The Brain Trauma Foundation (BTF) released the 4th Edition of the Guidelines for the Management of Severe Traumatic Brain Injury in September 2016 to help guide physicians in evidence-based care of traumatic brain injuries. The document provided recommendations only when there was evidence to support them and stratified the evidence and recommendations based on key criteria. Each recommendation was given a level of recommendation depending on the quality of the body of evidence, combined with the class of the studies.

I did my best to condense a 244-page document into 12 pages! Hopefully, you can locate exactly what you are looking for by using the find function (Ctrl+F or Cmd+F) and searching for any of the following topics:

1. Decompressive Craniectomy
2. Prophylactic Hypothermia
3. Hyperosmolar Therapy
4. Cerebrospinal Fluid Drainage
5. Ventilation Therapies
6. Anesthetics, Analgesics, and Sedatives
7. Steroids
8. Nutrition
9. Infection Prophylaxis
10. Deep Vein Thrombosis (DVT) Prophylaxis
11. Seizure Prophylaxis
12. Intracranial Pressure (ICP) Monitoring
13. Cerebral Perfusion Pressure (CPP) Monitoring
14. Advanced Cerebral Monitoring
15. Blood Pressure Thresholds
16. Intracranial Pressure (ICP) Thresholds
17. Cerebral Perfusion Pressure (CPP) Thresholds
18. Advanced Cerebral Monitoring Thresholds

Decompressive Craniectomy (DC)

- Cerebral edema can result from primary or secondary injury in TBI and cause brain tissue displacement and hernia. DC can relieve ICP and prevent herniation.
- **Bifrontal DC may reduce ICP and days in the ICU, but does not improve outcomes as measured by Glasgow Outcome Scale-Extended (GOSE) at 6 months (Level IIA)**
  - DECRA study ([PMID: 21434843](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3102126/)) found that early (<3 days) bifrontotemporoparietal DC decreased intracranial pressure and ICU LOS, but was also associated with worse scores
on GOSE. However, the study had issues with randomization and a high crossover rate; post hoc adjustment for difference in pupil reactivity at admission resulted in some outcome differences that were no longer significant. “A beneficial effect of craniectomy was excluded.”

- “Any potential improvement obtained by surgical decompression may well be offset by surgical morbidity.” (PMID: 23022646)
- “On the basis of its findings, we are able to conclude that bifrontal DC should not be used as a neuroprotective measure for moderate posttraumatic intracranial hypertension in well-resourced settings.” (PMID: 30473990)

- **Large frontotemporoparietal (FTP) DC is recommended over small frontotemporoparietal DC for reduced mortality and improved neurologic outcomes (Level IIA)**
  - Larger FTP DC had lower rates of poor neuro function (GOS 1 to 3) and higher rates of good neuro function (GOS 4 or 5) compared to smaller FTP DC (PMID: 15941372)
  - Larger DC improved outcomes but resulted in higher rates of complications, including delayed intracranial hematoma, subdural effusion (PMID: 19930556).

- **RESCUEicp trial (PMID: 27602507):** international, multicenter randomized controlled trial; showed that DC (within 10 days) can improve mortality but increases rates of vegetative state and severe disability at 6 months compared to medical care alone
- **No recommendations on DC vs craniotomy due to low-quality studies that reported lower, but not statistically significant, mortality rates and conflicting findings about function and complications (PMID: 19061378, PMID: 12516810)**
- **No recommendations on timing due to conflicting studies**

[https://www.youtube.com/watch?v=sEqkeJfG9Ys](https://www.youtube.com/watch?v=sEqkeJfG9Ys)

**Prophylactic Hypothermia**

- Hypothermia is well known for its ability to reduce intracranial pressure, but bears the risks of coagulopathy, immunosuppression, cardiac dysrhythmia, and death
- **Early (within 2.5 hours), short-term (48 hours post-injury) prophylactic hypothermia is not recommended (Level IIB)**
- **Body of literature shows inconsistent results**
  - Multiple studies do show improvement in mortality, mean and high ICPs, and neurologic function with hypothermia compared to normothermia
  - However, a 2011 study by Clifton et al. (PMID: 21169065) was terminated early due to futility of early hypothermia as it demonstrated increased mortality and poorer neurologic outcomes (both nonsignificant)
- **There may be some benefit in less severely injured patients and in patients undergoing surgical hematoma evacuation**
- **No recommendations with respect to length of cooling and head-only vs systemic cooling due to insufficient evidence.** Class 2 evidence shows:
  - longer (4-6 days) periods > shorter (1-3 days) periods (PMID: 16306933)
  - selective brain cooling > mild systemic cooling (33-35°C) – not statistically significant though (PMID: 16604824)
Hyperosmolar Therapy

- Hypertonic and hypotonic solutions can create dramatic changes in brain volume
- Mannitol and hypertonic saline work to reduce ICP by reducing blood viscosity, leading to improved microcirculatory flow of blood constituents and consequent constriction of pial arterioles, resulting in decreased cerebral blood volume and intracranial pressure
- **Hyperosmolar therapy may lower intracranial pressure; however, there was insufficient evidence available about clinical outcomes to support a formal recommendation**
- **Insufficient evidence to support use of a specific hyperosmolar agent**
- Restated 3rd Edition recommendations:
  - Mannitol is effective for control of raised ICP at doses of 0.25g/kg to 1g/kg; avoid hypotension (Level II in 3rd Edition)
  - Restrict mannitol use prior to ICP monitoring in patients with signs of transtentorial herniation or progressive neurological deterioration not attributable to extracranial causes (Level III in 3rd Edition)
- Mangat et al. ([PMID: 25380107](https://www.ncbi.nlm.nih.gov/pubmed/25380107)) found that hypertonic saline may be more effective than mannitol in lowering intracranial pressure and ICU length of stay but found that there was no difference in short-term mortality (Class 2 study).

Cerebrospinal Fluid Drainage

- Practice patterns with respect to external ventricular drainage (EVD) systems vary widely
  - Continuous monitoring of ICP with intermittent draining for ICP elevations
  - Continuous drainage of CSF with intermittent ICP measurements
  - Continuous drainage with EVD and continuous ICP measurements with intraparenchymal fiberoptic pressure monitor
- In pediatric population, continuous drainage improves ICP management and injury biomarkers ([PMID: 15453982](https://www.ncbi.nlm.nih.gov/pubmed/15453982))
- **EVD system zeroed at the midbrain with continuous drainage of CSF may be considered to lower ICP burden more effectively than intermittent use (Level III)**
- **Use of CSF drainage to lower ICP in patients with an initial GCS<6 during the first 12 hours after injury may be considered (Level III);** potentially higher mortality rates if performed in patients with GCS≥6.
- EVD use was associated with higher in hospital and 28-day mortality for patients with a GCS≥6 assessed during initial 12 hours of admission ([PMID: 20169772](https://www.ncbi.nlm.nih.gov/pubmed/20169772)).
- No Class 1 or 2 studies

Ventilation Therapies

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https://www.youtube.com/watch?v=AjuSH7x35YY#t=567

https://www.youtube.com/watch?v=AcgMf3CEWQ4
• Severe TBI patients are at increased risk of pulmonary aspiration or compromised respiratory drive and function.
• Cerebral blood flow is linearly responsive to PaCO$_2$ between a range of 20mmHg and 80mmHg.
• Recent studies have shown that after severe TBI, cerebral metabolic rate is variable; cerebral ischemia has been documented in several studies after severe TBI. Therefore, normoventilation should be used to prevent further ischemia and infarction.
• **Prolonged prophylactic hyperventilation with a PaCO$_2$ of 25mmHg or less is not recommended (Level IIB)**
• Restated 3rd Edition recommendations:
  1. Hyperventilation is recommended as a temporizing measure for the reduction of elevated ICP.
  2. Hyperventilation should be avoided during the first 24 hours after injury when cerebral blood flow is often critically reduced.
  3. If hyperventilation is used, jugular venous oxygen saturation or brain tissue O$_2$ partial pressure (BtpO$_2$) measurements are recommended to monitor oxygen delivery.
• Muizelaar et al. (PMID: 1919695) performed a RCT of severe TBI patients, comparing normal ventilation (PaCO$_2$ 35±2mmHg), hyperventilation (PaCO$_2$ 25±2mmHg), or hyperventilation with tromethamine. They found worse Glasgow Outcome Scale (GOS) at 3 and 6 months in the hyperventilated patients compared to normal ventilation group. However, there were small sample sizes, with an absence of power analysis.

**Anesthetics, Analgesics, and Sedatives**

• Anesthetics, analgesics, and sedatives are important in acute TBI for prophylaxis or control of intracranial hypertension and seizures.
• Potential mechanisms of benefit from sedatives:
  o Control ICP by preventing unnecessary movements, coughing, and straining against tubes
  o Suppression of metabolism
  o Alteration of cerebral vascular tone
  o Depressed cerebral metabolism and oxygen consumption
  o Improved coupling of regional blood flow to metabolic demands, decreasing cerebral blood volume and ICP
  o Inhibition of oxygen radical mediated lipid peroxidation
• Adverse events include hypotension, decreased cardiac output, increased intrapulmonary shunting, hypoxia, hyperkalemia, metabolic acidosis, myocardial failure, rhabdomyolysis, and death.
• **Do not use barbiturates to induce burst suppression measured by EEG as prophylaxis against the development of intracranial hypertension (Level IIB)**
• **Use high-dose barbiturates to control elevated ICP refractory to maximum standard medical and surgical treatment (Level IIB)**
• Although propofol is recommended for the control of ICP, it is not recommended for improvement in mortality or 6-month outcomes. High dose propofol can produce significant morbidity (Level IIB)
• Chiu et al. (PMID: 17071254) found that propofol significantly improved survival, decreased mean ICP at 3 days, and increased mean CPP at 5 days in head-injured patients.

Steroids
• Steroids can:
  o alter vascular permeability in brain edema
  o reduce CSF production
  o attenuate free radical production
• Studies of severe TBI patients failed to find a benefit for glucocorticoids
• Do not use steroids to improve outcomes or reduce ICP; high dose methylprednisolone was associated with increased mortality in patients with severe TBI (Level I)
• Corticosteroid Randomization After Significant Head Injury (CRASH) trial, a large, multicenter randomized controlled trial, found higher 2-week mortality and 6-month mortality (PMID: 15474134, PMID: 15936423)

Nutrition
• TBI may increase metabolism and requirement or caloric support by an unknown mechanism
• Increase in serum glucose is observed after severe TBI; Practice of “tight glucose control” could have deleterious effects in patients with severe TBI (PMID: 16505665)
• Feeding patients to attain basal caloric replacement at least by the 5th day and, at most, by the 7th day post-injury is recommended to decrease mortality (Level IIA)
• Transgastric jejunal feeding is recommended to reduce the incidence of ventilator-associated pneumonia (Level IIB)
• Timing of feeding:
  o Hartl et al. (PMID: 18590432) found that nutritional support within 5 days was associated with a significant reduction in 2-week mortality.
  o Lepelletier et al. (PMID: 20027012) found that early feeding was protective, resulting in lower rates of ventilator-acquired pneumonia.
  o Chourdakis et al. (PMID: 21965459) found no difference between early (initiated <48 hours) enteral feeding and delayed (initiated >48 hours) enteral feeding (outcomes: ventilator acquired pneumonia, non-ventilator acquired pneumonia, CNS infections, hyperglycemia, bacteremia, UTIs, diarrhea, constipation, and feeding intolerance).
  o Taylor et al. (PMID: 10579275) compared standard feeding (gastric based on tolerance) to early enhanced enteral feeding (full nutritional requirements from day 1). Found a trend toward better GOS at 3 months in accelerated feeding cohort, but no difference at 6 months.
Continuous gastric feeding had less feeding intolerance and trend towards less infection compared to bolus feeding, but no difference in mortality, GOS, or hospital or ICU LOS (Rhoney et al., PMID: 12238631).

- Method of feeding: Acosta-Escribano et al. (PMID: 20495781) found that transpyloric (jejunal) feeding had lower incidence of pneumonia compared to gastric feeding. Multiple studies show that parenteral nutrition seems to have a slight trend toward better outcomes, but the difference is not significant.

- Glycemic Control (evidence insufficient to make any recommendations):
  - Bilotta et al. (PMID: 18373223) compared intensive glucose control (80-120mg/dL) to conventional glucose control (<220mg/dL). Intensive glucose control had more episodes of hypoglycemia but shorter lengths of ICU stay. There was no difference in mortality or Glasgow Outcome Scale.
  - Coester et al. (PMID: 20032790) compared intensive (80-110mg/dL) to conventional (<180mg/dL) glucose control. They found no difference in neurologic outcome, mortality, infection rate, or duration of ICU stay. Intensive glucose control had significantly increased risk of hypoglycemic episodes.
  - Yang et al. (PMID: 19232615) compared intensive (insulin infusion to maintain glucose between 80mg/dL and 110mg/dL) vs conventional (maintained <200mg/dL) glycemic control. They found no difference in mortality. However, intensive insulin therapy was associated with reduced infection rate, fewer days in the neurologic ICU, and better functional outcome by GOS at 6 months.

- Vitamins and Supplements (evidence insufficient to make any recommendations):
  - Young et al. (PMID: 8714860) compared supplemental zinc to no zinc and found a nonsignificant trend towards higher mortality in the control group.
  - Vitamin E may decrease mortality and improve functional outcomes by GOS at discharge (Razmkon et al., PMID: 21916138); study had methodologic flaws.
  - Patients with low initial serum magnesium and high CSF magnesium were more likely to have a poor outcome (Stippler et al., PMID: 17711396); rapid correction does not reverse the prognostic value of these markers.

Infection Prophylaxis

- Rates of ventilator-associated pneumonia (VAP) are higher in TBI patients than non-TBI patients.
- Early tracheostomy is recommended to reduce mechanical ventilation days when the benefit outweighs the complications associated with such a procedure. However, there is no evidence that early tracheostomy reduces mortality or the rate of nosocomial pneumonia (Level IIA)
  - ***The Class 2 studies cited about timing of tracheostomy are small (N=62 and N=67) and do not show any statistical significance for mortality and pneumonia rates; both studies utilized different definitions of “early” intubation. Bouderka et al. (PMID: 15345969) demonstrated a decrease in total mechanical ventilation days in the early tracheostomy group (5 days). Sugerman et al. (PMID: 9390483) found no significant difference in the rates of pneumonia or death when comparing early vs later tracheostomy.
Class 3 studies: Ahmed et al. (PMID: 17635057) showed no difference in overall mortality, length of stay, incidence of pneumonia, or ventilator days between early and late tracheostomy placement. Wang et al. (PMID: 21536285) found that early tracheostomy patients had reduced ICU LOS and lower incidence of pneumonia with shorter duration of antibiotics; however, the results in this study have not been replicated in any other study. Dunham et al. (PMID: 24624310) performed a small RCT, comparing early (3-5 days post-injury) to late (10-14 days post-injury) tracheostomy, that showed no difference in VAP rates, ventilator/ICU days, or in-hospital mortality.

- Do not use povidone-iodine (PI) oral care to reduce ventilator-associated pneumonia; it may increase risk of ARDS (Level IIA)
  - Initial study by Seguin et al. (PMID: 16540962) showed decreased rates of VAP when PI was used compared to saline and usual care; however, the study was conducted at a single center and was nonblinded. A second study conducted in 2014 by the same investigators (PMID: 24105456) found no significant difference in VAP, ICU and hospital LOS, ICU and 90-day mortality; but they did find an increased risk of ARDS in the PI group.

- Consider antimicrobial-impregnated catheters (AICs) to prevent catheter-related infections during EVD (Level III; studies included multiple pathologies)
  - Pooled results in a meta-analysis by Ratilal et al. (PMID: 21833952) showed a significant decrease in shunt infection for the antibiotic-impregnated shunts (AIS). However, the statistical significance went away in a secondary analysis for the subset of studies with adequate allocation concealment and when AIS was compared to standard care.
  - Wang et al. (PMID: 23890254) performed another systematic review and meta-analysis and found that patients managed with AIC had significantly lower overall rates of cerebrospinal fluid infections, 20-day infection rate, and rate of catheter bacterial colonization.
  - Class 3 studies also show a positive effect of the use of AICs in minimizing infection (PMID: 20074964, PMID: 23634916)

- The 3rd Edition stated “Perioperative antibiotics for intubation should be administered to reduce the incidence of pneumonia.” This recommendation was not carried forward because general critical care practice has established protocols to prevent VAP; also, the benefits of prophylactic antibiotics may not outweigh the harms of developing resistant organisms. The Class 2 study that this recommendation was based on showed statistically significant difference in incidence of pneumonia when post-intubation cefuroxime (1.5g for two doses within 6 hours after intubation) was given, but they found no difference in mortality.

Deep Vein Thrombosis (DVT) Prophylaxis

- Patients with TBI are at significant risk for developing venous thromboembolism (VTE) (PMID: 6226216); risk increases with TBI severity (PMID: 25058248).

- Mechanisms:
  o Hypercoagulability from primary brain injury
  o Prolonged periods of immobilization

Deep Vein Thrombosis (DVT) Prophylaxis

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- Mechanisms:
  o Hypercoagulability from primary brain injury
  o Prolonged periods of immobilization
- Focal motor deficits
- **Low molecular weight heparin (LMWH) or low-dose unfractionated heparin (UFH) may be used in combination with mechanical prophylaxis. However, there is an increased risk for expansion of intracranial hemorrhage (Level III).**
  - Studies are conflicting, but most show that prophylactic anticoagulation decreased the incidence of VTE. Mohseni et al. ([PMID: 22416148](https://pubmed.ncbi.nlm.nih.gov/22416148/)) found that VTE prophylaxis was associated with a decrease in mortality and incidence of VTE. Scudday et al ([PMID: 21459632](https://pubmed.ncbi.nlm.nih.gov/21459632/)) found that prophylactic anticoagulation decreased rates of VTE and produced a nonsignificant trend towards injury progression. On the other hand, Kwait et al. ([PMID: 22929493](https://pubmed.ncbi.nlm.nih.gov/22929493/)) found higher rates of progression of bleed size and an increase in neurosurgical intervention in the prophylactic anticoagulation group. Incidence of VTE was also higher, but those treated with LMWH had lower mean GCS (more severely injured; 8.0 vs 11.4) and more lower-extremity duplex ultrasounds performed (42% vs 11%).
- There was not sufficient evidence for recommendations about whether to use a protocol or not for thromboprophylaxis
- There was not sufficient evidence for recommendations about early vs late administration of VTE prophylaxis

**Seizure Prophylaxis**
- Early post-traumatic seizures (PTS) = <7 days post-injury
- Late post-traumatic seizures (PTS) = >7 days post-injury
- Risk factors for early PTS:
  - GCS≤10
  - Immediate seizures
  - Post-traumatic amnesia lasting longer than 30 minutes
  - Linear or depressed skull fracture
  - Penetrating head injury
  - Subdural, epidural, or intracerebral hematoma
  - Cortical contusion
  - Ages≤65 years
  - Chronic alcoholism
- Risk factors for post-traumatic epilepsy
  - Severe TBI and early PTS prior to discharge
  - Acute intracerebral hematoma or cortical contusion
  - Posttraumatic amnesia lasting longer than 24 hours
  - Age>65 years
  - Premorbid history of depression
- **Prophylactic use of phenytoin or valproate is not recommended for preventing late PTS (Level IIA)**
  - Both medications have not shown any benefit for late PTS
- Phenytoin is recommended to decrease the incidence of early PTS, when overall benefit outweighs the complications associated with such treatment. However, early PTS has not been associated with worse outcomes (Level IIA).
- At the time of publication of the 4th Edition of the TBI guidelines, there was insufficient evidence to recommend levetiracetam over phenytoin regarding efficacy in preventing early PTS and toxicity.
  - ***There are many new studies since the release of these guidelines regarding levetiracetam (PMID: 19898966, 27395404, 29688078, 26619246, 29196247, 30465951, 23592358, 30459875). Levetiracetam seems to be equivalent to phenytoin and there is evidence of improved long-term outcomes with levetiracetam. Some studies show that the side-effect profiles favor levetiracetam over phenytoin.
- Difficult to conduct powerful studies because seizures are a relatively rare event

**Intracranial Pressure (ICP) Monitoring**

- **Management of severe TBI patients using information from ICP monitoring is recommended to reduce in-hospital and 2-week post-injury mortality (Level IIB)**
- Recommendations not carried forward from 3rd Edition:
  1. ICP should be monitored in all salvageable patients with a severe TBI (GCS 3-8 after resuscitation) and an abnormal CT scan (hematomas, contusions, swelling, herniation, or compressed basal cisterns)
  2. ICP monitoring is indicated in patients with severe TBI with a normal CT scan if two or more of the following are noted at admission: age>40 years, unilateral or bilateral motor posturing, or SBP<90mmHg.
  - These were restated in the 4th Edition to maintain recognition of the patient characteristics associated with risk of increased ICP
- **Class 1 studies:**
  - Chesnut et al. (PMID: 23234472) performed a RCT in 6 hospitals comparing treatment informed by ICP monitoring to treatment informed only by imaging and clinical exam. They found no difference in 6-month mortality and Extended GOS.
- **Class 2 studies:**
  - Gerber et al. (PMID: 24098983) found that, from 2001 to 2009, there was increased adherence to ICP and CPP monitoring and management; this increased adherence also correlated with decreased 2-week mortality.
  - Alali et al. (PMID: 23731257) performed a very large (N=10,628) retrospective cohort study of 155 Level 1 and 2 trauma centers in the US and Canada. They concluded that ICP monitoring was associated with significantly lower odds of death; this effect was more pronounced in patients under 65. However, the care likely varied across hospitals, thus restricting the ability to attribute the cause of the lower mortality to ICP monitor-driven treatment alone.
  - Talving et al. (PMID: 23971954) found that in-hospital mortality (all-cause and due to brain herniation) was significantly lower for monitored patients. Patients in the monitored group had longer ICU and hospital LOS.
Farahvar et al. (PMID: 22900846) enrolled patients if they received 1 of 5 intracranial hypertension-targeting treatments (mannitol, hypertonic saline, barbiturates, drainage of CSF, or decompressive craniectomy) and compared patients who received treatment and an ICP monitor to patients who received treatment without an ICP monitor. They found that use of an ICP monitor was associated with significantly lower mortality across all ages.

- **Class 3 studies (either neutral or negative trials):**
  
  - Haddad et al. (PMID: 22165356) found that ICP monitoring increased the need for tracheostomy, hospital LOS, ICU LOS, and mechanical ventilation duration. There was no significant impact on hospital and ICU mortality.
  
  - Kostic et al. (PMID: 22097111) found no difference in survival rates in ICP-monitored patients compared to no monitor.
  
  - Liew et al. (PMID: 20954551) found that the ICP-monitored group had higher risk of mortality, worse GCS improvement upon discharge, and longer ICU LOS. However, their ICP group had significantly more severe TBI (specifically diffuse axonal injury).
  
  - Mauritz et al. (PMID: 18365169) found no significant difference in hospital and ICU mortality at 32 centers in Austria.
  
  - Shafi et al. (PMID: 18301195) found that ICP monitoring was associated with a 45% reduction in survival.

**Cerebral Perfusion Pressure (CPP) Monitoring**

- **CPP = MAP-ICP**

- **Management of severe TBI patients using guidelines-based recommendations for CPP monitoring is recommended to decrease 2-week mortality (Level IIB)**
  
  - They cite the same Gerber study as above (PMID: 24098983): increased adherence to ICP and CPP monitoring and management, associated with decreased 2-week mortality from 2001 to 2009.
  
  - Class 3 studies show that CPP-targeted therapy might be better than ICP-targeted therapy (Huang et al., PMID: 16908157). Using dichotomized GOS-Extended, Johnson et al. (PMID: 21311298) found that in patients who had poor cerebral perfusion autoregulation, favorable outcomes were significantly higher in those treated at CPP levels below median compared to CPP levels above median. Howells et al. (PMID: 15739560) found that patients with intact autoregulation had better outcomes with CPP elevation while patients with defective autoregulation had better outcomes with ICP-targeted care and lower CPPs (50-60mmHg).

**Advanced Cerebral Monitoring**

- **Jugular bulb monitoring of arteriovenous oxygen content difference (AVDO₂), as a source of information for management decisions, may be considered to reduce mortality and improve outcomes at 3 and 6 months post-injury (Level III)**
• Brain Tissue Oxygen (PbrO$_2$) monitoring was associated with increased hospital costs and lower Functional Independence Measure scores; there was no difference in hospital mortality in patients who were managed with ICP and PbrO$_2$ compared to those who were managed with ICP monitoring alone (Martini et al., PMID: 19392603). Narotam et al. (PMID: 19463048) assessed PbrO$_2$-directed therapy and found significantly higher mean GOS at 6 months post-injury with 37% relative risk reduction in mortality. Spiotta et al. (PMID: 20415526) also found statistically significant lower mortality and favorable outcome (GOS) at 3 months post-injury for patients who received PbrO$_2$-directed care than those who received ICP- and CPP-based therapy. Overall odds ratio for favorable outcome was 2.1 for the PbrO$_2$ group in a systematic review (Nangunoori et al., PMID: 21845489).

• Four studies cited in these guidelines report improved outcomes in patients who received AVDO$_2$ monitoring and management of desaturation episodes.

• Compared to patients whose glutamate levels increased and remained elevated, patients whose glutamate levels tended to normalize over the 5-day monitoring period (performed via microdialysis monitoring of extracellular glutamate) had a lower mortality rate and better 6-month functional outcome among survivors (PMID: 21691895)

Blood Pressure Thresholds

• High mortality in patients admitted with a SBP<85mmHg after severe TBI

• If autoregulation remains intact, decrease in SBP triggers vasodilation to maintain adequate brain perfusion. If autoregulation is not intact, there is a dependency on SBP to prevent ischemia, the single most important secondary insult.

• Maintaining SBP at ≥100mmHg for patients 50-69 or at ≥110mmHg for patients 15-49 or over 70 years old may be considered to decrease mortality and improve outcomes (Level III).
  - For patients 50-69 years, keep SBP ≥100mmHg
  - For all other adult patients, keep SBP ≥110mmHg
  - These age groupings were predefined in a retrospective cohort study that determined optimal hypotension thresholds (Berry et al., PMID: 21939970, Class 2 study).

• Class 3 studies:
  - Brenner et al. (PMID: 22673237) found that SBP<110mmHg and <120mmHg within the first 48 hours was predictive of mortality and worse outcomes 12 months post-injury.
  - Butcher et al. (PMID: 17375997) found that targeting SBP 120-150mmHg and MAP 85-110mmHg improved outcomes.
  - The other Class 3 studies carried over from the 3rd Edition pushed for lower SBP and MAP targets

Intracranial Pressure (ICP) Thresholds

• Treating ICP above 22mmHg is recommended because values above this level are associated with increased mortality (Level IIB)

• A combination of ICP values and clinical and brain CT findings may be used to make management decisions (Level III)
Using chi square analysis to find the best discriminative value between patient outcomes, Sorrentino et al. ([PMID: 21964774]) determined that an ICP threshold for treatment of 22mmHg reduced mortality and improved GOS levels (Class 2 study). Subgroup analysis found that a threshold of 18mmHg increased favorable outcomes for patients over 55 years and women of all ages (though this may not have been adequately powered).

Older Class 3 studies that are carried forward from the 3rd Edition support a threshold of approximately 20mmHg (some studies support a lower threshold).

From the guidelines: “Patients can herniate at intracranial pressures less than 20-25mmHg. The likelihood of herniation depends on the location of an intracranial mass lesion. In the report by Marshall et al., 1979 pupillary abnormalities occurred with ICP values as low as 18 mm Hg. Therefore, at all points, any chosen threshold must be closely and repeatedly corroborated with the clinical exam and CT imaging in an individual patient.”

Cerebral Perfusion Pressure (CPP) Thresholds

- CPP = MAP - ICP
- Requires ICP monitoring
- CPP may be blood pressure metric to which brain autoregulatory mechanisms respond ([PMID: 7490638])
- The recommended target CPP value for survival and favorable outcomes is between 60 and 70mmHg; however, the optimal threshold is unclear and may depend upon the patient’s autoregulatory status (Level IIB)
  - Allen et al. ([PMID: 24196011]) found that mortality at 14 days post-injury was highest when patients were managed at a higher CPP (>60mmHg) threshold (Class 2 study).
  - Using chi square analysis to find the best discriminative value between patient outcomes, Sorrentino et al. ([PMID: 21964774]) determined that the optimal CPP threshold for mortality and neurological outcomes was 70mmHg; however, in patients >55 years, the threshold was 75mmHg (Class 2 study).
- Avoiding aggressive attempts to maintain CPP above 70mmHg with fluids and pressors may be considered because of the risk of adult respiratory failure (Level III)

Advanced Cerebral Monitoring Thresholds

- Jugular venous saturation of <50% may be a threshold to avoid in order to reduce mortality and improve outcomes (Level III)
  - PbrO₂ that remains <29mmHg in the first 72 hours is predictive of mortality (Eriksson et al., [PMID: 22673264], Class 2 study).
  - Chieregato et al. ([PMID: 17893572]) found that lactate variables were better predictors of death than AVDO₂ and AVDpCO₂ widening (Class 2 study).
  - 30% mortality when brain O₂ was >25mmHg; 43% if O₂ was <20mmHg; and 50% when O₂ was <15mmHg (Stiefel et al., [PMID: 17044560], Class 3 study).
  - In a study by Soustiel et al. ([PMID: 16156711]), 71.4% of patients with poor outcome had CBF <35mL/100g/min, compared to 16.7% of patients with favorable outcomes.