑ Prevent skin breakdown / decubitus ulcer formation through appropriate bed surface

### TIER ONE

The following interventions should be added in all patients with Glasgow Coma Score (GCS)  $\leq$  8:

- ❑ Ensure all physiologic goals from **Tier Zero** are met
- ❑ **Airway / Breathing**
  - Intubate patient if GCS  $\leq$  8 and as needed to protect the airway
  - Maintain PaCO<sub>2</sub> 35-40 mmHg
    - Consider obtaining arterial blood gas to correlate with end-tidal CO<sub>2</sub> (EtCO<sub>2</sub>)
  - Maintain PaO<sub>2</sub> 80-120 mmHg
- ❑ **Systemic Perfusion**
  - Insert an arterial line (leveled at the phlebostatic axis)
  - Maintain euvoolemia (fluid balance positive by 500-1000 mL in first 24 hrs)
  - Maintain MAP  $\geq$  80 mmHg if no ICP monitor is in place
    - Ensure adequate volume resuscitation
    - Ensure hemoglobin > 9 g/dL during the patient’s acute resuscitation phase
    - Consider advanced hemodynamic monitoring
    - Consider adding norepinephrine 0.05 mcg/kg/min – titrate to keep MAP  $\geq$  80 mmHg or CPP  $\geq$  60 mmHg
- ❑ **Cerebral Perfusion**
  - Consider intracranial pressure (ICP) monitoring if GCS  $\leq$  8 after resuscitation AND concern for elevated ICP on imaging or exam
  - Use of an ICP monitor with external ventricular drainage (EVD) is preferred over an ICP monitor alone.
  - Maintain cerebral perfusion pressure (CPP)  $\geq$  60 mmHg if ICP is available
  - If CPP < 60 mmHg:
    - Ensure adequate volume resuscitation
    - Consider advanced hemodynamic monitoring
    - Consider adding norepinephrine 0.05 mcg/kg/min – titrate to keep CPP > 60 mmHg
  - Management of sustained ICP > 22 mmHg for 10 minutes
    - Verify correct ICP waveform on EVD – notify neurosurgery if ICP waveform is incorrect or there is no cerebrospinal fluid (CSF) drainage
      - Level EVD at the external auditory meatus
      - Close EVD and level at 0 mmHg upon insertion to monitor ICP

- If ICP > 22 mmHg for 10 minutes AND EVD clamped – open EVD at 0 mmHg for 15 minutes
- If EVD is opened more than 3 times within 90 minutes, leave EVD open at 0 mmHg continuously and notify neurosurgery
- Consider osmolar therapy (see below)
- Consider short-term hyperventilation (PaCO<sub>2</sub> 30-34 mmHg) to acutely reduce ICP
  - Hyperventilation should be avoided in the first 24 hours after injury
- ❑ **Osmolar Therapy**
  - First line therapy for ICP > 22 mmHg for ≥ 10 minutes
    - 7.5% Sodium Chloride 250 mL IV bolus over 15 min x 1 if serum sodium < 160 mmol/L
  - Alternate therapy
    - Mannitol 0.25-1.0 gm/kg IV-push x 1 if serum sodium <160 and/or serum osmolality < 320 mOsm/L
  - Measure serum sodium every 4 hrs (and serum osmolality every 4 hrs if using mannitol)
  - Notify intensivist if serum sodium changes by > 2 mEq/L/4 hours from previous measurement
  - Hold hypertonic saline therapy for serum sodium ≥ 160 mEq/L
  - Hold mannitol therapy for serum sodium ≥ 160 mEq/L and/or serum osmolality ≥ 320 mOsm/L
- ❑ **Protect the Brain**
  - Provide judicious analgesia and sedation to control pain and agitation
  - Analgesia and sedation is preferred
    - Fentanyl 25-500 mcg/hr IV infusion
      - Bolus with dose increases for elevated ICP
      - Preferentially increase fentanyl (and/or oral opioid therapy) over propofol
    - Propofol 10-50 mcg/kg/min IV infusion
  - Rule-out seizure activity
    - Initiate continuous EEG monitoring to rule non-convulsive status epilepticus
    - Levetiracetam 1000 mg IV/PO every 12 hrs x 7 days (discontinue after 7 days if no seizure activity)
  - Avoid:
    - Hypotension (SBP < 100 mmHg) or CPP < 60 mmHg
    - Hypoxemia (SpO<sub>2</sub> < 92%)
    - Hypercarbia (PaCO<sub>2</sub> > 45 mmHg)
    - Hyponatremia (serum sodium < 140 mEq/L)
    - Hypoglycemia or Hyperglycemia (serum glucose <70 mg/dL or >180 mg/dL)
    - Hypovolemia
    - Fever
    - Anemia (maintain hemoglobin > 9 gm/dL) in the first seven days

## **TIER TWO**

**The following interventions should be considered if ICP is persistently > 22 mmHg for more than 60 minutes after discussion with neurosurgery and intensivist attendings:**

- ❑ Ensure all physiologic goals from **Tier One** are met
- ❑ Repeat osmolar therapy as long as serum sodium <160 mEq/L – recommend:
  - 23.4% sodium chloride 30mL IV-syringe x 1 over 15 minutes
  - Use 7.5% sodium chloride 250mL IV-bolus x 1 when volume resuscitation also needed
  - Continue serum sodium checks every 4 hrs
- ❑ Consider head CT scan to rule out space-occupying lesion
- ❑ Consider continuous EEG monitoring to rule out non-convulsive status epilepticus (if not already present)
- ❑ Consider bolusing and then increasing sedative and analgesic therapy
- ❑ Paralysis
  - Ensure RASS -5 before initiation of paralytic
  - Start rocuronium (50 mg IVP loading dose, then 8 mcg/kg/hr); adjust dose according to Train of Four 1/4
- ❑ Early (within 2.5 hrs), short-term (48 hrs post-injury), prophylactic hypothermia is not recommended to improve outcomes in patients with diffuse injury.
- ❑ Mild Hyperventilation
  - Begin mild hyperventilation with goal PaCO<sub>2</sub> 30-34 mmHg

### **TIER THREE**

**The following interventions should be considered if ICP remains > 22 mmHg despite all Tier Two goals being met:**

- ❑ Ensure that medical therapy with hypertonic saline is maximized (e.g. serum sodium 155-160 mEq/L)
- ❑ Consider revised ICP threshold of 25 mmHg with strict adherence to CPP > 60 mmHg
- ❑ Initiate continuous EEG (if not already present)
- ❑ Surgical decompression
  - Craniectomy solely for management of ICP does not improve long-term neurological outcome
  - Consider decompressive craniectomy / craniotomy in patients with a surgical lesion.
- ❑ Barbiturate Coma
  - If not a surgical candidate, and refractory to all above interventions, consider 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 – 3-5 bursts / minute (= 1-2 bursts per screen)
    - Discontinue all other sedative agents and paralytics after pentobarbital loading doses complete (4 hours)
    - Consider invasive hemodynamic monitoring (such as pulmonary artery catheter) due to the negative inotropic effects of pentobarbital
    - Once ICP ≤ 22 mmHg for 48 hrs, wean pentobarbital dose over the next 48-72 hrs
    - Discontinue or decrease tube feeds to trophic rate (10-20 mL/hr)

### **INTRODUCTION**

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](http://www.braintrauma.org)) or Neurocritical Care Society ([www.neurocriticalcare.org](http://www.neurocriticalcare.org)) (1-7). 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 guidelines outline 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 in order to regulate ICP. CSF may drain through the lumbar plexus and blood volume is tightly auto-regulated by both the PaCO<sub>2</sub> and PaO<sub>2</sub>. 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 in an attempt 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.

## **LITERATURE REVIEW**

### ***Initial Evaluation***

All patients who present with suspected TBI should undergo a rapid primary and secondary survey with thorough evaluation of their airway, breathing, and circulation. Airway patency and adequate oxygenation and ventilation are paramount to avoiding secondary brain injury (7). 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 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 "Gold Hour" and optimize the patient's outcome. Certain key resuscitative interventions should be initiated at the referring facility to minimize secondary cerebral injury (5,7) (Appendix 1).

### ***Hypotension***

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 recommendations in the 2016 guidelines are SBP >100 mmHg for patients aged 50 to 69 years, or SBP > 110 mmHg for patients 15 to 49 years old or over 70 years old (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 through the use of judicious isotonic intravenous fluids (without dextrose) until an ICP monitor is available. The goal should be to ensure an adequate CPP > 60 mmHg at all times (3,4,6). 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 with intravenous fluid alone (or CPP > 60 mmHg if ICP monitoring is available), low-dose norepinephrine should be initiated (3,4,6).

### ***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<sub>2</sub>) > 50% or brain tissue oxygen tension (PbO<sub>2</sub>) > 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 (8). 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° Celsius, temperatures in excess of 37° Celsius 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 also result in profound hypothermia, which can result in coagulopathy, cardiac arrhythmias, or depressed immune function (9-11).

Significantly worse outcomes occur in patients with intracerebral hemorrhage who develop a body temperature greater than 37.5° Celsius within the first 72 hours (9). Early fever following TBI has been associated with lower GCS, presence of diffuse axonal injury, cerebral edema, hypotension, hypoglycemia, and leukocytosis (10). Fever within the first week is associated with increased intracranial pressure, neurologic impairment, and prolonged ICU stay (11). Among 846 patients with TBI, fever at any time in the first week was associated with intermediate decline and poor overall long-term outcome (12).

Hypothermia is also associated with worse outcomes in TBI. Among 1,403 ICU patients with TBI, a core temperature less than 35° Celsius was observed in 10.9% of patients (13). 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 multivariable logistic regression model adjusted for demographics and injury characteristics, the odd's ratio for death among hypothermic patients was 1.7 times that of normothermic patients (14).

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° Celsius rather than waiting until the traditional definition of fever has been reached with a target temperature of 37° Celsius.

### ***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 (6). 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 (6,17).

In 2001, 392 TBI patients were randomly assigned to hypothermia (core body temperature of 33° Celsius 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 (18). Two additional randomized trials comparing therapeutic hypothermia with normothermia similarly found no benefit in TBI patients (19,20).

In 2011, Clifton et al. conducted a randomized multicenter trial of severe TBI patients. Patients were enrolled in the trial within 2-2.5 hours of injury and randomized to either hypothermia (target 33° Celsius) or normothermia. The patients in the hypothermia group were maintained at target temperature for 48h and then rewarmed. The investigators included 97 patients (67 hypothermia, 68 normothermia) Patients

in the hypothermia group had more episodes of intracranial hypertension 335 vs 148 ( $p=0.003$ ), There was no difference in mortality or Glasgow Outcome Scale (GOS) at 6 months between the two groups (20).

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). This study included 33 patients (17 control group, 16 hypothermia) and the patients in the hypothermia group were maintained at 34° C until ICP < 20 mmHg for at least 24 hours. The investigators found mild hypothermia to result 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 toward improved 6 month GOS in the hypothermia group (16).

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 versus normothermia. The study demonstrated no difference in 3-month or 6-month mortality, 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 ( $p=0.01$ ) (17).

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 (4,17).

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 also 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 (23).

### ***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 (24). 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 (29).

### ***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 (21,22). A step-wise approach to the prevention of

shivering appears appropriate. Pharmacologic options for the control of shivering include: benzodiazepines, buspirone, fentanyl, magnesium, meperidine, morphine, propofol, and neuromuscular blockers (23,30). It is important to consider that data on pharmacologic interventions for shivering control are based upon experience with either health volunteers or in the postoperative setting (25-28). 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 ( $\leq 7$  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) (3,4). Seizure prophylaxis can generally be discontinued after 7 days of therapy in the absence of seizure activity (4,30).

### **Corticosteroids**

Multiple prospective, randomized studies have demonstrated no benefit in lowering ICP or improvement in patient outcome through the use of 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**

Hypercapnea 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 used for years in the treatment of elevated ICP, but has been demonstrated to have a deleterious outcome (12). Prophylactic hyperventilation ( $\text{PaCO}_2 < 25$  mmHg) is no longer recommended (3,4). A  $\text{PaCO}_2$  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 of time, monitoring of cerebral oxygenation using either jugular venous bulb oximetry ( $\text{SjvO}_2$ ) or brain tissue oxygen tension ( $\text{PbrO}_2$ ) should be considered (4).

### **Hyperosmolar Therapy**

Hyperosmolar therapy, using either mannitol or hypertonic saline, has been demonstrated to be beneficial in reducing both cerebral edema and elevated ICP (3). Mannitol has the additional desirable properties of decreasing blood viscosity, increasing free radical scavenging, and inhibiting cellular apoptosis. These agents serve to establish an osmotic gradient across the blood brain barrier. They must be used with caution, however, as excessive use can lead to hypovolemia, hyponatremia, and worse patient outcome. Arterial pressure monitoring and serial sodium and osmolality measurements are essential to appropriate titration of these therapies.

Mannitol should be administered in doses of 0.25-1.0 gm/kg every 6 hours as needed to reduce ICP (33,34). Mendelow et al. have shown that mannitol improves MAP, CPP, cerebral blood flow, and ICP (34). 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 (31).

Hypertonic saline reduces cerebral edema while simultaneously lowering ICP and augmenting CPP by increasing MAP. 3%, 7.5%, and 23.4% hypertonic saline have all been studied in severe TBI. 3% saline may be administered in boluses of 100 mL every 2 hours as needed to reduce ICP. Hypotensive patients



with severe TBI may benefit from either 250 mL of 7.5% or 30 mL of 23.4% 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 hypertonic saline were twice as likely to survive compared to those that received normal saline resuscitation ( $p < 0.05$ ) (35). Vasser et al. showed that trauma patients with a GCS  $\leq 8$  receiving hypertonic saline had a significant improvement in survival to discharge compared to either normal saline or Lactated Ringer's solution (36).

#### ***Intracranial Pressure (ICP)*** (Appendix 4)

ICP  $\geq 15$  mmHg has been independently associated with increased mortality following TBI (30). ICP  $\leq 22$  mmHg has been demonstrated to predict improved outcome (3,4,38). The goal of ICP treatment should be to reduce ICP  $\leq 22$  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 reliably 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 who will not be examinable for a prolonged period of time

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).

#### ***Hemoglobin Resuscitation***

A restrictive red blood cell transfusion threshold of 7 gm/dL is commonly utilized in the critically ill based upon the results of the TRICC trial (39). It is important to recognize that this study evaluated patients who had already been resuscitated and excluded patients who were traumatically injured with ongoing blood loss. A subsequent subgroup analysis of patients with cardiac disease found that red blood cell transfusion was actually protective and improved survival (40). There is a theoretical benefit to maintaining elevated hemoglobin concentrations in the TBI patient who is at risk for cerebral ischemia. Retrospective clinical trials and meta-analyses to assess the potential benefit of a liberal red blood cell threshold in severe TBI have failed to identify a beneficial transfusion threshold, but may well have been underpowered. Sekhon et al. have recently conducted a retrospective cohort study of 273 TBI patients. They identified that a mean hemoglobin concentration  $< 9$  gm/dL during the first seven days post-injury is associated with an increased risk of mortality (relative risk 3.1; 95% confidence interval 1.5-6.3;  $p=0.03$ ) (41).

#### ***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”) (42). In general, doses  $\leq$  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 (6). 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 (43).

### ***Decompressive Craniectomy***

There have been four studies conducted between 2005 and 2016 reviewing clinical outcomes in patients with severe TBI who received decompressive craniectomies for refractory elevated ICP.

Jian et al. prospectively compared limited craniectomy (LC) versus standard trauma craniectomy (STC) for refractory intracranial hypertension in a randomized fashion. They included 486 patients (245 LC, 241 STC) with severe unilateral TBI. Forty percent of the STC had a favorable outcome (GOS 4-5) at 6 months compared to only 29% in the LC group ( $p<0.05$ ) (44). Similarly, Qui et al. conducted a prospective, randomized trial evaluating severe TBI patients with a midline shift > 5 mm for either a decompressive craniectomy (DC) or routine temporoparietal craniectomy (RTC). Significantly more patients who underwent DC had good neurologic recovery (GOS 4-5) at 6 months (57% vs 32%). These first two studies led to the recommendation in the 2007 TBI Guidelines to consider decompressive craniectomy (3,46),

In 2011, Cooper et al. published the results of an 8-year prospective, randomized, multicenter controlled trial to assess the efficacy of biofrontotemporoparietal decompressive craniectomy (DC) versus standard care (SC) in adults age 15-59 years with a severe TBI, elevated ICP, and CT evidence of swelling and/or midline shift. They enrolled 155 patients (73 DC, 82 SC). Patients in the DC group had a mean lower ICP after surgery (14 vs. 19,  $p<0.001$ ). At 6 months, the primary outcome, functional status on GOS, was worse in the DC group (median 3 DC vs. 4 SC, OR 1.84 [95% CI 1.05-3.24],  $p=0.03$ ). Post-hoc adjustment for pupillary reactivity resulted in no difference between the groups. The DC group also had a significantly higher proportion of patients with an unfavorable GOS score (3-5) (70% vs. 51%,  $p=0.02$ ). Mortality was similar between the two groups (19% DC, 18% SC) (47).

The most recent trial, RESCUEicp, published in 2016 by Hutchison et al. randomized patients (age 10-65 years) with severe TBI and refractory elevated ICP (ICP > 25 mmHg) to either DC or standard medical care (SMC) (similar to the trial in 2011). The primary outcome was functional assessment using the Extended GOS (GOS-E) at 6 months. Secondary outcomes included GOS-E scores at 12 months and 24 months, mortality and quality of life (Short-Form 36). 409 patients were randomized (202 DC, 196 SMC). 19% of the DC and 24% of the SMC groups did have a mass lesion on head CT. The primary outcome, overall function at 6 months on GOS-E was not different between the two groups, but trended toward higher disability in the DC group. The mortality rate in the DC group was significantly lower than the SMC group (23-30% vs 48-52%,  $p<0.001$ ). The lower mortality rate contributed significantly to overall higher disability scores in the DC group – ~63% of the additional survivors would either be in a persistent vegetative state or severely disabled. This remained the same at 12 months (48).

In summary, all of these trials specifically evaluated severe TBI patients with refractory elevated ICP, but no evidence of a surgical lesion contributing to the elevated ICP (e.g. subdural or epidural hematoma). The older two trials suggested that there may be long-term positive functional outcomes (44,45), However, the two most recent trials both demonstrated that DC does not improve long-term functional outcomes as assessed by GOS or GOS-E, compared to standard therapy (46,47). Therefore, the 2016 TBI guideline update recommends against the use of DC solely for refractory intracranial hypertension (4). Currently, DC only benefits this patient population in the short term by lowering ICP and decreasing ICU LOS (4,45-48).

### ***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 (3,4,6).

### ***Infection Prevention***

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 through the use of 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).

### ***Deep Vein Thrombosis Prophylaxis***

TBI patients are 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 unfractionated 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 using subcutaneous heparin 5000 units SQ every 8 hrs or enoxaparin 30 mg SQ every 12 hrs (see “Deep Venous Thrombosis Prophylaxis in the Critically Ill” guideline) (49).

### ***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<sub>2</sub>-blocker or proton pump inhibitor (see “Stress Ulcer Prophylaxis” guideline). 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” for the full recommendations) (4). Skin breakdown and decubitus ulcer formation should be prevented through the use of appropriate pressure-reduction bed surfaces.

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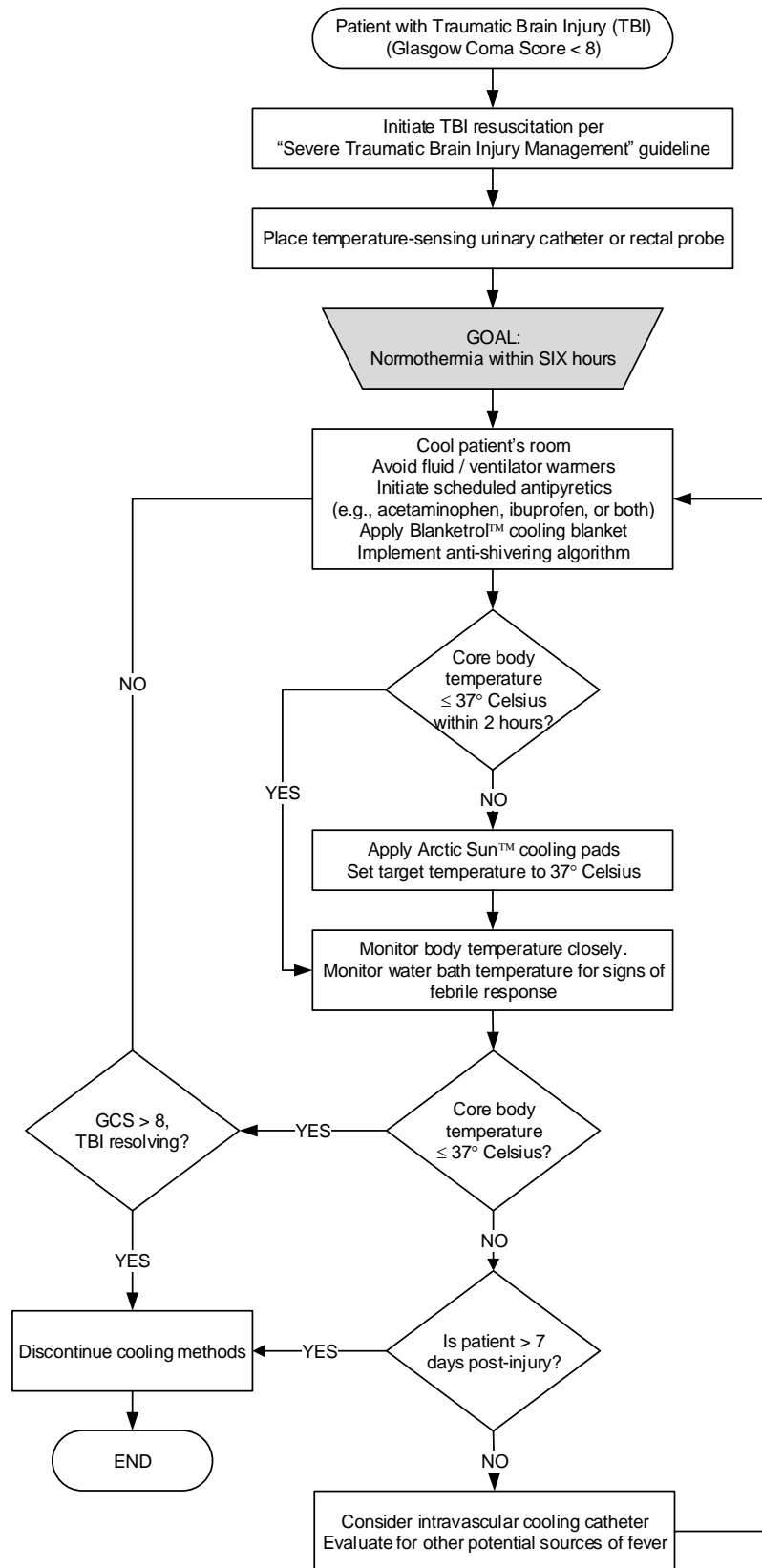
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## APPENDIX 1: TRAUMATIC BRAIN INJURY – EMERGENCY DEPARTMENT CHECKLIST

The following interventions should be implemented in all patients with TBI who are awaiting transfer to definitive neurosurgical care:

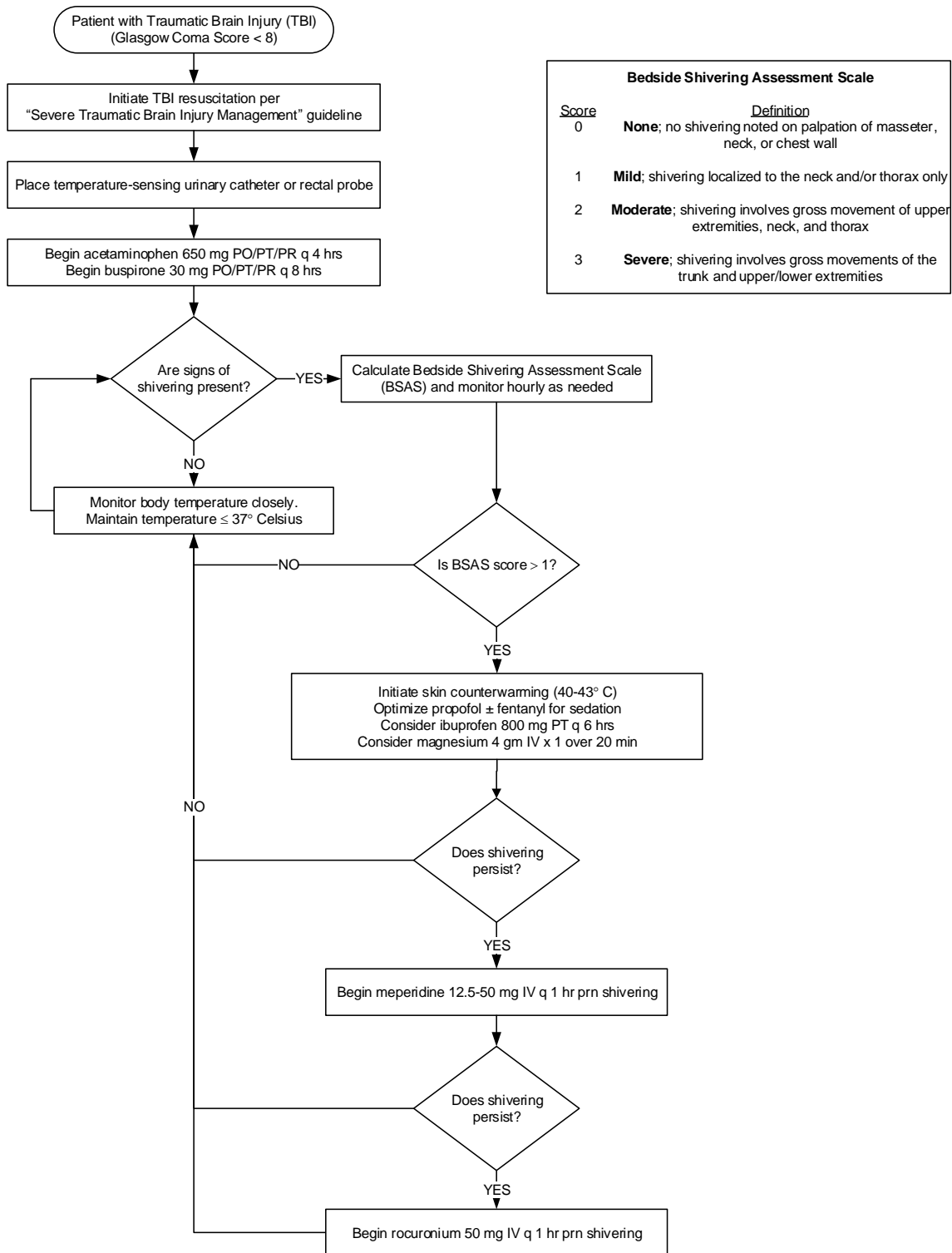
- Perform head CT scan to define extent of TBI
- Do not delay transfer to obtain other radiographic studies
- Maintain mean arterial pressure (MAP)  $\geq$  80 mmHg if GCS  $\leq$  8; otherwise target MAP  $>$  70 mmHg
- Administer supplemental oxygen to maintain SpO<sub>2</sub>  $\geq$  92%
- Intubate patient if GCS  $<$  8 and as needed to protect the airway
- Maintain PaCO<sub>2</sub> 35-40 mmHg, PaO<sub>2</sub> 80-120 mmHg
- Elevate head of bed to 30 degrees (use Reverse Trendelenburg position if spine precautions)
- Maintain head in neutral position to avoid jugular vein constriction
- Administer isotonic intravenous fluids (no dextrose)
- Correct coagulopathy with the appropriate reversal agent in life-threatening bleeds
  - Patient on warfarin AND INR  $>$  2: FEIBA NF 1000 units IV-syringe infusion over 20 minutes
  - Patient on Factor Xa inhibitors:
    - FEIBA NF 2000 units IV-syringe infusion over 20 minutes
    - Tranexamic acid 1g IVPB x 1 over 10 minutes
  - Patient on dabigatran: idarucizumab 2.5 gm IVPB q 10 minutes x 2 doses (total dose = 5 gm)
- Consider platelet transfusion in patients requiring neurosurgical intervention and documented platelet dysfunction secondary to ADP-inhibitors (clopidogrel, prasugrel, ticagrelor, etc.) (see “Antiplatelet Agent Reversal in Adults with Traumatic Intracranial Hemorrhage” guideline)
- Consider hypertonic saline (7.5% 250mL) or mannitol bolus if patient demonstrates blown pupil and imminent cerebral herniation
- Avoid:
  - Hypotension (MAP  $<$  70 mmHg)
  - Hypoxemia (SpO<sub>2</sub>  $<$  92%)
  - Hypercarbia (PaCO<sub>2</sub>  $>$  45 mmHg)
  - Hyperglycemia (glucose  $>$  180 mg/dL)
  - Hypovolemia
  - Fever (temperature  $>$  37° Celsius)

**APPENDIX 2: TARGETED TEMPERATURE MANAGEMENT IN TBI PATIENTS (4,10,11,13,17,19)**





### APPENDIX 3: SHIVERING MANAGEMENT IN TBI PATIENTS (4,25,26,31)



## APPENDIX 4: TROUBLESHOOTING EXTERNAL VENTRICULAR DRAINS

