**Appendices**

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# Appendix A. Research Team

Methods Team

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# Appendix B. Inclusion and Exclusion Criteria

|  | **Include** | **Exclude** |
| --- | --- | --- |
| **Population** | Age 0-18  Traumatic Brain Injury  GCS <9 | >15% adult and results of children not separated  >15% mixed pathologies and results not separated  >15% mixed severities (GCS >9 and results not separated)  Neonatal, newborn birth injuries  Non-traumatic brain injuries (e.g., asphyxiation) |
| **Intervention(s)** | Treatments  Hyperosmolar Therapy  Temperature Control  Prophylactic Hypothermia  Cerebrospinal Fluid Drainage  Barbiturates  Decompressive Craniectomy  Hyperventilation  Corticosteroids  Analgesics, Sedatives, and Neuromuscular Blockade  Glucose and Nutrition  Seizure Prophylaxis  Monitoring  Intracranial Pressure  Cerebral Perfusion Pressure  Advanced Neuromonitoring  Thresholds  Intracranial Pressure  Cerebral Perfusion Pressure  Advanced Neuromonitoring  Other  Neuroimaging | Evaluation of the reliability or other performance aspects of measures or tests. |
| **Comparators** | Treatments, Monitoring and Thresholds (compared with each other or no treatment/monitoring or a different threshold) | In general, studies with no control or comparison group; however, treatment series may be considered if no higher levels of evidence are available. |
| **Outcomes** | Mortality  Neurological Function (GOS)  Harms  Morbidity  Intracranial Pressure | None |
| **Timing** | Intervention must be in acute phase  Outcomes prior to 1 year post injury | Outcomes only more than 1 year or longer after initial injury |
| **Setting(s)** | In-hospital | Rehabilitation  Outpatient  Prehospital |
| **Study Design** | Randomized controlled trials  Cohort (Observational)  Case control  Treatment series | Descriptive studies  Case reports  Nonsystematic narrative reviews  Prognostic studies  Prevention studies |
| **Publication Type** | Peer reviewed journals | Editorials or commentaries  Training articles/CME materials |

Abbreviations: CME= GCS=Glasgow Coma Scale, GOS=Glasgow Outcome Scale,

# Appendix C. Major Changes from Second to Third Edition

Each recommendation is identified as “To Improve Overall Outcomes,” “For ICP Control,” or “For Seizure Prevention.” Recommendations are provided as Level I, II, or III. Within each topic, text describing the changes is included immediately following the Recommendations.

The table below lists the major changes for each topic.

| ***Topic*** | ***Change*** |
| --- | --- |
| **Intracranial Pressure Monitoring** | No content changes to the recommendations. |
| **Advanced Neuromonitoring** | No content changes to the recommendations.  Note on use of Pbr02 was added.  Note on use of advanced neuromonitoring was added. |
| **Neuroimaging** | Recommendation III.1. is new to this edition. |
| **ICP Thresholds** | No content changes to the recommendations. |
| **Cerebral Perfusion Pressure** | No content changes to the recommendations. |
| **Hyperosmolar Therapy** | Recommendations II.1. and III.2. are new to this edition.  Safety Recommendation was added.  A level II recommendation from the previous edition suggesting the use of hypertonic saline in general was removed and replaced with Recommendation II.1.  The recommendation from the previous edition to maintain serum osmolarity <360 mOsm/L was removed from this edition. |
| **Analgesics, Sedatives, and Neuromuscular Blockade** | Recommendation III.1. is new to this edition.  The recommendation about the use of Thiopental from the Second Edition has been removed. |
| **Cerebrospinal Fluid Drainage** | The recommendation about the use of a lumbar drain from the Second Edition has been removed. |
| **Seizure Prophylaxis** | No content changes to the recommendations.  Note on Levetiracetam was added. |
| **Ventilation Therapies** | No content changes to the recommendations.  This title was changed from Hyperventilation. |
| **Temperature Control** | Recommendation II.1. is modified from the Second Edition of these guidelines with regard to timing.  The level II recommendation from the Second Edition about the use of hypothermia for ICP control has been downgraded to level III.  The level II recommendation about rewarming rate from the Second Edition was removed and replaced with Safety Recommendation 1.  The level III recommendation from the Second Edition about use of moderate hypothermia was removed.  Safety Recommendation 2 on rewarming and phenytoin was added. |
| **Barbiturates** | No content changes to the recommendations. |
| **Decompressive Craniectomy** | The specification in the recommendation from the Second Edition, “. . . with duraplasty, leaving the bone flap out . . .” was removed and the recommendation is made specifically for ICP Control. |
| **Nutrition** | The level III Recommendation from the Second Edition was removed.  Recommendation III.1. is new to this edition. |
| **Corticosteroids** | The level II recommendation from the Second Edition has been downgraded to level III.  Note about use of replacement corticosteroids was added. |

Abbreviations: CPP=cerebral perfusion pressure, CSF=cerebrospinal fluid, ICP=intracranial pressure, NA=not applicable, TBI=traumatic brain injury.

# Appendix D. Search Strategy

|  |
| --- |
| **Database:** Ovid MEDLINE(R) without Revisions <2010 to July Week 1 2017>  Search Strategy:  --------------------------------------------------------------------------------   1. Exp craniocerebral trauma 2. (cereb$ adj (injur$ or traum$ or wound$)).mp. 3. (brain$ adj (injur$ or traum$ or wound$)).mp. 4. (head adj (injur$ or traum$ or wound$)).mp. 5. 1 or 2 or 3 or 4 6. limit 5 to English language 7. limit 6 to abstracts 8. 6 or 7 9. Limit 8 to humans 10. Limit 9 to "all child (0 to 18 years)"   -------------------------------------------------------------------------------- |

# Appendix E. Excluded Studies

**Intracranial Pressure Monitoring**

1. Bailey BM, Liesemer K, Statler KD, et al:. Monitoring and prediction of intracranial hypertension in pediatric traumatic brain injury: clinical factors and initial head computed tomography. *J Trauma Acute Care Surg* 2012; 72:263-270

2. Behmanesh B, Setzer M, Noack A, et al:. Noninvasive epicutaneous transfontanelle intracranial pressure monitoring in children under the age of 1 year: a novel technique. *J Neurosurg Pediatr* 2016; 18:372-376

3. Bennett Colomer C, Solari Vergara F, Tapia Perez F, et al:. Delayed intracranial hypertension and cerebral edema in severe pediatric head injury: risk factor analysis. *Pediatr Neurosurg* 2012; 48:205-209

4. Davidson GH, Maier RV, Arbabi S, et al:. Impact of operative intervention delay on pediatric trauma outcomes. *J Trauma Acute Care Surg* 2012; 73:162-167

5. Exo J, Kochanek PM, Adelson PD, et al:. Intracranial pressure-monitoring systems in children with traumatic brain injury: combining therapeutic and diagnostic tools. *Pediatr Crit Care Med* 2011; 12:560-565

6. Falk AC. Impact of elevated ICP on outcome after paediatric traumatic brain injury requiring intensive care. *Childs Nerv Syst* 2012; 28:1069-1075

7. Forsyth RJ, Parslow RC, Tasker RC, et al:. Prediction of raised intracranial pressure complicating severe traumatic brain injury in children: implications for trial design. *Pediatr Crit Care Med* 2008; 9:8-14

8. Guerra SD, Carvalho LFA, Affonseca CA, et al:. Factors associated with intracranial hypertension in children and teenagers who suffered severe head injuries. *J Pediatr (Rio J)* 2010; 86:73-79

9. Kouvarellis AJ, Rohlwink UK, Sood V, et al:. The relationship between basal cisterns on CT and time-linked intracranial pressure in paediatric head injury. *Childs Nerv Syst* 2011; 27:1139-1144

10. Kristiansson H, Nissborg E, Bartek J, Jr., et al:. Measuring elevated intracranial pressure through noninvasive methods: a review of the literature. *J Neurosurg Anesthesiol* 2013; 25:372-385

11. Wainwright MS, Lewandowski R. Bioinformatics analysis of mortality associated with elevated intracranial pressure in children. *Acta Neurochir Suppl* 2012; 114:67-73

**Advanced Neuromonitoring**

1. Adelson PD, Srinivas R, Chang Y, et al:. Cerebrovascular response in children following severe traumatic brain injury. *Childs Nerv Syst* 2011; 27:1465-1476

2. Ragan DK, McKinstry R, Benzinger T, et al:. Depression of whole-brain oxygen extraction fraction is associated with poor outcome in pediatric traumatic brain injury. *Pediatr Res* 2012; 71:199-204

3. Rohlwink UK, Zwane E, Fieggen AG, et al:. The relationship between intracranial pressure and brain oxygenation in children with severe traumatic brain injury. *Neurosurgery* 2012; 70:1220-1231

**Neuroimaging**

1. Colbert CA, Holshouser BA, Aaen GS, et al:. Value of cerebral microhemorrhages detected with susceptibility-weighted MR Imaging for prediction of long-term outcome in children with nonaccidental trauma. *Radiology* 2010; 256:898-905

2. Figaji AA, Zwane E, Fieggen AG, et al:. Transcranial Doppler pulsatility index is not a reliable indicator of intracranial pressure in children with severe traumatic brain injury. *Surg Neurol* 2009; 72:389-394

3. LaRovere KL, O'Brien NF, Tasker RC. Current opinion and use of transcranial doppler ultrasonography in traumatic brain injury in the pediatric intensive care unit. *J Neurotrauma* 2016; 33:2105-2114

4. Melo JR, Di Rocco F, Blanot S, et al:. Transcranial Doppler can predict intracranial hypertension in children with severe traumatic brain injuries. *Childs Nerv Syst* 2011; 27:979-984

5. Shetty VS, Reis MN, Aulino JM, et al:. ACR appropriateness criteria head trauma. *J Am Coll Radiol* 2016; 13:668-679

6. Smitherman E, Hernandez A, Stavinoha PL, et al:. Predicting outcome after pediatric traumatic brain injury by early magnetic resonance imaging lesion location and volume. *J Neurotrauma* 2016; 33:35-48

7. Steinborn M, Schäffeler C, Kabs C, et al:. CT and MR imaging of primary cerebrovascular complications in pediatric head trauma. *Emerg Radiol* 2010; 17:309-315

8. Suskauer S. Emerging data in pediatric traumatic brain injury. *J Pediatr Rehabil Med* 2015; 8:269

9. Young JY, Duhaime A-C, Caruso PA, et al:. Comparison of non-sedated brain MRI and CT for the detection of acute traumatic injury in children 6 years of age or less. *Emerg Radiol* 2016; 23:325-331

**Intracranial Pressure Thresholds**

1. Guiza F, Depreitere B, Piper I, et al:. Visualizing the pressure and time burden of intracranial hypertension in adult and paediatric traumatic brain injury. *Intensive Care Med* 2015; 41:1067-1076

2. Sigurta A, Zanaboni C, Canavesi K, et al:. Intensive care for pediatric traumatic brain injury. *Intensive Care Med* 2013; 39:129-136

**Cerebral Perfusion Pressure Thresholds**

1. Kumar R, Singhi S, Singhi P, et al:. Randomized controlled trial comparing cerebral perfusion pressure-targeted therapy versus intracranial pressure-targeted therapy for raised intracranial pressure due to acute CNS infections in children. *Crit Care Med* 2014; 42:1775-1787

**Hyperosmolar Therapy**

1. Bennett TD, Statler KD, Korgenski EK, et al:. Osmolar therapy in pediatric traumatic brain injury. *Crit Care Med* 2012; 40:208-215

2. Carcillo JA. Intravenous fluid choices in critically ill children. *Curr Opin Crit Care* 2014; 20:396-401

**Analgesics, Sedatives and Neuromuscular Blockade**

1. Bar-Joseph G, Guilburd Y, Guilburd J. Ketamine effectively prevents intracranial pressure elevations during endotracheal suctioning and other distressing interventions in patients with severe traumatic brain injury. *Crit Care Med* 2009; 37:A402

2. Zeiler FA, Teitelbaum J, West M, et al:. The ketamine effect on ICP in traumatic brain injury. *Neurocrit Care* 2014; 21:163-173

**Cerebrospinal Fluid Drainage**

None

**Seizure Prophylaxis**

1. Klein P, Herr D, Pearl PL, et al:. Results of phase 2 safety and feasibility study of treatment with levetiracetam for prevention of posttraumatic epilepsy. *Arch Neurol* 2012; 69:1290-1295

**Ventilation Therapies**

1. Cirulis MM, Hamele MT, Stockmann CR, et al:. Comparison of the new adult ventilator-associated event criteria to the Centers for Disease Control and Prevention pediatric ventilator-associated pneumonia definition (PNU2) in a population of pediatric traumatic brain injury patients. *Pediatr Crit Care Med* 2016; 17:157-164

2. Hansen G, Vallance JK. Ventilation monitoring in severe pediatric traumatic brain injury at nontrauma centers. *Air Med J* 2015; 34:278-282

3. Ramaiah VK, Sharma D, Ma L, et al:. Admission oxygenation and ventilation parameters associated with discharge survival in severe pediatric traumatic brain injury. *Childs Nerv Syst* 2013; 29:629-634

**Temperature Control**

1. Fink EL, Kochanek PM, Clark RS, et al:. Fever control and application of hypothermia using intravenous cold saline. *Pediatr Crit Care Med* 2012; 13:80-84

2. Mancera M, DeCou J. Towards evidence based emergency medicine: best BETs from the Manchester Royal Infirmary. BET 1: efficacy of hypothermia for traumatic brain injury in children. *Emerg Med J* 2012; 29:683-685

3. Salonia R, Empey PE, Poloyac SM, et al:. Endothelin-1 is increased in cerebrospinal fluid and associated with unfavorable outcomes in children after severe traumatic brain injury. *J Neurotrauma* 2010; 27:1819-1825

4. Schibler A, Humphreys S. Increased brain tissue oxygen tension in children with traumatic brain injury using temperature-corrected guided ventilation during prophylactic hypothermia. *Crit Care Resusc* 2012; 14:20-24

5. Zhang BF, Wang J, Liu ZW, et al:. Meta-analysis of the efficacy and safety of therapeutic hypothermia in children with acute traumatic brain injury. *World Neurosurg* 2015; 83:567-573

**Barbiturates**

None

**Decompressive Craniectomy**

1. Adamo MA, Drazin D, Smith C, et al:. Comparison of accidental and nonaccidental traumatic brain injuries in infants and toddlers: demographics, neurosurgical interventions, and outcomes. *J Neurosurg Pediatr* 2009; 4:414-419

2. Aghakhani N, Durand P, Chevret L, et al:. Decompressive craniectomy in children with nontraumatic refractory high intracranial pressure. Clinical article. *J Neurosurg Pediatr* 2009; 3:66-69

3. Beuriat P, Javouhey E, Szathmari A, et al:. Decompressive craniectomy in the treatment of post-traumatic intracranial hypertension in children: our philosophy and indications. *J Neurosurg Sci* 2015; 59:405-428

4. Davidson GH, Maier RV, Arbabi S, et al:. Impact of operative intervention delay on pediatric trauma outcomes. *J Trauma Acute Care Surg* 2012; 73:162-167

5. Fayeye O, Ushewokunze S, Stickley J, et al:. Does direct admission from an emergency department with on-site neurosurgical services facilitate time critical surgical intervention following a traumatic brain injury in children? *Br J Neurosurg* 2013; 27:326-329

6. Glick RP, Ksendzovsky A, Greesh J, et al:. Initial observations of combination barbiturate coma and decompressive craniectomy for the management of severe pediatric traumatic brain injury. *Pediatr Neurosurg* 2011; 47:152-157

7. Gouello G, Hamel O, Asehnoune K, et al:. Study of the long-term results of decompressive craniectomy after severe traumatic brain injury based on a series of 60 consecutive cases. *ScientificWorldJournal* 2014; 2014:207585

8. Guresir E, Schuss P, Seifert V, et al:. Decompressive craniectomy in children: single-center series and systematic review. *Neurosurgery* 2012; 70:888-889

9. Jacob AT, Heuer GG, Grant R, et al:. Decompressive hemicraniectomy for pediatric traumatic brain injury: long-term outcome based on quality of life. *Pediatr Neurosurg* 2011; 47:81-86

10. Melo JR, Di Rocco F, Bourgeois M, et al:. Surgical options for treatment of traumatic subdural hematomas in children younger than 2 years of age. *J Neurosurg Pediatr* 2014; 13:456-461

11. Simma B, Tscharre A, Hejazi N, et al:. Neurologic outcome after decompressive craniectomy in children. *Intensive Care Med* 2002; 28:1000

12. Weintraub D, Williams BJ, Jane J, Jr. Decompressive craniectomy in pediatric traumatic brain injury: a review of the literature. *NeuroRehabilitation* 2012; 30:219-223

**Nutrition**

1. Fivez T, Kerklaan D, Mesotten D, et al:. Early versus late parenteral nutrition in critically ill children. *N Engl J Med* 2016; 374:1111-1122

2. Malakouti A, Sookplung P, Siriussawakul A, et al:. Nutrition support and deficiencies in children with severe traumatic brain injury. *Pediatr Crit Care Med* 2012; 13:e18-24

3. Mtaweh H, Smith R, Kochanek PM, et al:. Energy expenditure in children after severe traumatic brain injury. *Pediatr Crit Care Med* 2014; 15:242-249

4. Smith RL, Lin JC, Adelson PD, et al:. Relationship between hyperglycemia and outcome in children with severe traumatic brain injury. *Pediatr Crit Care Med* 2012; 13:85-91

5. Vavilala MS, Kernic MA, Wang J, et al:. Acute care clinical indicators associated with discharge outcomes in children with severe traumatic brain injury. *Crit Care Med* 2014; 42:2258-2266

**Corticosteroids**

None

**Miscellaneous**

1. Leeper CM, Nasr I, McKenna C, et al:. Elevated admission international normalized ratio strongly predicts mortality in victims of abusive head trauma. *J Trauma Acute Care Surg* 2016; 80:711-716

2. Lichte P, Andruszkow H, Kappe M, et al:. Increased in-hospital mortality following severe head injury in young children: results from a nationwide trauma registry. *Eur J Med Res* 2015; 20:65

**Second Edition Class 3 Excluded Studies**

| **Topic** | **Study** | **Reason** |
| --- | --- | --- |
| ICP Thresholds | Esparza et al., 1985 | Treatments not consistent with current practice |
| Analgesics | De Bray et al., 1993 | Single dose of thiopental not used as a sedative |
| Temperature Control | Hendrick et al., 1959 | Uncontrolled treatment series, topic now has higher level of evidence |

# Appendix F. Criteria for Quality Assessment of Individual Studies

**Study Quality Assessment Criteria**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Randomized Controlled Trials** | **Cohort Studies (Prospective and**  **Retrospective)** | **Case-Control Studies** | **Treatment Series** | **Thresholds Studies** |
| * Was the allocation sequence generated adequately? * Was the treatment allocation adequately concealed? * Were patients/intervention providers/outcome assessors blinded? * Were groups similar at baseline? * Was loss to follow up 20% or less? * Was loss to follow up similar across groups? (that is were comparable groups maintained) * Was intention-to-treat analysis used? (narrow definition—people analyzed according to group assigned, not about loss to follow up). * Was the study registered? * Were outcomes pre specified and were primary/pre specified outcomes reported? * Were outcomes assessed using valid and reliable measures? | * Was the selection of patients into the cohort non biased? * Were outcome assessors blinded? * Was loss to follow up 20% or less? * Was loss to follow up similar across groups? * Were groups similar at baseline or * Were statistical analyses used to control for confounders (minimum age, CGS, pupil status, CT scan, hypotension)? * Was study registered? * Were outcomes pre specified and were primary/pre specified outcomes reported? * Were confounding variables and outcomes assessed using valid and reliable measures? | * Were cases and controls selected appropriately? * Were groups similar at baseline or * Were statistical analyses used to control for confounders (minimum age, CGS, pupil status, CT scan, hypotension)? * Were outcomes pre specified and were primary/pre specified outcomes reported?   Were confounding variables/ outcomes assessed using valid and reliable measures? | * Was there consecutive patient enrollment? * Were the inclusion and exclusion criteria explicitly stated? * Was there a well-defined study (treatment) protocol? * Were patients similar at baseline or were statistical analyses used to control for confounders (minimum age, CGS, pupil status, CT scan, hypotension)? * Were outcomes pre specified and were primary/pre specified outcomes reported? * Were confounding variables/ outcomes assessed using valid and reliable measures? | * What was the study type? * Was a rationale given for a specific threshold value or criteria established to determine one? * Was there a non-biased selection of patients into the cohort; or selection of cases and controls using the same exclusion criteria in case control? * Prospective Cohort: Was there blind or independent assessment of outcomes? * Case-control: Was there an accurate ascertainment of cases? * Was there an adequate sample size? * Follow-up rate: Outcomes data available for > or = 85%? * Is the monitoring technology and procedure the same or equivalent for all patients? * Was the treatment protocol similar for similar patients? |

# Appendix G. Quality of the Body of Evidence Assessment

Quality of the Body of Evidence Ratings and Criteria

**Criteria**

Assessing the quality of the body of evidence involves four domains: the aggregate quality of the studies, the consistency of the results, whether the evidence provided is direct or indirect, and the precision of the evidence. These are defined below:

Quality of Individual Studies: This considers the quality of the individual studies. It details how many are Class 1, Class 2, and Class 3.

Consistency: Consistency is the extent to which the results and conclusions are similar across studies. It is rated High (all are similar), Moderate (most are similar), Low (no one conclusion is more frequent). It is NA (not applicable) when the body of evidence consists of a single study.

Directness: We define directness as whether the study population is the same as the population of interest and whether the study includes clinical rather than intermediate outcomes. We included two types of indirect evidence in this edition:

* Evidence that improvement in an intermediate outcome is associated with important health outcomes.
* Evidence from samples with mixed ages, severities, or pathologies.

When indirect evidence was included, it is noted in the table describing the quality of the body of evidence and in the evidence table.

Precision: Precision is the degree of certainty surrounding the effect estimate for a given outcome. Precision is rated as High, Moderate, and Low. How this is determined depends on the type of analysis used in a specific study but may include consideration of the range of confidence intervals or the significance level of p-values.

**Ratings**

These criteria are then considered when assigning a rating to the body of evidence.

The ratings are defined as follows:

* High—High confidence that the evidence reflects the true effect. Further research is very unlikely to change the confidence in the estimate of effect.

This rating requires either multiple high-quality studies with consistent findings and precise estimates of effect or a single, multi-site RCT with definitive results.

* Moderate—Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of effect and may change the estimate.

This rating requires at least one high-quality study or moderate-quality with a precise estimate of effect. It may include several moderate quality studies that are generally consistent but with wide confidence intervals (low precision) or a group of studies with some inconsistent findings, but with a majority of studies with similar findings.

* Low—Low confidence that the evidence reflects the true effect. Further research is likely to change the confidence in the estimate of effect and is likely to change the estimate.

A low-quality body of evidence may be a single moderate-quality study or multiple studies with inconsistent findings or lack of precision.

* Insufficient— Evidence either is unavailable or does not permit a conclusion.

Insufficient is most common when no evidence was identified. However, it can occur when there is inconsistency across studies and precision is low or varies widely.