



# ProTECT™ III

Progesterone for the Treatment of Traumatic Brain Injury

## Clinical Standardization Guidelines

Version 4

Supported by:  
National Institute for Neurological Disorders and Stroke

Project Number: 1U01NS062778  
FDA IND #: 104,188

David W. Wright, MD - Principal Investigator

## Management Guidelines for Patients with Traumatic Brain Injury

These guidelines are a TEMPLATE for the care of patients at sites participating in the multicenter clinical trial ProTECT™ III. These guidelines are not meant to change your practice in NON-ProTECT patients unless you are so inclined. However, in ProTECT™ III patients, these measures are critical in order to minimize treatment variability across multiple centers.

We recognize the existence of legitimate treatment variability within this heterogeneous population of patients, and thus the following guidelines do not circumvent clinical acumen. However, treatment variability has undermined several notable Phase III clinical trials in traumatic brain injury (TBI). Given the heterogeneity of both clinical presentation and clinical therapy in patients with TBI, **adherence to these guidelines for treatment in ProTECT™ III is imperative if we are to conduct a successful trial.**

The ProTECT™ III Clinical Standardization Team (CST), a national committee of experts in Neurological Surgery, Trauma Surgery, Neurocritical Care, and Emergency Medicine, developed the ProTECT III™ guidelines (see members listed below). They are based on **both** the *Guidelines for the Management of Severe Traumatic Brain Injury* (Brain Trauma Foundation - Third Edition, 2007) **and** the majority consensus of clinical practices across the participating ProTECT™ III sites.

The guidelines follow a Goal Directed Therapy approach. Since both MODERATE and SEVERE patients are included in the study, the parameters were developed to cover the management of both groups. As such, not all parameters will apply to all patients. Some guidelines are specific to injury type, i.e. recommendations about cerebral perfusion pressure will only be applicable to those patients with ventriculostomy or Licox monitor.

### ProTECT™ III Clinical Standardization Team:

- **Geoff Manley, MD, PhD – Neurosurgery, University of California, San Francisco, (Chairman)**
- Bizhan Aarabi, MD – Neurosurgery, University of Maryland
- Odette Harris, MD, MPH - Neurosurgery, Stanford
- Claude Hemphill, MD – NeuroIntensivist, UCSF
- Peter LeRoux, MD – Neurosurgery, University of Pennsylvania
- Lisa H. Merck, MD, MPH – Emergency Medicine, Emory University
- Raj Narayan, MD - Neurosurgery, University of Cincinnati
- David O. Okonkwo, MD, PhD - Neurosurgery, University of Pittsburgh
- Jose Pascual MD, PhD - Trauma Surgery and Critical Care, University of Pennsylvania
- Jeff Salomone, MD – Trauma Surgery and Critical Care, Grady Memorial Hospital, Atlanta, GA
- William Schwab, MD – Trauma Surgery and Critical Care, University of Pennsylvania
- Alex Valadka, MD – Neurosurgery, Seton Brain and Spine Institute, Austin, Texas
- David W. Wright, MD - Emergency Medicine, Emory University

As participants in the ProTECT™ III clinical trial and the NETT network, it is expected that each site will develop site-specific protocols that incorporate these guidelines for the clinical management of patients enrolled in ProTECT™ III. Furthermore, it is expected that all healthcare providers involved in the care of ProTECT™ III patients adhere to these protocols.

## I. PRIMARY SERVICE / CONSULTING SERVICE

### A. Multisystem Trauma Patients

1. In general, TBI patients who have also suffered injuries to organ systems in addition to the central nervous system should be admitted to and managed by the Trauma Service or Trauma Critical Care service, with Neurosurgeons and Neurointensivists providing consultation for management of the brain injury. Other shared arrangements are acceptable, but must be consistently applied.
2. Neurosurgery consultation should occur in any patient with suspected brain injury at the earliest time possible, ideally soon after patient arrives in the Emergency Department. If neurosurgical representation is not available for the initial trauma resuscitation, CT scan imaging and subsequent consultation should occur within 2 hours of arrival of the patient to the emergency department/hospital.

### B. Isolated Brain-Injured Patients

Care of patients with brain injuries can be admitted to or transferred to the Neurosurgical service/Neurointensivist service once other injuries are ruled out, or the patient is sufficiently stabilized. Those patients with an isolated brain injury may be admitted directly to the Neurosurgical service/Neurointensivist service.

## II. RESUSCITATION AND BASIC PHYSIOLOGIC GOALS

Physiologic goals will be discussed in detail throughout this text. For the purpose of all patients enrolled in the ProTECT™ III trial, the following physiological parameters should be maintained as part of the goal-directed TBI treatment. Parameters should be applied in the context of critical versus noncritical patient care (e.g., CPP, ICP are specific to the care of severe TBI patients in an ICU setting; systolic BP and O<sub>2</sub> saturation are applicable in both severe and moderate TBI patients). **In general, CPP is the most important physiological parameter to follow for the management of severe TBI patients. Other parameters should be adjusted appropriately to optimize CPP.**

Pulse Ox ≥ 90%	ICP < 20 mmHg	Physiologic Na <sup>+</sup> 135-145*
PaO <sub>2</sub> ≥ 100 mmHg	PbtO <sub>2</sub> ≥ 15 mmHg	INR ≤ 1.4
PaCO <sub>2</sub> 35-45 mmHg	<b>CPP ≥ 60 mmHg</b>	PLTS ≥ 75 x 10 <sup>3</sup> / mm <sup>3</sup>
SBP ≥ 100 mmHg	Temp 36.0-38.3°C	Hgb ≥ 8 gm/dl
pH 7.35-7.45	Glucose 80-180 mg/dL	

*\*Hypertonic saline therapy: Na<sup>+</sup> range: 145 mmol/L (minimum) to 160 mmol/L (maximum)*

### A. Airway Management

1. **Patients with a GCS ≤ 8 should be intubated for airway protection** – Patients with a Glasgow Coma Score (GCS) equal to or less than eight, and those unable to protect their airway, should undergo endotracheal intubation with inline cervical spine immobilization. Rapid sequence intubation is the preferred method.

2. **Sedative and analgesic choices should include short acting agents** through the initial resuscitation, as temporal assessment of neurological status is critical. The selection of specific agents is left up to the site, however, in general we recommend the following agents:

- **Etomidate** - sedation/induction
- **Succinylcholine, Rocuronium bromide** - paralytic
- **Propofol** - maintenance of sedation, prevention of agitation. Propofol is strongly recommended as the choice for sedation, as it allows for rapid titration and has a short half life, allowing for frequent reassessment of the neurological exam.

#### **B. Oxygenation/Ventilation – The Target Oxygen status is PaO<sub>2</sub> ≥ 100 mmHg and O<sub>2</sub> Sat ≥ 90%**

Oxygen saturation should be monitored continuously, both in the prehospital and hospital setting. End-tidal CO<sub>2</sub> (ETCO<sub>2</sub>) should be monitored both in the prehospital and ED setting.

1. **Avoidance of hypoxia** - Efforts should be made to avoid hypoxia at all times.
  - Patients with moderate TBI who do not require intubation should have **pulse oximetry maintained to at least 90%**.
  - Intubated patients **PaO<sub>2</sub> should be maintained at ≥ 100 mmHg**, except during weaning.
  - Pulse oximetry > 90 % remains goal during ventilation wean.
  - Monitoring via arterial line placement and serial arterial blood gas testing should be performed in patients who are intubated or who have a ventriculostomy in place.
2. **Ventilation** - Hyperventilation should be intensively avoided during the initial resuscitation.
  - **The Target PaCO<sub>2</sub> is (35-45 mmHg).**
  - A CO<sub>2</sub> monitor and other devices to assist in the prevention of hypocarbia / hypercarbia should be utilized to **maintain PaCO<sub>2</sub> at 35-45 mmHg**.
  - EMS services that employ intubation should use ETCO<sub>2</sub> monitors or ventilation counters to maintain a eucarbic state and to avoid rapid ventilation during transport and evaluation.
  - Prophylactic hyperventilation (PaCO<sub>2</sub> < 35 mmHg) is prohibited.
  - Therapeutic hyperventilation may be necessary for brief periods when there is acute neurological deterioration that coincides with a cerebral herniation syndrome or for refractory elevations in ICP (see Tier II section on management of ICP).
  - Advanced cerebral monitoring (brain tissue oxygen monitoring or jugular venous oxygen saturation monitoring) should be employed when extended hyperventilation is utilized.

#### **C. Blood Pressure, Volume Resuscitation, Anemia, and Coagulopathy**

1. **Blood Pressure** – Systolic blood pressure (SBP) and mean arterial pressure (MAP) readings should be recorded from a functioning arterial line when present and from the Non-invasive blood pressure (NIBP) cuff when an arterial line is not present or presumed inaccurate.
  - **A systolic blood pressure (SBP) should be kept between 100 mmHg and 180 mmHg**
  - Recognize that lower blood pressures can represent a “relative” hypotensive state in TBI patients (especially with elevated ICP)
  - Normal Saline Fluid should be used as the initial method of maintaining euvolemia to achieve the target blood pressure.
  - Assessment for transfusion and/or implementation of vasoactive drugs should be considered for treatment of hypotension. Such Vasopressors or Inotrops include Phenylephrine (Neosynephrine), Levophed, Epinephrine, Dobutamine, and Vasopressin.

2. **Euvolemia – The primary target is euvolemia.** Monitoring euvolemia will be per site protocol. In many cases a central venous pressure (CVP) monitor will be placed. A CVP goal of 5-7 mmHg correlates with euvolemia, but should be assessed in the context of the individual patient's clinical picture. CVP or other types of invasive monitoring are recommended in patients with severe TBI requiring ventriculostomy or intubation. The specific tools for assessing euvolemia may be determined per site protocols.
  - Brain-injured patients should be maintained in a euvolemic state with volume replacement of blood products and crystalloid.
  - The initial resuscitation fluid should be normal saline. Hypertonic saline should only be used as a secondary osmotic agent in ICP control (see Section IV Tier 2).
  - Volume resuscitation to achieve euvolemia should NOT be withheld to prevent concerns with cerebral edema.
  - Conversely, hypervolemia should be avoided as it is associated with increased incidence of ARDS in TBI patients.
  - Refer to the section on blood pressure management for the list of acceptable vasopressors and inotropic adjuncts.
  
3. **Anemia - The target is to keep hemoglobin concentration at 8 g/dl or above.** We recognize this is a highly controversial area with limited data for evidence-based guidelines. The target goals were determined by consensus from our national site survey, as well as in discussion with the Clinical Standardization Team. The hemoglobin goal of  $\geq 8$  g/dl should be used to maintain consistency between sites.
  - The hemoglobin concentration (Hgb) of the patient should be maintained at  $\geq 8$  g/dL
  - Blood should be transfused for Hg  $< 8$  g/dL.
  
4. **Coagulation – Coagulation panels should be followed closely.** These target goals were determined by consensus from our national site survey, as well as in discussion with the Clinical Standardization Team. It is acceptable to use a stricter transfusion criteria, such as Platelet count of  $\geq 100 \times 10^3/\text{mm}^3$ .
  - The **Target INR is less than or equal to 1.4 and platelets should be maintained above  $75 \times 10^3 / \text{mm}^3$ .**
  - FFP, Vitamin K, Factor VII, DDAVP, or prothrombin complex concentrate should be administered, as clinically indicated, in order to correct coagulopathy.
  - INR and platelet count should be corrected in anticipation of placement of ventriculostomy, or other intracranial surgery.
  - Platelets should be transfused for a platelet count  $< 75 \times 10^3 / \text{mm}^3$ .

### III. INTRACRANIAL PRESSURE (ICP) MONITORING

**All patients with signs and symptoms of increased intracranial pressure (ICP) and/or GCS  $\leq$  8 should receive a ventriculostomy for ICP monitoring** (unless there is a direct contraindication to invasive monitoring, such as INR  $>1.4$  or platelet count of  $<75 \times 10^3 / \text{mm}^3$ , in which case attempts should be made to correct these parameters in order to place a ventriculostomy).

1. ICP should be monitored in patients with a traumatic brain injury if the GCS is eight or less following initial resuscitation and the admission CT scan of the brain is abnormal (hematomas, contusions, edema or compressed cisterns). **All patients with suspected increased intracranial pressure and GCS  $\leq$  8 should receive a ventriculostomy and/or a ventriculostomy with PbtO<sub>2</sub> monitoring (PbtO<sub>2</sub> monitoring is site specific and not a requirement). Intraparenchymal pressure monitors *without concurrent ventriculostomy* are not recommended as the primary method for ICP monitoring.** A parenchymal ICP monitor may be added to the ventriculostomy according to local protocol. This recommendation is based on the Brain Trauma Foundation Guidelines, the summary of responses to the ProTECT III Clinical Standardization Team national survey, and the consensus of the CST panel.
2. ICP monitoring should additionally be considered for those patients with a normal admission CT scan of the brain if two or more of the following criteria are met:
  - age over 40 years
  - unilateral or bilateral motor posturing
  - systolic blood pressure  $< 100$  mmHg

In addition, **ICP monitoring should be highly considered in all patients undergoing emergent surgical procedures (orthopedic repair, etc) in whom a moderate to severe brain injury is suspected** (GCS 3-12) to guide appropriate intraoperative Cerebral Perfusion Pressure (CPP) management.

3. **A ventriculostomy is the preferred device for monitoring ICP. Increased ICP is defined as  $\geq 20$  mmHg/27.2 cmH<sub>2</sub>O.** See section IV for treatment of increased ICP guidance on Tier Based therapy. See section V for brain tissue oxygen monitoring recommendations if applicable.
4. The preferred method for ICP monitoring and drainage is to leave the ICP device to the transducer for continuous monitoring and to drain only for elevations above the threshold (20 mm/Hg). When ICP is  $\geq 20$ , the drain should be opened and allowed to drain to 10 cmH<sub>2</sub>O, then returned to the transducer. Recurrent elevations and the need for multiple repeat ICP drainage actions should prompt additional therapy to lower the ICP.
5. For the determination of CPP, both the ventriculostomy (ICP) and the arterial line (MAP) would ideally be zeroed at the Foramen of Monroe using the tragus of the ear as a marker. However, because most sites are not currently using this method, the standardized method for ProTECT III is to zero the art line at the left atrium. PLEASE NOTE – when the art line is measured at the left atrium, the actual CPP can be 15-20 mmHg lower than the calculated, depending on the degree of elevation of the patient (e.g. calculated CPP = 60, actual CPP = 45!)
6. Routine ventricular catheter changes, prophylactic antibiotic use, and routine surveillance cultures for ventricular catheters are not recommended.

7. **Cerebral Perfusion Pressure (CPP) of  $\geq 60$ -mmHg should be maintained.** CPP is equal to the mean arterial pressure (MAP) minus the intracranial pressure (ICP). **Neosynephrine infusion or other vasoactive adjuncts** - may be used to improve the CPP in the euvolemic patient in whom measures to decrease intracranial pressure have not been effective. Do not push the CPP greater than 70 mmHg. Spontaneous elevations of CPP greater than 70 mmHg are acceptable and should not be actively lowered.

#### IV. TREATMENT OF INCREASED INTRACRANIAL PRESSURE

**Treatment for intracranial hypertension should be initiated when the ICP  $\geq 20$  mmHg/27.2 cmH<sub>2</sub>O.** A tiered algorithm will be used for increased ICP. Items within a Tier are not necessarily listed in order of completion. The tiers represent increased levels of intensity for the treatment of elevated ICP, and patients should be initiated in Tier I, then staged through Tier 3. Many of these interventions will be occurring simultaneously. If the treatments in a given Tier have not sufficiently lowered the ICP within 120 minutes of implementation, then advancement to the next Tier should be promptly initiated.

A reasonable attempt to employ all the measures in Tier I should occur before moving to Tier II. Some measures will be difficult to achieve (slit ventricles, failed attempts at Ventriculostomy). These cases should be documented. Once in Tier II, 2 of the 3 measures should be employed before moving to Tier III.

---

## MANAGEMENT OF INCREASED INTRACRANIAL PRESSURE

---

### GENERAL RECOMMENDATIONS

- **Ventilation** – Keep O<sub>2</sub> Sat >90, and PaO<sub>2</sub>>100, and PCO<sub>2</sub> = 35-45.
  - **Monitor Systolic BP and MAP** - avoid hypotension, Systolic >100 mmHg.
  - **Normothermia goal <38.3°C**: treat fever with acetaminophen and/or cooling blankets.
  - **Adjust cervical collar** placement if applicable.
  - **Consider repeat CT**: a repeat CT scan of the brain should be considered to rule out the development of a surgical mass or unexpected intracranial lesion.
  - **Craniotomy for surgical lesions**: see outline in section IV.
- 

#### TIER 1

- **Head of patient's bed** to be placed at ≥ 30 degrees.
- **Sedation and analgesia** using recommended agents (propofol, fentanyl, and versed) in intubated patients. Pain relief and sedation are appropriate initial modalities for treatment of intracranial hypertension.
- **Ventriculostomy - extraventricular drain**; drain to 10 cmH<sub>2</sub>O for ICP ≥ 20 mmHg sustained for ≥ 5min. The preferred method for ICP monitoring and drainage is to leave the ICP device to the transducer for continuous monitoring and to drain only for elevations above the threshold (20 mm/Hg). When ICP is ≥ 20, the drain should be opened and allowed to drain to 10 cmH<sub>2</sub>O, then returned to the transducer.
- **Mannitol** – 0.25-1.0g/kg; IV bolus x 1 dose.

*Tier 1 completed within 120 minutes, if ICP ≥ 20 mmHg/27.2 cm H<sub>2</sub>O mmHg proceed to Tier 2.*

---

#### TIER 2

- **HyperOsmolar Therapy**
  - **Mannitol**: intermittent boluses of mannitol (0.25 - 1 gm/kg body weight) should be administered. Attention must be placed upon maintaining a euvolemic state when osmotic diuresis is instituted with mannitol. The serum sodium and osmolality must be assessed frequently (every 6 hr) and additional doses should be held if the serum osmolality exceeds 320 mOsm/L. Maintain a serum OSM <320 mOsm or alternative - Osmolar gap <20. Mannitol may be held if there is evidence of hypovolemia.
  - **Hypertonic saline**: boluses of 3% sodium chloride solution (250 cc over ½ hour) or other concentrations (e.g. 23.4% - 30 cc) may be used. Serum sodium and osmolality must be assessed frequently (every 6 hr) and additional doses should be held if the serum sodium exceeds 160 mEq/L.
- **PCO<sub>2</sub> goal** 30 - 35 mmHg, as long as brain hypoxia is not encountered
- **Neuromuscular paralysis**: pharmacologic paralysis with a continuous infusion of a neuromuscular blocking agent should be employed if the above measures fail to adequately lower the ICP and restore CPP. The infusion should be titrated to maintain at least two twitches (out of a train of four) using a peripheral nerve stimulator. Adequate sedation must be utilized if pharmacologic paralysis is employed.

*Tier II completed within 120 minutes, if ICP ≥ 20 cmH<sub>2</sub>O/mmHg proceed to Tier 3.*

---

#### TIER 3

*(includes potential salvage therapies)*

- **Decompressive hemi-craniectomy or bilateral craniectomy** should only be performed if Tiers 1 and 2 are not sufficient. Procedure per site surgical protocol.
  - **Barbiturate or Propofol (anesthesia dosage) coma**: an induced coma is an option for those patients who have failed to respond to aggressive measures to control malignant intracranial hypertension, however it should only be instituted if a test-dose of barbiturates or Propofol results in a decrease in ICP, thereby identifying the patient as a "responder". Hypotension is a frequent side effect of high dose therapy. Therefore, meticulous volume resuscitation (measured with a PA catheter) should be insured. A neosynephrine infusion may also be required.
- 

#### OTHER

- **Hypothermia**: Hypothermia (<36 °C) is not currently recommended as an early TBI treatment. Hypothermia should be reserved for "rescue" or salvage therapy after reasonable attempts at ICP control from the Tier treatments above have failed.
-

## V. ADDITIONAL CEREBRAL MONITORING

The following cerebral oxygen monitoring techniques are not required as part of the ProTECT™ III protocol. However, if a site is going to employ techniques such as those below, then a formal monitoring and treatment protocol should be employed and consistently applied to ALL eligible TBI patients. Consistent use of these techniques within an institution will prevent potential bias and variability.

- brain tissue oxygen (PbtO<sub>2</sub>) monitors (if used, see parameters in the box below)
- jugular venous saturation monitors
- trans-cranial venous Doppler
- thermal diffusion CBF probes
- Xe CT
- PET
- near infra-red monitors
- cerebral microdialysis

**The following guidelines are submitted for management of brain tissue oxygen tension (PbtO<sub>2</sub>)  
PbtO<sub>2</sub> goal ≥ 15 mmHg**

1. If PbtO<sub>2</sub> < 15 mmHg or changes more than 50% (increase or decrease) then check ABG.
2. Adjust ventilation to maintain PaO<sub>2</sub> of ≥100 mmHg and PaCO<sub>2</sub> of 35-45 mmHg.
3. Continue IVF or IV blood pressure adjuncts to achieve CPP goal of 60-70.
4. Transfuse blood products if Hg concentration is < 8 g/dL.
5. Drain CSF as necessary.
6. Perform FiO<sub>2</sub> challenge every shift to insure probe function (increase FiO<sub>2</sub> to 100% for 20 minutes and record peak PbtO<sub>2</sub> value).

## VI. ADJUNCTIVE MEDICATIONS AND PREVENTION OF COMPLICATIONS

### A. Antiseizure Prophylaxis

Phenytoin has proven efficacy in preventing early post-traumatic seizures in patients with traumatic brain injury. **Phenytoin (or Fosphenytoin) is recommended as seizure prophylaxis in all TBI patients upon admission for 7 days.** Dose to therapeutic level. Stop medication after 7 days if no seizure activity.

Phenytoin (or Fosphenytoin) is the recommended initial drug of choice for seizure prophylaxis in the first seven days, or in any patient demonstrating posttraumatic seizure. Use of Keppra is not recommended for seizure prophylaxis. Multiple drug regimens may be utilized at site discretion for intractable seizure treatment. There is a paucity of data studying the use of Keppra in TBI patients; additionally not all study sites have the Keppra drug on formulary. As such, the recommendation is to use Phenytoin in order to standardize across sites.

**Late therapy (Prophylactic)** is defined as anti-seizure treatment 7 days post trauma in patients who have not had seizure activity. “Prophylactic Therapy” or “Late Therapy” in patients without evidence of prior seizure has not been shown to be effective and may cause harm to the patient, and therefore **should not be employed.**

### B. Glucocorticoids

The use of glucocorticoids is not effective at improving outcome or reducing intracranial hypertension, and should **NOT** be administered.

### C. Stress Ulcer Prophylaxis

Patients with significant traumatic brain injury requiring mechanical ventilation as well as those with coagulopathies or a history of gastric or duodenal ulcers should receive stress ulcer prophylaxis with an intravenous H-2 blocking agent, proton pump inhibitor, or sucralfate.

### D. Deep Venous Thrombosis (DVT) Prophylaxis

All patients with significant traumatic brain injury requiring mechanical ventilation and sedation should receive DVT prophylaxis in the form of sequential compression stockings upon admission. Subcutaneous low-dose heparin may also be initiated within 72 hours of admission, unless contraindicated due to evidence of bleeding, need for surgery, or indwelling intracranial monitor.

### E. Early Tracheostomy

Tracheostomy is recommended in ventilator dependent patients to reduce total days of ET intubation.

## VII. METABOLIC MONITORING

### A. Serum Electrolyte

The baseline goal for electrolytes (such as, sodium) will be to maintain within normal range (Na 135-145 mmol/L). Patients with documented or suspected diabetes insipidus (DI) or syndrome of inappropriate antidiuretic hormone (SIADH) should have frequent (every 6 hr) monitoring of serum sodium and osmolality levels. Aggressive attempts should be made to normalize these values. In the treatment of elevated ICP with HTS, Na goal increases to a target of 145 mmol/L (lower threshold) and 160 mmol/L (upper threshold).

### B. Glucose Monitoring

Hyper- and hypoglycemia are both detrimental to the outcome of patients with TBI. Therefore, serum glucose levels should be monitored in all TBI patients. **The glucose level should be maintained between 80 and 180 mg/dl.** Serum glucose should be monitored frequently following the initiation of nutritional support, particularly in patients with known or suspected diabetes mellitus. In the ICU, initial treatment with regular insulin for hyperglycemia is recommended, with subsequent transition to other patient specific regimens per team.

## VIII. NUTRITIONAL SUPPORT

- 1. Nutritional support should be initiated via gastric or enteral route within 72 hours post injury.** Frequent assessment of residual volumes of gastric nutrition should be performed, as patients with TBI frequently do not tolerate intragastric feeding, and are at risk for emesis and aspiration. Should this occur, efforts should be made to obtain small bowel feeding access.
- 2. TPN should be utilized cautiously in patients with TBI due to the high glucose concentrations of hyperalimentation solutions.** If TPN use is considered unavoidable, monitoring must be done to insure that the patient remains euglycemic.
- 3. Nonparalyzed patients should receive 140% of basal energy (caloric) expenditure. Paralyzed patients should receive 100% of basal energy expenditure. At least 15% of calories should be provided as protein.** An immune enhancing enteral formula should be considered.

**IX. NON-Emergency Surgery:**

Non-Emergent surgeries that require general anesthesia, such as orthopedic procedures and plastic surgery, should be avoided in BOTH moderate and severe TBI patients until it is clear that the brain injury has stabilized or resolved. Single episodes of hypotension induced during surgery can result in rapid deterioration and death.

In the case of Emergency surgeries, priority should be given to maintaining target physiological parameters such as systolic blood pressure  $\geq 100$  mmHg (or higher if ICP is elevated), and oxygenation ( $\text{PaO}_2 \geq 100$  mmHg and Pulse Ox  $\geq 90\%$ ) in all patients suspected of having a TBI. An ICP monitor should be considered in all moderate to severe TBI patients undergoing general anesthesia.

**X. SURGICAL MANAGEMENT OF TBI** (*consistent with Brain Trauma Foundation Guidelines*)**A. Epidural Hematomas**

An epidural hematoma (EDH) of greater than  $30 \text{ cm}^3$  should be surgically removed regardless of GCS. Patients with an acute EDH, GCS  $<9$ , and anisocoria should undergo emergent EDH evacuation. EDH of less than 5 mm midline shift in patients with GCS  $>8$  and no focal neurological deficit can be closely monitored in an ICU with serial CT scans.

**B. Acute Subdural Hematomas**

Acute subdural hematomas (SDH) with a thickness of greater than 10 mm or 5 mm of midline shift on CT scan should be evacuated emergently regardless of the GCS (clinical judgment should be used in patients with significant underlying atrophy). A SDH less than 10 mm thickness and less than 5 mm midline shift should be evacuated emergently if the patient has: GCS decrease by 2 points, asymmetric pupils or fixed pupils, or ICP  $\geq 20$  mmHg.

**C. Subarachnoid Hemorrhage**

All patients with GCS  $<9$  and SAH should have a ventriculostomy inserted.

**D. Parenchymal Lesions**

Intraparenchymal hemorrhage (IPH) causing progressive neurological deterioration, medically refractory ICP elevations, or significant mass effect should be emergently evacuated. Frontal or temporal contusions with IPH  $>20 \text{ cm}^3$  and  $>5$  mm shift or cistern compression in patients with GCS 6-8 should be evacuated. IPH  $>50 \text{ cm}^3$  should be evacuated. IPH in patients with no evidence of neurological change, and ICP  $<20$  mmHg, and no signs of mass effect can be managed non-operatively with intensive monitoring and serial imaging.

**E. Diffuse Medically-Refractory Cerebral Edema and Elevated ICP**

Decompressive craniectomy for refractory elevated ICP (unilateral or bilateral) within 48 hours of injury is an option in TIER 3. Ultra early decompressive craniectomy prior to ICP monitoring is not recommended, unless surgery is performed for a mass occupying lesion (hematoma) and the bone flap is not replaced. The procedure should be applied according to individual center protocol consistently in eligible patients. Other decompressive procedures: subtemporal decompression, temporal lobectomy, and hemispheric decompressive craniectomy are treatment options for refractory increased ICP and diffuse parenchymal injury with signs of impending herniation.

## **F. Posterior Fossa Mass Lesions**

Patients with posterior fossa (PF) lesions that show distortion, dislocation, or obliteration of the 4th ventricle, or compression or loss of visualization of the basal cisterns, or obstructive hydrocephalus on CT should be evacuated. PF lesions that show no evidence of mass effect and no clinical deterioration can be intensively monitored with serial imaging.

## **G. Depressed Skull Fractures**

Open skull fractures depressed greater than the thickness of the inner and outer table should undergo operative management. Open depressed fractures that are less than 1cm depressed *and* have no dural penetration, no significant intracranial hematomas, no frontal sinus involvement, no gross cosmetic deformity, no pneumocephalus, and/or no gross wound contamination may be managed non-operatively. All open skull fractures should be treated with prophylactic IV antibiotics, such as Vancomycin and Ceftriaxone.

## **XI. BRAIN DEATH AND WITHDRAWAL OF CARE**

It is recommended that brain death be determined per the AAN Guidelines. The following information should be documented for all patients:

- Etiology and irreversibility of condition
- Absence of brainstem reflexes
- Absence of motor response to pain
- Absence of respiration with  $PCO_2 \geq 60$  mmHg
- Confirmatory test (if utilized) and result of confirmatory test (angiography, EEG, TCD, Technetium-99 scan, SSEP, etc.)
- Repeat neurologic examination. *Option:* repeat neurological exam per site protocol (6-hour interval is reasonable).

Time and date of determination of brain death should be recorded. Please contact the site Study Coordinator immediately upon determination of brain death to discontinue the study infusion. If the patient will serve as organ donor, please record brain death as above. Participation in study will stop at time of brain death and care may proceed as per local ICU protocols.

Should the patient's family decide to withdraw care, please continue to document patient progress as per study protocols. Please date and time initial decision to withdraw care. Additionally, on each Daily Checklist CRF, note that patient is Withdrawal of Care.