# 

|  |  |
| --- | --- |
| **Policy #:** | Medication Guideline #9.65 |
| **Issued:** | March 2007 |
| **Reviewed:** | 4/2011, 4/2013, 10/2015, 11/2016 |
| **Revised:** | 4/2011, 4/2013, 10/2015, 11/2016 |
| **Section:** | Pharmacy |

Intracranial Pressure (ICP) Management - Adult

## Introduction

Severe brain injury, defined as a Glasgow Coma Score (GCS) < 8, and the subsequent elevation in ICP are challenging problems in the management of critically ill patients.1 Nearly 1.6 million head injuries occur every year in the United States, many of which can lead to an elevation in ICP.2 However, other processes such as intracranial hemorrhage, malignancy, meningo-encephalitis, and severe metabolic derangements may also cause an elevation in ICP.1

Severe brain injury is the result of two distinct phases, primary and secondary brain injury. Following primary brain injury (i.e. head trauma), secondary brain injury may occur resulting in neuronal damage due to the physiologic response from the initial insult.2 Edema and an increase in the ICP may occur secondary to a defect in the blood-brain barrier and an increase in osmolality from the breakdown of cellular structures within the brain.1 The Monro-Kellie principle states that the cranial vault is a fixed space (closed box) comprised of brain tissue, cerebrospinal fluid (CSF), extracellular fluid, and blood.2 Several mechanisms exist to compensate for the elevation in ICP such as shunting CSF to the spinal subarachnoid space, decreasing CSF production, and shunting venous blood out of the skull.1 Once these mechanisms become overwhelmed, an elevation in ICP can occur. This may cause a reduction in cerebral perfusion pressure (CPP) and subsequent cerebral ischemia.

CPP is a derived clinical parameter that is used to predict cerebral blood flow and cerebral oxygenation. CPP is the difference between mean arterial pressure (MAP) and ICP:2, 3

CPP = MAP – ICP

Continuous ICP monitoring can aid in the management of the severely head-injured patient. ICP monitoring is indicated for patients with a GCS < 8 and an abnormal CT scan upon admission. ICP monitoring may be indicated in patients with a normal CT scan if any two of the following are present upon admission: age over 40 years, unilateral or bilateral motor posturing, SBP < 90 mmHg.3

The Brain Trauma Foundation recommends maintaining a CPP > 60 mmHg and initiating treatment when the ICP reaches an upper threshold of 20-25 mm Hg.3 Lowering ICP can be achieved by elevating the head-of-bed >45°, inducing hypothermia, providing pharmacologic sedation, reducing edema (i.e. mannitol or hypertonic saline), CSF drainage, hyperventilation-induced vasoconstriction, and surgical procedures.1

**Figure 1. Initial Management of Severe Brain Injury**

Severe Brain Injury (GCS < 8)

Endotracheal Intubation

[Intracranial Hemorrhage W/](#_Section_F._Correction)

[Coagulopathy?](#_Section_F._Correction)

[Correct Hypotension](#SectionE)

[Oxygenation](#SectionD)

[& Ventilation](#SectionD)

[Herniation?](#SectionF)

[Deterioration?](#SectionF)

Consider [Intracranial Pressure Monitor](#Section G. Intracranial Pressure Monitoring) Placement?

A

G

1. SaO2: > 94%
2. PaO2 > 60 mmHg
3. SpO2 > 90 mmHg

[Pre-Induction Agents](#Section A. Endotracheal Intubation: Pre-Induction Agents)

1. Fentanyl 50-100 mcg IVP
2. Lidocaine100 mg IVP

D

E

* [3% saline](#SectionL) 250 mL IV bolus or [23.4% saline](#SectionL) 30cc IV bolus (given via central line)
* [Mannitol](#SectionL) 0.75-1.5 g/kg IV bolus
* [Hyperventilation](#SectionD) (PaCO2: 30-35 mmHg) for short period
* Neurosurgery?

F

H

1. Normal saline
2. Vasopressors, if indicated

B

1. CPP ≥ 60 mmHg
2. ICP ≤ 20 mmHg

Drug induced?

1. [See reversal guidelines](http://internal.bmc.org/pharmacy/guidelines/mdg_reversal_anticoagulation_oral.pdf)

Acquired? Goals:

1. INR <1.5
2. Platelets >100K

[Induction Agents](#Section B. Endotracheal Intubation: Induction Agents)

1. Etomidate 0.3 mg/kg IVP

C

[Neuromuscular Blocking Agents](#Section C. Endotracheal Intubation: Neuromuscular Blocking Agents)

1. Succinylcholine 1.5mg/kg IVP
2. Rocuronium 1mg/kg IVP
3. Vecuronium 0.1mg/kg IVP

ICU Admission

Q

L

K

J

I

H

[Sedation & Analgesia](#SectionI)

1. Fentanyl 25-100 mcg/hr
2. Propofol 5-50 mcg/kg/min
3. Midazolam 0.02-0.2 mg/kg/hr

[Hypotension?](#SectionG)

Monitor & Table 1 if [PbtO2](#SectionP) monitor

[EVD placement](#SectionJ)

1. CSF drainage

No

[External cooling](#SectionK): Normothermia

(goal 37°C)

Yes

* [Oxygenation](#SectionH)

(SaO2 > 94%)

1. [Ventilation](#SectionH) (PaCO2 35-40 mmHg)

**ICP > 20 mmHg**

**Figure 2. ICU Management of Elevated ICP (without PbtO2 monitoring)**

Yes

No

Yes

P

ICP > 20 mmHg

ICP > 20 mmHg

M

**General ICU care**

1. [Maintain Euvolemia](#SectionOGlycemic)
2. [Maintain Proper Head/Neck Position](#_Maintain_Proper_Head/Neck)
3. [Glycemic Control](#_Glycemic_Control)
4. [Seizure prophylaxis](#SectionOSzProphy) x 7 days with levetiracetam or phenytoin
5. [Treat/prevent hyperthermia](#SectionOHyperthermia)
6. [Stress ulcer prophylaxis](#SectionOSUProphy)
7. [DVT prophylaxis](#SectionODVT) at 48 hrs
8. [Eye care](#SectionOEye)
9. [Bowel preparation](#SectionOBowel)
10. [Nutrition](#SectionONutrition) at 48 hrs
11. HOB > 30°

* [Mannitol](#SectionL) 0.25-1 g/kg IV, may repeat Q3-6 hrs prn *or*
* [HTS](#SectionL) 23.4% 30 mL IV‡, may repeat Q3-6 hrs prn *or*
* 3% [HTS](#SectionL) 250 mL IV Q3-6 hrs prn‡

No

Yes

Fluids (NS50-150 mL/hr‡ or 3% [HTS](#SectionL) 250 mL bolus‡

HGb <7 or

Active major bleeding

ICP > 20 mmHg

Use

Vasopressors

N

[Maximize sedation](#SectionM) (Riker score: 1)

No Yes

Give blood (PRBCs)

ICP > 20 mmHg

N

[NMB](#SectionM) (see [NMB in ICU](http://internal.bmc.org/pharmacy/guidelines/mdg_neuromuscularblocker_icu.pdf) guideline)

ICP > 20 mmHg

Yes

L

O

[External cooling](#SectionK):

Hypothermia

(goal 32-35°C)

[Pentobarbital](#SectionN)

10 mg/kg IV over 1 hr OR

5 mg/kg IV q1 hr x 3 THEN

1-3 mg/kg/hr IV infusion

**CSF: cerebrospinal fluid; CPP: cerebral perfusion pressure; CVP: Central venous pressure; DVT: deep vein thrombosis; EVD: external ventricular drain; HTS: hypertonic saline; ICP: intracranial pressure; LR: Lactated Ringer’s; NMB: neuromuscular blockade; NS: normal saline; pbtO2: brain tissue oxygen); SvO2: mixed venous saturation**

**‡ At the discretion of trauma or neurosurgery or neurocritical care attending**

Decompressive Craniectomy

**TABLE 1:** **ICU Management of Brain Tissue Oxygen and ICP (Section R)**

|  |  |  |
| --- | --- | --- |
| **Pbt02 < 20 mm Hg**  **ICP < 20 mmHg** | **Pbt02 < 20 mm Hg**  **ICP > 20 mm Hg** | **Pbt02 > 20 mm Hg**  **ICP > 20 mm Hg** |
| Administer FiO2 100% x 15 min  ↑ PaCO2 to 40-45 mm Hg range as tolerated, carefully monitor both ICP and Pbt02  Optimize CPP  Administer fluids to euvolemia  Give pRBCs for anemia  Optimize sedation/analgesia  Cooling measures for Brain temp > 37 º C  Consider Head CT  Consider paralytics  Consider barbiturate therapy  (Titrate BIS 10-20 and Suppression Ratio (SR) > 60%) | Drain CSF  Administer FiO2 100% x 15 min  Optimize CPP  Administer fluids to euvolemia  Give pRBCs for anemia  Optimize sedation/analgesia  Administer Mannitol 0.25-1 gm/kg  Administer Hypertonic Saline (3% or 23.4%)  Cooling measures for Brain temp > 37 º C  Consider Head CT  Consider paralytics  ↑ PaCO2 slowly; monitor for ↑ ICP  Consider barbiturate therapy  (Titrate BIS 10-20 and Suppression Ratio (SR) > 60%)  Consider craniectomy | Drain CSF  ↓ PaC02 to ↓ ICP  Administer fluids to euvolemia  Optimize CPP  Optimize sedation/analgesia  Administer Mannitol  0.25-1 g/kg  Administer Hypertonic Saline (3% or 23.4%)  Cooling measures for Brain temp > 37 º C  Consider Head CT  Consider paralytics  Consider barbiturate therapy  (Titrate BIS 10-20 and Suppression Ratio (SR) > 60%)  Consider craniectomy |

# Initial Management of Elevated ICP

# Section A. Endotracheal Intubation: Pre-Induction Agents

**Rationale & Recommendation:** Endotracheal intubation is associated with increased sympathetic discharge resulting in hypertension and tachycardia. Fentanyl, when used as a pre-induction agent, reduces the hypertensive response following intubation.4 Lidocaine may be used to blunt the catecholamine response seen with intubation and prevent elevations in ICP. These agents should be given 2-5 minutes prior to intubation.

# Section B. Endotracheal Intubation: Induction Agents

**Rationale & Recommendation:** Induction agents such as etomidate are used to facilitate endotracheal intubation by providing immediate unconsciousness. Etomidate has a rapid onset, short duration of action, and does not cause hypotension.4 This agent should be given 1 minute prior to intubation

# Section C. Endotracheal Intubation: Neuromuscular Blocking Agents

**Rationale & Recommendation:** NMBAs facilitate endotracheal intubation by causing relaxation of the skeletal muscle. Succinylcholine, a depolarizing NMBA, has a rapid onset and short duration of action. Succinylcholine is contraindicated in patients with a personal or family history of malignant hyperthermia, burn, or crush injury, personal history of myopathy, serum potassium > 5.5mEq/L)4 Rocuronium and vecuronium, both non-depolarizing NMBAs, may also be used. These agents have a rapid onset, but a longer duration of action than succinylcholine. Succinylcholine and rocuronium should be given 1 minute before intubation and vecuronium should be given 3-5 minutes prior to intubation.

## Section D. Oxygenation & Ventilation

**Rationale:** In patients with severe head injury, hypoxemia can propagate secondary brain injury. Adequate oxygenation (SaO2 > 94%) must be maintained at all times during both the initial management and ICU care of these patients.3, 5 Hyperventilation is thought to lower ICP by causing cerebral vasoconstriction, thereby reducing cerebral blood flow (CBF) and cerebral blood volume (CBV). However, reducing CBF below a critical threshold by hyperventilation may further compromise perfusion to already ischemic regions of the brain. Thus, aggressive hyperventilation (PaCO2 < 35 mmHg) should be avoided.3 Hyperventilation should be limited to life threatening situations (herniation) for preferably less than 20 minutes as a temporizing measure only.

**Recommendation:**

1. Maintain SaO2 > 94%, PaO2 > 60 mm Hg
2. Maintain PaCO2 35-40 mmHg

# Section E. Correct Arterial Hypotension

**Rationale:** Hypotension is one of the five most powerful predictors of outcome. A single hypotensive episode (systolic blood pressure [SBP] < 90 mmHg) is associated with increased morbidity and mortality. The goal is to maintain SBP > 90 mmHg in an attempt to maintain a CPP of ≥ 60 mmHg.3 Hypotonic solutions should not be used because they may worsen cerebral edema.2

**Recommendations:**

1. Use 0.9% normal saline (preferred) or Lactated Ringer’s or blood products if volume resuscitation is indicated
2. Maintain SBP > 90 mmHg and CPP ≥ 60 mmHg

* May use vasopressors (phenylephrine, norepinephrine) if indicated

1. Consult neurosurgery or neurocritical care for patient-specific hemodynamic parameters

# Section F. Correction of Coagulopathies

**Rationale:** Pre injury use of warfarin and presumably target specific oral anticoagulants is associated with a higher mortality especially when admission INR is > 4. 46  Patients with a TBI induced intracranial hemorrhage need rapid identification and correction of medication induced coagulopathies to help decrease hemorrhage size.47

**Recommendation**:

1. Reverse medication induced coagulopathies using appropriate products including: Kcentera, Fresh Frozen Plasma and Vitamin K
   1. For specific recommendations see anticoagulation reversal guidelines
2. Acquired coagulopathies: Correct used Fresh Frozen Plasma, Platelets and additional products as clinically appropriate.

## Section G. Herniation or Deterioration?

**Rationale:** If an ICP monitor has not yet been placed, Mannitol is indicated if there are clinical signs of herniation or neurologic deterioration, such as Cushing response (severe hypertension, bradycardia, apnea), fixed midposition or dilated pupil(s), posturing. Mannitol should be given only in the presence of adequate volume resuscitation.3 Hypertonic Saline may expand plasma volume and be more useful than Mannitol in hypotensive patients.

**Recommendation**:

1. 3% Saline (HTS) 250 mL IV bolus

* May repeat q3-6hrs for herniation or ICP>20mmHg
* See Section N for more complete instructions on the dosing, monitoring, and administration of 3% HTS

1. Mannitol 0.75-1.5 g/kg IV push

* May repeat 0.25 g-1g/kg q3-6hrs as needed for herniation or ICP >20 mm Hg
* See Section N for more complete instructions on the dosing, monitoring, and administration of mannitol

1. 23.4% HTS 30 mL IV bolus

* May repeat q3-6hrs for herniation or ICP>20mmHg
  + See Section N for more complete instructions on the dosing, monitoring, and administration of 23.4% HTS

1. In an acute setting, may hyperventilate the patient to a PaCO2 of no less than 25 mmHg for a short period of time only (preferably less than 20 minutes). Thereafter, allow PaCO2 to rise slowly over 1-2 hours to avoid rebound intracranial hypertension.
2. Consult neurosurgery STAT regarding potential surgical treatment such as hematoma evacuation, craniectomy, or external ventricular drain placement

## Section H. Intracranial Pressure Monitoring

**Rationale:** Cerebral perfusion pressures < 50 mmHg and intracranial pressures > 20 mmHg are associated with poor outcome.5 ICP monitoring is the only reliable way to measure ICP and calculate CPP to ensure these parameters stay within goal ranges. ICP monitors also allow for improved neuromonitoring when physical exam is suboptimal.

**Recommendation:**

* 1. ICP monitors should be considered in salvageable traumatic brain injury (TBI) patients if the GCS is 3-8 after resuscitation and the admission CT scan of the brain is abnormal (hematomas, contusions, edema or compressed cisterns).
  2. ICP monitors may also be considered in patients with a normal admission CT scan if two or more of the following criteria are meet: age ≥ 40, unilateral or bilateral motor posturing, systolic blood pressure < 100 mmHg.6
  3. The type of monitor utilized is at the discretion of the neurosurgery service. See the following policy form more information regarding intracranial pressure monitoring.
* 14.11 Intracranial Pressure Monitoring

### ICU Management of Elevated ICP

Indication: If ICP is >20mmHg without sustained rises above 30 mmHg or clinical signs of herniation

Ensure that all prophylactic measures from Section Q on General ICU Care are fully implemented.

# Section I. Correct Arterial Hypotension

**Rationale:** As stated in section E a single hypotensive episode (systolic blood pressure [SBP] < 90 mmHg) is associated with increased morbidity and mortality. The goal is to maintain SBP > 90 mmHg in an attempt to maintain a CPP of 60-80 mmHg.3

**Recommendation:**

1. Fluids – indicated for hypotensive patients (SBP < 90 mmHg) with hypovolemia indicated by; elevated lactate (>2 mmol/L), decreased urine output (<0.5 ml/kg/hr),SVV >15, or bedside ultrasound evaluating IVC collapsibility (Normal saline preferred. Avoid hypotonic fluids which can worsen cerebral edema.)
2. Packed red blood cells – indicated for patients with a HGb < 7 mg/dL or hypotensive patients (SBP < 90 mmHg) with active major bleeding or symptoms of anemia
3. Vasopressors – indicated for patients adequately resuscitated, via A and B above, who remain hypotensive (SBP < 90 mmHg).

## Section J. Oxygenation & Ventilation

**Rationale:** Maintaining adequate oxygenation in the ICU is essential to prevent cerebral ischemia and subsequent secondary brain injury in patients with elevated ICP.3 Hypoventilation and the consequent rise in PaCO2 cause intracranial vasodilation which can significantly raise the ICP in patients with compromised intracranial compliance. Conversely, hyperventilation can cause cerebral vasoconstriction and a reduction in CBF, thereby reducing CBV and ICP. Reducing CBF below a critical threshold may further compromise perfusion to already ischemic regions of the brain. Prophylactic, slight hyperventilation is not recommended in all patients, particularly within the first 24 hours of hospital management. Even beyond 24 hours, some data suggests that slight hyperventilation (~30 mmHg) increases ischemic brain volume and reduces regional cerebral oxygen metabolism despite a marked increase in oxygen extraction.7 The long-term neurological and cognitive outcomes of these observations remain unknown. Nonetheless, this suggests that hyperventilation should be reserved for clear instances of sustained, moderate or severe intracranial hypertension.

**Recommendation:**

1. Maintain SaO2 > 94% and PaO2 >60 mmHg (preferably >80 mmHg)
2. Maintain PaCO2 35-40 mmHg

## Section K. Sedation & Analgesia

**Rationale:** Agitation is a common ICU problem that may result in sympathetic hyperactivity causing tachycardia, tachypnea, diaphoresis, and increased posturing. In patients with severe head injury and elevated ICP where cerebral oxygen supply is already compromised, any increase in cerebral oxygen metabolism may have deleterious consequences. Propofol, the sedative of choice when frequent neurological examinations are necessary, has been shown to independently decrease ICP, CBF, and cerebral metabolism in head injury patients.8 Additionally, fentanyl should be added for acute pain control.

**Recommendation:**

1. Propofol 5-60 mcg/kg/min IV continuous infusion

* Titrate to a Riker score of 1-2
* Monitoring
  + - Hypotension and bradycardia
    - Pancreatitis
    - Hypertriglyceridemia – obtain baseline triglyceride level and every 3-5 days thereafter
    - Propofol-related infusion syndrome – cardiac arrhythmias, metabolic acidosis, rhabdomyolysis (Infusion rates higher than 65 mcg/kg/min (4mg/kg/hr) administered for longer than 48 hrs are associated with this syndrome and should be avoided)9

1. Fentanyl 25-200 mcg/hr IV continuous infusion in all patients with traumatic brain injury
   * Titrate to a Riker score of 1-2
   * Monitoring: Constipation and delayed gastric emptying in patients receiving enteral nutrition
2. Benzodiazepines may be used if there are contraindications to or intolerance of propofol or if recommended doses above are inadequate
   * Midazolam 0.05-0.2 mg/kg/h IV continuous infusion
   * Lorazepam 1-4 mg IV bolus q4-6 hrs prn
3. Please see the Sedation and Acute Pain Control in the ICU medication guideline for more information

## Section L. Drainage of CSF Through an external Ventricular Drain

**Rationale:** Drainage of CSF decreases intracranial volume, thereby decreasing ICP. This can be done continuously (i.e. by leaving the drainage valve open while raised to a specified height relative to the external auditory canal) or intermittently as needed for episodes of intracranial hypertension.

#### Prophylactic Antibiotics for Ventriculostomy

There are no randomized, controlled trials evaluating the effect of prophylactic antibiotics on reducing the rate of infections in patients with a ventriculostomy. Only small, observational studies have shown a reduction in infection rates when prophylactic antibiotics were part of a larger practice guideline aimed at minimizing infectious complications.10

**Recommendation:**

1. For episodes of elevated ICP not responsive to sedation and osmotherapy, consider drainage of CSF with an external ventricular drain.
2. See the following policies and procedures for more information regarding the use and management of a ventriculostomy catheter for the monitoring of ICP:

* 14.11 Intracranial Pressure Monitoring
* 10.2.01 Ventriculostomy/External Cerebrospinal Fluid Drainage System

1. Prophylactic antibiotic initiation may be warranted in certain clinical situations, per discretion of critical care, neurocritical care. and neurosurgery service

## Section M. Prevention of Hyperthermia & External Cooling

**Rationale:** Fever is common in patients with acute neurologic illness and is an independent predictor of poor outcome.11 Avoiding hyperthermia protects against secondary ischemic insult by decreasing oxygen consumption and ICP. For each 1°C drop in temperature, the cerebral metabolic rate of oxygen drops by 6-7%. Therefore it is recommended to keep temperature < 38°C or < 38.5°C (internal) to prevent the exacerbation of preexisting hypoxia and damage.

**Normothermia Recommendations:**

1. Acetaminophen 650 mg Q 4 hours (Max 4000 mg/day)
2. If fever persists > 38.5°C consider culturing the patients and adding Arctic Sun surface cooling device to cool the patient to 37°C.
3. If cooling is initiated, interventions to prevent shivering should be utilized and medications to treat shivering may be necessary. Shivering causes an elevation in metabolic rate and oxygen consumption, which can increase ICPs, decrease PbtO2,12 and potentially worsen outcomes.
   * Shivering should be monitored and documented every hour using the Bedside Shivering Assessment Scale (BSAS)

0 = No Shivering

1 = Mild: Shivering localized to neck/thorax, may only be slight ECG artifact or felt by palpation

2 = Moderate: Intermittent involvement of upper extremities

3 = Severe: Generalized shivering or sustained upper/lower extremity shivering

* + Shivering should be prevented through the following interventions
    - Surface counter warming (Bair hugger set to 43°C) 13,14
    - Buspirone 20 mg q8h14-16
    - Magnesium repletion to obtain a magnesium level of 2.5-3.5 mg/dL (use with caution patients receiving neuromuscular blocking agents)14,17
      * Check serum magnesium concentrations every 8 hours
    - Adequate analgesia/sedation
* Pharmacologic options to treat shivering include
  + Meperidine 50 mg q6h prn (avoid in patients with recent seizures or renal failure)14,15
  + Maximize sedation in intubated patients
    - Consider utilizing/adding propofol for sedation (may decrease the shivering threshold)18
  + Neuromuscular blockade in intubated, maximally sedated patients (See Neuromuscular Blocker Use in the ICU)

Inducing hypothermia (33-36°C) in human clinical trials has not consistently been shown to improve outcomes but may be used to lower ICP. 19

**Hypothermia Recommendations:**

1. If ICP remains elevated >20 mmHg despite induced normothermia, sedation, and osmotherapy, then induced hypothermia (32-35°C) may be considered
2. In hypothermia patients, shivering should be avoided through counter current warming, maximizing sedation or adding a neuromuscular blocker (See Neuromuscular Blocker Use in the ICU)

**Section N. Mannitol & Hypertonic Saline (HTS)**

**Rationale:** Cerebral edema following primary brain injury is a result of the disruption in the blood-brain barrier (BBB) and a marked increase in osmolality due to a breakdown of cellular structures.1 Osmotic agents such as mannitol and HTS can be used to reduce cerebral edema and thus, decrease ICP. In addition to its osmotic effects, HTS has vasoregulatory, immunomodulatory, and neurochemical effects when used in severe head injury.20,21 There is some data to suggest that HTS lowers ICP greater than mannitol and has a longer duration of action.23 Due to a lower affinity for crossing the BBB when compared to mannitol, HTS may not cause a rebound increase in ICP after discontinuation following prolonged use. Although not substantiated by any case reports, HTS carries the risk of causing central pontine myelinolysis if the serum sodium increases by more than 10-20 mEq/L in 24 hours.20,21

When monitoring mannitol use, serum osmolality >325 mOsm and an osmolal gap >15 can be used as indicators to hold Mannitol administration due to the concern for inadequate clearance of mannitol and potential higher risk of acute renal failure. The osmolal gap may correlates with mannitol serum concentrations better than serum osmolality, and may indicate sufficient clearance for a new mannitol dose.22 Osmolal gap is calculated by subtracting the calculated serum osmolality from the measured serum osmolality. The following formula is typically used to calculate osmolality:

Calculated Osmolality = (2 \* Serum Na) + (Serum Glucose/18) + (Serum BUN/2.8)

Osmolal Gap = Measured Serum Osmolality – Calculated Osmolality

**Recommendations:**

1. 3% HTS 250 mL IV bolus every 3-6 hours for ICP > 20 mmHg
   * Infuse via **CENTRAL LINE or IO device** over 20-30 minutes
     + In an emergency, a dose of 3% HTS may be administered via a peripheral line while a central line is obtained.
   * Supplied in 500 mL bags
   * May consider 5 mL/kg dosing of 3% HTS (up to 500 mL per dose) for patients refractory to lower doses
   * Monitoring

* Continuous ICP monitoring – goal < 20 mmHg
* Measure serum sodium every 3-6 hours – goal < 155 mEq/L

1. 23.4% HTS 30 mL IV q3-6 hrs for ICP > 20 mmHg
   * Infuse over 15-30 minutes via **CENTRAL LINE only**
   * Supplied as 30 mL of 23.4% HTS undiluted in a 50 mL or 100 mL via flex bag
   * May consider 0.65 mL/kg dosing of 23.4% HTS (up to 60 mL per dose) for patients refractory to lower doses
   * Monitoring

* Continuous ICP monitoring – goal < 20 mmHg
* Serum sodium every 3-6 hours – goal < 155 mEq/L (i.e. hold if serum sodium > 154)
* Central pontine myelinolysis – although not substantiated by case reports, do not increase serum sodium more than 10-20 mEq/L in 24 hours
* Nursing instructions
* Prime the line using normal saline to avoid wasting any HTS
* Hang the bag of HTS and infuse over 15-30 minutes via a central line only
* After the infusion of HTS has been completed, infuse normal saline at a rate of 60 mL/hr for 20-30 minutes to ensure that the HTS has been completely flushed from the line

1. Mannitol 0.25-1 g/kg IV every 3-6 hours for ICP > 20 mmHg
   * Infuse over 15-30 minutes via peripheral or central line with a 0.22 micron filter
   * Supplied as (20%)100 g/500 mL bag
   * Inspect solution for crystals before use
   * See IV Administration Table for more information
   * Monitoring

* Continuous ICP monitoring – goal < 20 mmHg
* Hypovolemia
  + Consider replacing output on a 1:1 basis with normal saline or lactated ringers.
* Measure serum osmolality prior to each dose – goal serum osmolality < 325 mOsm and osmolal gap <15 (i.e. would hold mannitol dose if serum osmolality >325 or osmolal gap >15, unless advised otherwise by neurocritical care or neurosurgery)
* Serum sodium, potassium, BUN and glucose every 3-6 hours
* Central venous pressure every 2 hours
* Serum creatinine and BUN every day

1. 3% HTS IV continuous infusion at a rate of 50 to 150 mL/hr for ICP > 20 mmHg
   * Bolus doses may have a great reduction in ICP and are considered first line. Continuous HTS for ICP management should be used with Neuro Critical Care or Neurosurgery involvement.
   * Infuse via **CENTRAL LINE**
   * Supplied in 500 mL bags
   * Monitoring

* Continuous ICP monitoring – goal < 20 mmHg
* Measure serum osmolality prior to each dose – goal serum osmolality < 325 mOsm
* Serum sodium every 3-6 hours – goal < 155 mEq/L (i.e. hold if serum sodium >154 mEq/L)

# Caution with use > 24 hours

# Section O. Neuromuscular Blockade

**Rationale:** After mannitol and HTS have been exhausted and/or are no longer effective for reducing ICP, and sedation and temperature control have been maximized, NMBAs may be used. However, osmotherapy may still be given. NMBAs may be beneficial in attenuating intractable elevated ICP by preventing skeletal muscle contraction, thereby reducing energy expenditure and oxygen consumption. Since NMBAs have NO sedative or analgesic properties, it is imperative that sedation be maximized to a Riker score of 1 prior to initiating therapy. **Intermittent bolus dosing is preferred over a continuous infusion to reduce the risk of prolonged paralysis and potentially devastating myopathies.**

**Recommendation:**

1. See the Neuromuscular Blocker Use in the ICU medication guideline for more extensive information on the selection, dosing, and monitoring of NMBAs

**Section P: Pentobarbital Coma**

**Rationale:** Barbiturate coma may be considered in hemodynamically stable patients with refractory ICP. There are no randomized controlled trials assessing the effects on outcomes. Barbiturates decrease the metabolic requirements of the brain by decreasing cerebral blood flow requirements and subsequently reducing CBV and ICP.3,6,24

**Recommendations:**

1. Loading dose:
   * Low dose: 5-10 mg/kg IVPB over 1-2 hours, based on actual body weight (ABW)
   * High dose: 25-30 mg/kg ABW IVPB over 3 hours
   * *Do not administer faster than 50 mg/min*
   * Wean all other sedatives once pentobarbital loading is complete
     1. Pentobarbital has no effect on pain threshold, continue analgesia
2. Maintenance dose: 1-3 mg/kg/hr continuous infusion
3. Breakthrough dosing: 100-200 mg IVP Q 30 min prn ICP > 20 mmHg or breakthrough observed on EEG monitor
4. Monitoring

* Continuous ICP monitoring with a goal ICP < 20 mmHg
* Maintain burst suppression on EEG monitor
* EEG pattern of burst suppression correlates well with observed maximal reductions in cerebral metabolic rate of oxygen
* Observation is dose-dependent & therefore a more reliable marker for monitoring the efficacy of a pentobarbital infusion (BTG)
* Monitor cardiac status
* Hypotension frequently occurs and may require concomitant vasopressor use
* Serum pentobarbital levels do not correlate with clinical outcomes and toxicity
* Do not use to titrate dosing
* Pentobarbital contains propylene glycol. Monitor osmol gap if there is prolonged use or if the patient is receiving a concomitant lorazepam continuous infusion.

1. Supportive Care

* Eye Care (see General ICU Care)
* Bowel Regimen (see General ICU Care)
* Aggressive pulmonary toilet as cough reflex may be impaired with pentobarbital use
* Nutrition
* Patients in a pentobarbital coma can be fed enterally use a gastric tube. Intolerance is common and often refractory to prokinetic agents. Considerplacement of a post-pyloric feeding tube.25,48
* Consult nutrition support team
* Please see the Nutrition Section for further recommendations

1. The decision to initiate pentobarbital for intractable elevated ICP should be made between the critical care attending, neurocritical care attending, and the neurosurgery service

# Section Q. General ICU Care

# [Maintain Euvolemia](#SectionOGlycemic)

Rationale:Patients with TBI are at risk for intravascular hypovolemia from a number of causes, including hemorrhage, insensible losses from fever and hyperventilation, and third-spacing. It is important to avoid this because of the aforementioned profound adverse effect of hypotension on outcomes in these patients. On the other hand, overly aggressive fluid administration is associated with complications such as increased days on mechanical ventilation and in the ICU.26 Finally, hypotonic solutions should be strictly avoided in patients with TBI as they may increase cerebral edema.

# Recommendation:

1. Fluid and blood product management for hypotension as per Section G above
2. Maintenance fluids: normal saline 1-1.5 ml/kg/h
3. Assessing euvolemia:
   * Goal SVV <15 (or CVP 8-12 mmHg)
   * Goal urine output ≥0.5 ml/kg/h
   * Evaluate for normalization of Lactate (<2)
   * Evaluation of IVC collapsibility by bedside ultrasound

# [Maintain Proper Head/Neck Position](#_Maintain_Proper_Head/Neck)

# Rationale: ICP may rise in patients with compromised intracranial compliance if the head is not raised above the level of the rest of the body.27 This also decreases risk of aspiration pneumonia in intubated patients.28 Compromised venous outflow from the intracranial space can lead to elevated ICP and be caused by excessive neck rotation, flexion, or rotation or direct neck vein compression.29

# Recommendation:

# Maintain head of bed elevated 30 degrees

# Maintain neutral anatomic head and neck positioning

# Avoid compression of neck with overly tight cervical collar or endotracheal tube ties

# [Glycemic Control](#_Glycemic_Control)

**Rationale:** The stress response and subsequent increase in circulating catecholamines following severe brain injury may cause hyperglycemia. In trauma patients, particularly those with head injury, hyperglycemia is a predictor of poor outcome.30,31 Conversely, some evidence also suggests that hypoglycemia may worsen neuronal injury and functional outcome after TBI. 32,33

**Recommendation:**

1. Initiate intravenous continuous insulin therapy in patients with two consecutive blood glucose values > 180 mg/dL with a goal blood glucose of 120-180 mg/dL

* Use the “Insulin Infusion-Critical Care” order set protocol built into Sunrise Clinical Manager
* Titrate the infusion according Critical Care insulin infusion order set.
* While on a continuous insulin infusion, attempts should be made to minimize the amount of intravenous dextrose a patient receives to prevent worsening cerebral edema

# Seizure Prophylaxis

**Rationale:** Post-traumatic seizures (PTS) occur in up to 20% of head-injured patients and are classified as either early (within 7 days of injury) or late (after 7 days of injury).1 When used for seizure prophylaxis, phenytoin has been shown to reduce the risk of early PTS when compared to placebo. However, AEDs do NOT reduce the risk of late PTS and should not be used as prophylaxis beyond 7 days from the initial injury.3, 34, 35  Fosphenytoin is a prodrug of phenytoin that does not require propylene glycol solvent. It is therefore associated with lower likelihood of injection site reactions (purple hand syndrome) and episodes of hypotension than phenytoin while maintaining equal anti-seizure efficacy. Levetiracetam when compared to phenytoin has; less protein binding, renal clearance, resulting in a liner kinetic profile it also has; a lower side effect profile, minimal monitoring and potentially improved long term outcomes. Levetiracetam has growing data supporting its efficacy in early onset PTS when compared the phenytoin36,37,45 and may be used interchangeable based on patient characteristics and provider preference.

**Recommendation:**

1. Fosphenytoin or phenytoin:
   1. Loading dose: 15-20 mg/kg IV dose for head-injury patients at high risk for PTS38
   2. Phenytoin 5-7 mg/kg/day (based on ideal body weight) IV maintenance dose for 7 days
      1. Begin maintenance dose 4 hours after loading dose, provided 2-hour post-load level is within the therapeutic range
   3. Monitoring
      1. Therapeutic range: 10-20 mcg/mL (1-2 mcg/mL free phenytoin level)
      2. Draw a level 2 hours after the loading dose
      3. Levels should be monitored 1-2 times over the course of 7 days
   4. Please see the Diphenylhydantoin Therapy medication guideline for more information on dosing, monitoring, and interpreting levels
2. Levetiracetam
   1. Loading dose 1000 - 2000 mg IV or PO/NG
   2. Maintenance dose 500 mg PO q12h for 7 days
      1. CrCl < 30ml/min 250 mg PO q12h
      2. HD patients 500 mg daily after dialysis
      3. Consult pharmacist for aid in dosing patients with PD or on CRRT
   3. Monitoring:
      1. Levels are not readily available or typically useful
      2. Scr and BUN every 48 -72 hours while on therapy

## Hyperthermia

See Section M. Prevention of Hyperthermia & External Cooling

## Stress Ulcer Prophylaxis

**Rationale:** Stress-related mucosal damage (SRMD) is common following traumatic brain injury. Maintaining adequate perfusion through aggressive fluid resuscitation is the key to preventing SRMD.39

**Recommendation:**

1. Famotidine (an H2 antagonist) 20 mg bid is recommended as first line therapy
2. Proton pump inhibitors (pantoprazole or lansoprazole) may be considered in patients taking these medications as outpatients

# DVT Prophylaxis

**Rationale:** The incidence of DVT in neurosurgery patients is approximately 22%. However, the benefits of pharmacologic thromboprophylaxis must be carefully balanced against the risk for intracranial bleeding. Head injury without overt hemorrhage is NOT a contraindication to pharmacologic thromboprophylaxis.40 No difference in the incidence of intracranial bleeding was found when UFH was started within 72 hours of severe head injury compared to beyond 72 hours.41

**Recommendation:**

1. Intermittent pneumatic compression boots should be placed on all patients upon admission unless contraindicated
2. UFH 5,000 units sq tid, or Enoxaparin 30 mg twice daily42
3. Pharmacologic thromboprophylaxis can be safely commenced within 48 hours of head injury
4. See the VTE Prophylaxis and Treatment medication guideline for more information
5. Please consult neurosurgery for when to safely initiate thromboprophylaxis

## Eye Care

**Rationale:** Impaired eyelid closure and loss of corneal reflex often occurs in paralyzed or heavily sedated patients. When the cornea is exposed, the eye is at risk for serious complications including infection, corneal ulceration, and loss of vision.

**Recommendation:**

1. Apply an ophthalmic lubricantQID

## Bowel Preparation

**Rationale:** Care should be taken to ensure that all patients with TBI, particularly those in a pentobarbital coma or receiving opioids for analgesia have regular bowel movements. All patients in a pentobarbital coma must have scheduled bowel regimens to ensure regular bowel movements.

**Recommendation:** The following should be ordered for all patients in a pentobarbital coma and should be considered in patients receiving scheduled doses of opiates for sedation:

1. Senna 374 mg PO/PT qhs
2. Docusate sodium 100 mg PO/PT bid
3. Bisacodyl 10 mg PR daily
4. Monitor for every 24-48 hour bowel movements

* If no bowel movement after 72 hours, give magnesium citrate 300 mL PO/PT x 1

## 

## Nutrition

**Rationale:** Initiation of adequate nutritional support can impact neurologic recovery following TBI. Activation of the sympathetic nervous system following traumatic brain injury results in a hypermetabolic and catabolic state. In addition, there is an inverse correlation between GCS and energy expenditure.25 Early enteral nutrition is the preferred route because it maintains the integrity of the gastrointestinal mucosa, attenuates the metabolic response to stress and has been shown to decrease mortality rate if given within 7 days. Patients with a TBI may experience delayed gastric emptying with risk of aspiration and feeding intolerance, therefore, duodenal or jejunal access may be required for reliable absorption.25

**Recommendation:**

* 1. Obtain nutrition support consult within 24 hours of admission.
  2. Initial feeding may be done through an OG or NG tube. If longer term feeding is needed consider establishing enteral access by placing small bore feeding tube.
  3. Initiate enteral nutrition as soon as possible (within 24 hours of admission)
* Utilize a more calorie dense (1.2-1.5 Kcal/ml) tube feed product to prevent excessive free water administration
  1. Stabilized severe TBI/ICP patients including those in a pentobarbital coma may benefit from metabolic cart monitoring. Patient selection and timing of monitoring should be coordinated with clinical nutrition support.
  2. Protein should be at least 15% of calories for patients with a TBI or in a pentobarbital-induced coma
  3. Monitor for feed intolerance (vomiting, abdominal distention). Patients not tolerating tube feeds may benefit from transpyloric placement.
  4. Use smallest amount of water for medication administration via tube.
  5. Routine flushes are not necessary for most continuous tube feeds. See nutrition recommendations for flush requirements.
  6. HOB > 30° if clinically appropriate

**SECTION R. BRAIN TISSUE OXYGEN (PbtO2) MONITORING**

**Rationale:** Continuous PbtO2 monitoring may be used in some patients in conjunction with ICP monitoring. Studies have shown that low PbtO2 can be associated with worse outcome and can occur even when the ICP is normal.43 Treating low PbtO2 may be associated with better outcome.44 Measures such as increasing FiO2, increasing CVP, and slowly increasing paCO2 can be utilized to improve PbtO2. The goal of therapy is to keep PbtO2 > 20 mmHg and ICP <20 mmHg.

**Recommendation:**

**General Guidelines for PbtO2-directed Therapy:**

**GOAL = PbtO2 >20 mm Hg and ICP <20 mm Hg**

* Decrease ICP
* Increase CPP (fluid resuscitation, pressors)
* O2 challenge (100% FiO2 for few mins)
* Pulmonary/ventilator causes evaluated
  + Auscultate chest
  + Check ABG, chest Xray
  + Suction
  + Maximize pulmonary toilet, chest physiotherapy, percussion/vibration bed, turning
* ?Increased metabolic demand🡪treat fever, seizures, pain
  + If temp > 37 º C, could use acetaminophen and/or surface cooling or intravascular cooling device **(Section M)**
  + If seizures suspected, obtain EEG
  + Sedation and Analgesia (**Section K)**
* Consider PRBC transfusion to keep Hgb>10mg/dl
* Consider Head CT to eval if monitor is in contused tissue or new bleed
* Consider Head CTA or CT perfusion or TCDs if cerebral vasospasm suspected

**SCENARIOS 1-3 (Summarized on Table 1):**

**1. Pbt02 < 20 mm Hg and ICP < 20 mmHg**

* Administer FiO2 100% x 15 min to check catheter function
* ↑ PaCO2 slowly to 40-45 mm Hg range as tolerated, carefully monitor both ICP and Pbt02
* Optimize the CPP
* Administer fluids to euvolemia (watch for signs and symptoms of fluids overload🡪 E.g. Check I/O, CVP, PCWP, and chest X-ray)
* Give blood products for anemia
* Optimize sedation/analgesia (**Section K**)
* Cooling measures for Brain Temp > 37 º C **(Section M)**
* Consider Head CT to evaluate if monitor is in contused tissue or new bleed
* Consider paralytics particularly if shivering or problems with ventilation **(Section N)**
* Consider barbiturate therapy (May use Bispectral Index (BIS) monitor and titrate BIS to 10-20 and Suppression Ratio (SR) > 60%) **(Section P)**

**2. Pbt02 < 20 mm Hg and ICP > 20 mm Hg**

* Consider drain CSF **(Section L)**
* Administer FiO2 100% x 15 min to check PBtO2 catheter function
* Optimize CPP (goal >60 and may need to be higher based on PbtO2)
  + Administer fluids to euvolemia, watching fluid volume closely
    - Give IV NS to increase CVP (goal 5-10) or PCWP (goal 10-15)
  + Give pRBCs if anemic (i.e. Hgb ≤ 10mg/dl)
  + Vasopressors if euvolemic and not anemic
* Optimize sedation/analgesia **(Section K)**
* Administer mannitol 0.25-1.0 gm/kg IV q4hr prn **(Section N)**
* Administer Hypertonic Saline 3% NaCl 250 mL bolus or 23.4% NaCl 30 mL bolus IV q4hr prn **(Section N)**
* Cooling measures for Brain Temp > 37 º C **(Section M)**
* Consider Head CT to evaluate if monitor is in contused tissue or new bleed
* Consider paralytics particularly if shivering or problems with ventilation **(Section O)**
* ↑ PaCO2 slowly by decreasing minute ventilation; monitor for ↑ ICP
  + Do not decrease rate on vent by more than one breath at a time
  + Monitor end tidal CO2
* Consider barbiturate therapy (May use BIS monitor and titrate BIS to 10-20 and Suppression Ratio (SR) > 60% or use EEG to keep >60% suppressed) **(Section P)**
* Consider craniectomy

**3. Pbt02 > 20 mm Hg and ICP > 20 mm Hg**

* Follow BMC’s ICP management guidelines (**Sections H-P**)
* Elevate HOB as much as BP and spinal clearance allows
* Consider drain CSF **(Section L)**
* Optimize sedation/analgesia **(Section K)**
* Administer Mannitol 0.25-1.0 g/kg IV q4h prn **(Section N)**
* Administer Hypertonic Saline 3% NaCl 250 mL bolus or 23.4% NaCl 30 mL bolus IV q4hr prn **(Section N)**
* Cooling measures for Brain Temp > 37 º C **(Section M)**
* Slowly ↓ PaC02 to ↓ ICP (increase rate on vent by one breath at a time, monitor end tidal CO2 and do not lower <30 mm Hg)
* Administer fluids to euvolemia, watching fluid volume status closely
* Optimize CPP
* Consider Head CT
* Consider paralytics particularly if shivering or problems with ventilation **(Section O)**
* Consider barbiturate therapy (May use BIS monitor and titrate BIS to 10-20 and Suppression Ratio (SR) > 60%) **(Section P)**
* Consider craniectomy

### Responsibility: Physicians, pharmacists, and nurses

**Other Related Guidelines or Policies:** 10.2.01 Ventriculostomy/External Cerebrospinal Fluid Drainage System, 14.11 Intracranial Pressure Monitoring, Diphenylhydantoin Therapy, Neuromuscular Blockade in the ICU, Sedation and Pain Control in the ICU, Venous Thromboembolism Prophylaxis and Treatment, Reversal of Oral Anticoagulation in Adults

**Section:** Pharmacy

#### **Medication Guideline #:** 9.65

**Title:** Intracranial Pressure (ICP) Management - Adult

#### **Initiated by:** Suresh Agarwal, MD, Laura Aykroyd, Pharm.D., Peter Burke, MD, Kevin Horbowicz, Pharm.D., Pamela Lada, Pharm.D., BCPS, John Marshall, Pharm.D., BCPS, Stella Papadopoulos, Pharm.D.

**Revision proposal initiated by:** Deborah Green, MD, Joseph Burns, MD

# Approved by: Critical Care Committee April 2007, March 2010; P&T Committee May 2007, April 2010, April 2013

**Yearly Review:** Jason Mordino, Pharm.D.

#### **Contributing Departments:** surgery critical care, neurosurgery, neurocritical care and pharmacy, nursing

**References**

1. Vincent J, Berre J. Primer on medical management of severe brain injury *Critical Care Medicine.* 2005;33:1392-1399.

2. Marik PE, Varon J, Trask T. Management of Head Trauma. *Chest.* August 1, 2002 2002;122:699-711.

3. The Brain Trauma Foundation. The American Association of Neurological Surgeons. The Joint Section on Neurotrauma and Critical Care. Management and prognosis of severe traumatic brain injury. *Journal of Trauma.* 2000;17:457-627.

4. Reynolds SF, Heffner J. Airway management of the critically ill patient: rapid-sequence intubation. *Chest.* April 1, 2005 2005;127:1397-1412.

5. Marik M, Chen K, Varon J, et al. Management of increased intracranial pressure: a review for clinicians *The Journal of Emergency Medicine.* 1999;17:711-719.

6. Guidelines for the management of severe traumatic brain injury. J Neurotrauma. 2007;24:Suppl 1:S14-S106.

7. Coles J, Fryer T, Coleman M, et al. Hyperventilation following head injury: effect on ischemic burden and cerebral oxidative metabolism. *Critical Care Medicine.* 2007;35:567-578.

8. Jacobi J, Fraiser G, Coursin D, et al. Clinical practice guidelines for the sustained use of sedatives and analgesics in the critically ill patient. *Critical Care Medicine.* 2002;30:119-141.

9. Kam PC, Cardone D. Propofol infusion syndrome. Anaesthesia 2007;62(7):690-701.

10. Bader M, Littlejohns L, Palmer S. Ventriculostomy and intracranial pressure monitoring: in search of a 0% infection rate. *Heart & Lung.* 1995;24:166-172.

11. Diringer M. Treatment of fever in the neurologic intensive care unit with a catheter based heat exchange. *Critical Care Medicine.* 2004;32:559-564.

12. Oddo M, Frangos S, Maloney-Wilensky E, et al. Effects of shivering on brain tissue oxygentation during induced normothermia in patients with severe brain injury. Neurocricial Care 2010;12:10-16.

13. Badjatia N, Strongilis E, Prescutti M, et al. Metabolic benefits of surface counter warming during therapeutic temperature modulation. Crit Care Med. 2009;37:1893–7.

14. Choi AH, Sang-Bae K, Presciutti M. Prevention of Shivering During Therapeutic Temperature

Modulation: The Columbia Anti-Shivering Protocol. *Neurocrit Care* (2011) 14:389–394

15. Mokhtarani M, Mahgoub AN, Morioka N, et al. Buspirone and meperidine synergistically reduce the shivering threshold. Anesth Analg. 2001;93:1233–9.

16. Orhan-Sungur M, Komatsu R, Lenhardt R et al. Buspirone and dexmedetomidine synergisitically ruduce the shivering threshold in humans. Anesthesiology 2006; 105:A122

17. Zweifler RM, Voorhees ME, Mahmood MA, Parnell M. Magnesium sulfate increases the rate of hypothermia via surface cooling and improves comfort. Stroke. 2004;35:2331–4.

18. Matsukawa T, Kurz A, Sessler DI et al. Propofol linearly reduces the vasoconstriction and shivering thresholds. Anethesiology 1995; 82:1169-1180.

19. Crossley S, Reid J, McLatchie R, et al. A systematic review of therapeutic hypothermia for adult patients following traumatic brain injury. *Critical* Care. 2014;18:R75

20. Doyle J, Davis D, Hoyt D. The use of hypertonic saline in the treatment of traumatic brain injury. *Journal of Trauma* 2001;50:367-383.

21. Qureshi A, Suarez J. Ue of hypertonic saline solutions in treatment of cerebral edema and intracranial hypertension. *Critical Care Medicine.* 2000;28:3301-3313.

22. Garcia-Morales EJ, et al. Osmole gap in neurologic-neurosurgical intensive care unit: Its normal value, calculation, and relationship with mannitol serum concentration. Crit Care Med 2004;32(4):986-91

23. Battison C, Andrews P, Graham C, et al. Randomized, controlled trial on the effect of 20% mannitol solution and a 7.5% saline/6% dextran solution on increased intracranial pressure after brain injury. *Critical Care Medicine* 2005;33:196-202.

24. Wilberger JE, Cantella D. High-dose barbiturates for intracranial pressure control. *New Horizons.* 1995;3:469-473.

25. Magnuson B, Hatton J, Williams S, et al. Tolerance and efficacy of enteral nutrition for neurosurgical patients in pentobarbital coma. *Nutrition of Clinical Practice.* 1999;14:131-134.

26. Stewart RM, Park PK, Hunt JP. Less is more: improved outcomes in surgical patients with conservative fluid administration and central venous catheter monitoring. J Am Coll Surg 2009;208:725-37.

27. Schneider GH, vonHelden GH, Franke R, et al. Influence of body position on jugular venous oxygen saturation, intracranial pressure and cerbral perfusion pressure. Acta Neurochir Suppl (Wien). 1993;59:107-12

28. Muscedere J, Dodek P, Keenan S et al. Comprehensive evidence-based clinical practice guidelies for ventilator-associated pneumonia: prevention. J Crit Care. 2008;23:126-37.

29. Ho AM, Fung KY, Joynt GM et al. Rigid cervical collar and intracranial pressure of patients with severe head injury. J Trauma. 2002;53:1185-88.

30. Rovlias A, Kotsou S. The influence of hyperglycemia on neurological outcome in patients with severe head injury. *Neurosurgery.* 2000;46:335-342.

31. Vogelzang V, Nijboer J, VanderHorst I, et al. Hyperglycemia has a stronger relation with outcome in trauma patients than in other critically ill patients. *Journal of Trauma.* 2006;60:873-879.

32. Vespa PM, McArthur D, O'Phelan K et al Persistently low extracellular glucose correlates with poor outcome 6 months after human traumatic brain injury despite a lack of increase lactate: a microdialysis study. J Cereb Blood Metab 2003;23:865-77

33. Vespa P, Boonyaputthikul R, McArthur DL et al. Intensive insulin therapy reduces microdialysis glucose values without altering glucose utilization or improving the lactate/pyruvate ratio after traumatic brain injury. Crit Care Med 2006;34:850-6

34. Chang B, Lowenstein D. Practice parameter: antiepileptic drug prophylaxis in severe traumatic brain injury. *Neurology* 2003;60:10-16.

35. Temkin NR, Dikmen SS, Wilensky AJ, et al. A randomized, double-blind study of phenytoin for the prevention of post-traumatic seizures. *N Engl J Med.* August 23, 1990 1990;323:497-502.

36. Jones KE, Puccio AM, Harshman KJ, et al. Levetiracetam versus phenytoin for seizure prophylaxis in severe traumatic brain injury. Neurosurg Focus 2008;25(4):1-5.

37. Szaflarski JP, Sangha KS, Lindsell CJ et al. Prospective, randomized, single-blinded comparative trial of intravenous levetiracetam versus phenytoin for seizure prophylaxis. Neurocritical Care 2010;12:165–172.

38. Boucher BA, Feler CA, Dean JC et al. The safety, tolerability, and pharmacokinetics of fosphenytoin after intramuscular and intravenous administratoin in neurosurgery patients. Pharmacotherapy 1996;16:638-45.

39. Marik P, Zaloga G. Contemporary strategies for the prevention of stress-related mucosal bleeding. *American Journal of Health-System Pharmacy.* 2005;62:S11-S17.

40. Geerts WH, Pineo GF, Heit JA, et al. Prevention of venous thromboembolism: The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest.* September 1, 2004 2004;126(3\_suppl):338S-400.

41. Kim J, Gearhart M, Zurick A, et al. Preliminary report on the safety of heparin for deep vein thrombosis prophylaxis after severe head injury. *Journal of Trauma.* 2002;53:38-43.

42. Gould MK, Garcia DA, Wren SM, et al. Prevention of VTE in nonorthopredic surgical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence Based Clinical Practice Guidelines. Chest. 2012; 141(2)(Suppl):e227S–e277S

43. Chang JJJ, Youn TS, Benson D, et al. Physiologic and functional outcome correlates of brain tissue hypoxia in traumatic brain injury. *Crit Care Med* 2009;37:283-290.

44. Narotam PK, Morrison JF, Nathoo N. Brain tissue oxygen monitoring in traumatic brain injury and major trauma: outcome analysis of a brain tissue oxygen-directed therapy. *J Neurosurg* May 22, 2009:1-11.

45. Inuba K, Menaker J, Branco B, et al. A prospective multicenter comparison of levetiracetam versus phenytoin for early posttraumatic seizure prophylaxis. *J Trauma* 2013;74:766-773

46. Franko, Jan, et al. "Advanced age and preinjury warfarin anticoagulation increase the risk of mortality after head trauma." *Journal of Trauma and Acute Care Surgery* 2006:61;107-110.

47. Ivascu, Felicia A., et al. "Rapid warfarin reversal in anticoagulated patients with traumatic intracranial hemorrhage reduces hemorrhage progression and mortality." *Journal of Trauma and Acute Care Surgery* 2005:59;1131-1139.

48. Bochicchio, Grant V., et al. "Tolerance and efficacy of enteral nutrition in traumatic brain–injured patients induced into barbiturate coma." *Journal of parenteral and enteral nutrition* 30.6 (2006): 503-506.