Guidelines for the Management of Pediatric Severe Traumatic Brain Injury, Third Edition: Update of the Brain Trauma Foundation Guidelines

Patrick M. Kochanek, MD, MCCM[1]; Robert C. Tasker, MA, MD, FRCP[2]; Nancy Carney, PhD[3]; Annette M. Totten, PhD[4]; P. David Adelson, MD, FACS, FAAP, FAANS[5]; Nathan R. Selden, MD, PhD, FACS, FAAP[6]; Cynthia Davis-O'Reilly, BS[7]; Erica L. Hart, MST[8]; Michael J. Bell, MD[9]; Susan L. Bratton, MD, MPH, FAAP[10]; Gerald A. Grant, MD[11]; Niranjan Kissoon, MD, FRCP(C), FAAP, MCCM, FACPE[12]; Karin E. Reuter-Rice, PhD, CPNP-AC, FCCM, FAAN[13]; Monica S. Vavilala, MD[14]; Mark S. Wainwright, MD, PhD[15]

[1]Ake N. Grenvik Professor of Critical Care Medicine, Vice Chair, Department of Critical Care Medicine, Professor of Anesthesiology, Pediatrics, Bioengineering, and Clinical and Translational Science, Director, Safar Center for Resuscitation Research, University of Pittsburgh School of Medicine, UPMC Children's Hospital of Pittsburgh, Pittsburgh, PA.

[2]Department of Neurology and Department of Anesthesiology, Critical Care and Pain Medicine, Boston Children's Hospital, Harvard Medical School, Boston, MA.

[3]Professor, Pacific Northwest Evidence-based Practice Center, Department of Medical Informatics and Clinical Epidemiology, Oregon Health & Science University, Portland, OR.

[4]Associate Professor, Pacific Northwest Evidence-based Practice Center, Department of Medical Informatics and Clinical Epidemiology, Oregon Health & Science University, Portland, OR.

[5]Diane and Bruce Halle Endowed Chair in Pediatric Neurosciences, Chief, Pediatric Neurosurgery, Director, BARROW Neurological Institute at Phoenix Children's Hospital, Phoenix, AZ.

[6]Chair, Department of Neurological Surgery, Oregon Health & Science University, Portland, OR.

[7]Research Associate, Pacific Northwest Evidence-based Practice Center, Department of Medical Informatics and Clinical Epidemiology, Oregon Health & Science University, Portland, OR.

[8]Research Assistant, Pacific Northwest Evidence-based Practice Center, Department of Medical Informatics and Clinical Epidemiology, Oregon Health & Science University, Portland, OR.

[9]Professor and Chief, Critical Care Medicine, Children's National Medical Center, Washington, DC.

[10]Emeritus Professor of Pediatrics, University of Utah, Salt Lake City, UT.

[11]Department of Neurosurgery, Stanford University, Stanford, CA.

[12]Department of Pediatrics, British Columbia's Children's Hospital, Clinical Investigator, Child and Family Research Institute, University of British Columbia, Vancouver, BC. Canada.

[13]School of Nursing/School of Medicine, Department of Pediatrics, Division of Pediatric Critical Care Medicine, Duke University, Durham, NC.

[14]Professor & Vice Chair Strategic Affairs, Anesthesiology & Pain Medicine, Professor, Pediatrics, Director, Harborview Injury Prevention and Research Center (HIPRC), University of Washington, Seattle, WA.

[15]Herman and Faye Sarkowsky Endowed Chair, Head, Division of Pediatric Neurology, University of Washington, Seattle Children's Hospital, Seattle, WA.

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Severe Traumatic Brain Injury in Infants, Children, and Adolescents in 2019: Some Overdue Progress, Many Remaining Questions, and Exciting Ongoing Work in the Field of Traumatic Brain Injury Research

In this Supplement to *Pediatric Critical Care Medicine*, we are pleased to present the Third Edition of the Guidelines for the Management of Pediatric Severe Traumatic Brain Injury (TBI). This body of work updates the Second Edition of the guidelines that was published in 2012 (1). It represents a substantial effort by a multidisciplinary group of individuals assembled to reflect the team approach to the treatment of these complex, critically ill patients that is essential to optimizing critical care and improving outcomes. This work also represents the strong and always-evolving partnership between investigators from the medical and research communities, forged in Chicago in 2000, from which the first pediatric TBI guidelines were developed. The mutual trust and respect we share have been the foundation of our commitment to bringing evidence-based care to children with TBI.

Updating these guidelines was particularly exciting to the individuals who have participated in the previous two editions because several new studies have been published which begin to address a number of major gaps in the pediatric TBI literature—gaps that were specifically identified as targets for future research in earlier editions. For example, we are now able to include reports on the effects of commonly used sedatives and analgesics on intracranial pressure (ICP). Similarly, initial head-to-head comparisons of the influence of agents in routine "real world" use such as hypertonic saline (HTS), fentanyl, and others now inform these guidelines (2, 3). A total of 48 new studies were included in this Third Edition. Although some progress has been made and should be celebrated, overall the level of evidence informing these guidelines remains low. High-quality randomized studies that could support level I recommendations remain absent; the available evidence produced only three level II recommendations, whereas most recommendations are level III, supported by low-quality evidence.

Based in part on a number of requests from the readership to individual clinical investigators, we have included a companion article in the regular pages of *Pediatric Critical Care Medicine* that presents a "Critical Pathway" algorithm of care for both first-tier and second-tier (refractory intracranial hypertension) approaches. The algorithm reflects both the evidence-based recommendations from these guidelines and consensus-based expert opinion, vetted by the clinical investigators, where evidence was not available. An algorithm was provided in the First but not Second Editions of the guidelines, and we believe that given the new reports available, along with the existing gaps in evidence, a combination of evidence-based and consensus-based recommendations provides additional and much-needed guidance for clinicians at the bedside. The algorithm also addresses a number of issues that are important but were not previously covered in the guidelines, given the lack of research and the focus on evidence-based recommendations. This includes addressing issues such as a stepwise approach to elevated ICP, differences in tempo of therapy in different types of patients, scenarios with a rapidly escalating need for ICP-directed therapy in the setting of impending herniation, integration of multiple monitoring targets, and other complex issues such as minimal versus optimal therapeutic targets and approaches to weaning therapies. We hope that the readership finds the algorithm document helpful, recognizing that it represents a challenging albeit important step.

Designing and developing this pediatric TBI evidence-based guidelines document required an expert administrative management team, and to that end, we are extremely grateful to the staff of the Pacific Northwest Evidence-based Practice Center, Oregon Health & Science University, for their vital contribution to this work. We are also grateful to the Brain Trauma Foundation and the Department of Defense for supporting the development and publication of these guidelines documents. We are grateful to the endorsing societies for recognizing the importance of this work and for the considerable work of the clinical investigators in constructing the final document. We are also pleased to have collaborated with the Congress of Neurological Surgeons and the journal *Neurosurgery* that is copublishing the Executive Summary document of these guidelines for its readership. We are also grateful to Hector Wong for serving as Guest Editor, along with the external reviewers of this final document. Finally, we thank each of the clinical investigators and coauthors on this project. We believe that the considerable uncompensated time and effort devoted to this important project will help to educate clinicians worldwide and enhance the outcomes of children with severe TBI. Clinical investigators provided Conflict of Interest Disclosures at the beginning of the process, which were re-reviewed at the time of publication. No clinical investigator made inclusion decisions or provided assessments on publications for which they were an author.

Looking forward, it is important to recognize that these guidelines were written as the Approaches and Decisions in Acute Pediatric TBI Trial (ADAPT) (4–6), one of the most important in the field of pediatric TBI, was coming to a close. The ADAPT completed enrollment of 1,000 cases of severe pediatric TBI and is one example of the recent heightened general interest in TBI as a disease. This new interest in the importance of TBI has emerged in part from the recognition of the high prevalence of TBI across the injury severity spectrum, particularly concussion, and from

the need for new classification systems and new trial design for TBI in both children and adults (7, 8). In addition, the emerging links between TBI and a number of neurodegenerative diseases have broadened the interest in TBI, have led to additional support of TBI research, and have produced an unprecedented level of research in TBI and a quest for new therapies (9–11). We expect that the results of ADAPT, along with those of other ongoing and recently completed research in the field, will help provide new insight and clarity into the acute medical management (MM) of infants, children, and adolescents with severe TBI, and mandate further refinement of the recommendations in these documents. We know that we speak for the entire team of clinical investigators in welcoming the opportunity to incorporate additional high-level evidence into future updates of these guidelines.

METHODS

The methods for developing these guidelines were organized in two phases: a systematic review, assessment, and synthesis of the literature; and use of that product as the foundation for evidence-based recommendations. These guidelines are the product of the two-phased, evidence-based process.

Based on almost 2 decades of collaboration, the team of clinical investigators and methodologists (**Appendix A**, Supplemental Digital Content 1, http://links.lww.com/PCC/A774) is grounded in and adheres to the fundamental principles of evidence-based medicine to derive recommendations, and is committed to maintaining the distinction between evidence and consensus. It is important that this distinction is clear to promote transparency and inspire innovative future research that will expand the evidence base for TBI care.

Because these guidelines only provide recommendations based on available evidence, most often they do not provide direction for all phases of clinical care. Ideally, clinically useful protocols begin with evidence-based guidelines, and then use clinical experience and consensus to fill the gaps where evidence is insufficient. The goal is to use the evidence and the evidence-based recommendations as the backbone to which expertise and consensus can be added to produce protocols appropriate to specific clinical environments (**Fig. 1**, "*Future Research* section"). In a process independent from developing this Third Edition of the guidelines, the team engaged in a consensus process and produced the algorithm for treatment of severe TBI in pediatric patients.

The following "*Methods* section" describes the process we used to produce the systematic review and evidence-based recommendations. The methods used to develop the algorithm are described in that document (12).

Phase I: Systematic Evidence Review and Synthesis

Scope of the Systematic Review

Criteria for Including Publications

Appendix B (Supplemental Digital Content 1, http://links.lww.com/PCC/A774) lists the criteria for including studies for review using the categories of population, interventions,

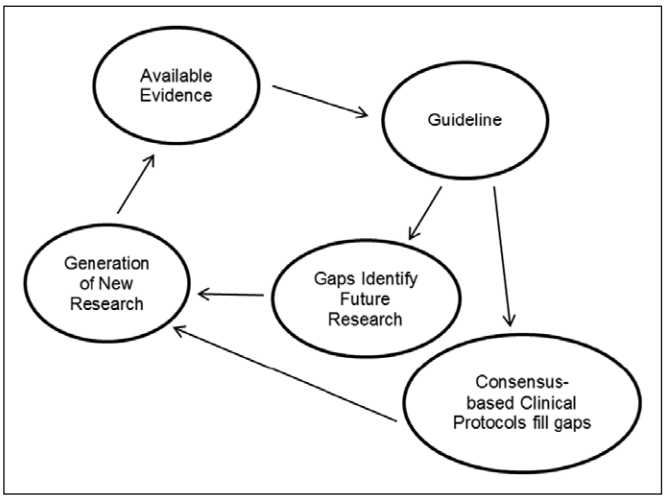

Figure 1. Dynamic process for guidelines, protocols, and future research. The diagram shows the flow of information from available evidence to a guideline. The guideline leads to gaps that identify future research and consensus-based clinical protocols that fill gaps, both of which lead to a generation of new research.

comparators, outcomes, timing, settings, study designs, and publication types. The criteria for population are as follows:

- Age 18 years old or younger
- TBI
- Glasgow Coma Scale (GCS) score less than 9

Included Topics. The team chose to carry forward topics from the Second Edition of these guidelines. No new topics were added. The topics are organized in three categories that are specific to severe TBI in children: monitoring, thresholds, and treatments.

Monitoring

1. ICP
2. Advanced neuromonitoring
3. Neuroimaging

Thresholds

4. ICP
5. Cerebral perfusion pressure (CPP)

Treatments

6. Hyperosmolar therapy
7. Analgesics, sedatives, and neuromuscular blockade (NMB)
8. Cerebrospinal fluid (CSF) drainage
9. Seizure prophylaxis
10. Ventilation therapies
11. Temperature control
12. Barbiturates
13. Decompressive craniectomy
14. Nutrition
15. Corticosteroids

Major Changes for This Edition. Major changes for this edition are summarized here, and details are provided in **Appendix C**

(Supplemental Digital Content 1, http://links.lww.com/PCC/A774).

- The clinical investigators and methods team identified three primary endpoints considered important health outcomes for pediatric patients with TBI:
- To improve overall outcomes (mortality, morbidity, function)
- To control ICP
- To prevent posttraumatic seizures (PTSs)
- Two new meta-analyses were added to the evidence base for temperature control.
- The title of "Hyperventilation" was changed to "Ventilation Therapies."
- Recommendations are provided as level I, II, or III.

In some cases, publications from the second edition were not included in this 3rd Edition. Our rationale for excluding previously included studies was based on identification of current material that superseded our earlier work (See **Appendix E**, Supplemental Digital Content 1, http://links.lww.com/PCC/A774). Similarly, we removed or changed recommendations from the 2nd Edition when the current literature provided new and/or more accurate information (see Appendix A, Supplemental Digital Content 1, http://links.lww.com/PCC/A774).

Study Selection and Compilation of Evidence

Literature Search Strategies. The research librarian who worked on the Second Edition reviewed and updated the search strategies for that edition and executed the searches for this Third Edition. Ovid/MEDLINE was searched from 2010 to May of 2015, and an update was performed to include articles published and indexed through June of 2017. Publications recommended by peers that were not captured in the search were reviewed, and those meeting inclusion criteria were included in the final library. The search strategy is in **Appendix D** (Supplemental Digital Content 1, http://links.lww.com/PCC/A774).

Abstract and Full-Text Review. Abstracts for publications captured in the search were reviewed independently by two members of the methods team. Articles were retained for full-text review if at least one person considered them relevant based on the abstract. Two methods team members read each full-text article and determined whether it met the inclusion criteria (Appendix B, Supplemental Digital Content 1, http://links.lww.com/PCC/A774). The included and excluded full-text articles for each topic were also reviewed by one or more clinical investigators who took the lead on each topic, and full-text articles were available for review by all authors. The key criteria for inclusion were as follows: the study population was pediatric patients (age, ≤ 18 yr old) with severe TBI (defined as GCS score of 3–8) and the study assessed an included outcome. Publications with samples that included adults, moderate or mild severities, or pathologies other than TBI (indirect evidence) were considered when direct evidence was limited or not available. Discrepancies between reviewers were resolved via consensus or by a third reviewer. A list of studies excluded after full-text review is in Appendix E (Supplemental Digital Content 1, http://links.lww.com/PCC/A774).

Use of Indirect Evidence and Intermediate Outcomes

Direct evidence comes from studies that compare important health outcomes (e.g., mortality, morbidity, function) between two or more intervention groups or between an intervention group and a control group that represent the population of interest, in this case pediatric patients with severe TBI. When direct evidence was limited or not available, indirect evidence was used to support a recommendation. Indirect evidence has been defined in previous work by this methods team (1, 13, 14) and other evidence-based methods groups (15, 16). In this edition, we included two types of indirect evidence.

1. Evidence That Improvement in an Intermediate Outcome Is Associated With Important Health Outcomes

In some cases, there is a lack of direct evidence that utilization of a specific treatment option results in improved patient outcomes such as mortality or morbidity, but there is evidence about changes in an intermediate outcome, which is then associated with improved mortality or morbidity. The most notable intermediate outcome for the treatment of TBI is management of ICP. Multiple studies (cited in the ICP Monitoring topic of this guideline) consistently demonstrate that patients whose ICP is successfully maintained at or under a maximum threshold have reduced mortality and improved function. As a consequence, the clinical investigators elected to identify "Control of ICP" as an important intermediate outcome, and use the available indirect evidence to support the recommendations about monitoring ICP and for treatments designed to lower ICP.

Intermediate outcomes and indirect evidence of this nature were used in three topics for this edition of the guidelines: ICP Monitoring, Ventilation Therapies, and Temperature Control. In each of these topics, an intermediate outcome was used as the endpoint because, although direct evidence was lacking that intervening improves mortality or function, indirect evidence was available associating management of the intermediate outcome with improved mortality or function.

For ICP monitoring, the intermediate outcome was managed ICP; indirect evidence that patients with managed ICP had better outcomes was used to support the recommendation. For ventilation therapies, the intermediate outcomes were prevention of severe hypocarbia (SH). There were no pediatric studies that directly related hyperventilation to poor outcomes. However, there was evidence of an association between SH and mortality; thus, studies that demonstrated this association were used as indirect evidence. For temperature control, the intermediate outcomes were mean and peak CSF myelin basic protein concentrations and phenytoin levels.

2. Evidence From Samples With Mixed Ages, Severities, or Pathologies

In some cases, when direct evidence was lacking, we considered studies that included patients with mixed severities (mild, moderate, and severe TBI), mixed ages, or mixed pathologies (traumatic and non-TBI) using the following criteria:

1. How relevant to (or different from) our target population is the population in the indirect study?

2. To what extent does the relevant physiology of the population in the indirect study approximate the relevant physiology of the population of interest?
3. To what extent are differences in physiology expected to influence the outcome?
4. In what direction would these differences influence the observed effect?

In this edition, indirect evidence from studies with mixed severities, ages, or pathologies was included in the topics about analgesics, sedatives, and NMB; CSF drainage; and seizure prophylaxis.

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

Quality Assessment of Individual Studies

All included studies were assessed for potential for bias, which is an approach to assessing the internal validity or quality of an individual study. This assessment is a core component of systematic review methods. It is an approach to considering and rating studies in terms of how the study design and conduct addressed issues such as selection bias, confounding, and attrition. The criteria used for this edition are described in **Appendix F** (Supplemental Digital Content 1, http://links.lww.com/PCC/A774).

Two reviewers independently evaluated each study using the criteria appropriate for the study design (i.e., randomized controlled trials [RCTs], observational studies, studies of thresholds) and rated the study as class 1, 2, or 3 evidence based on the combination of study design and conduct. Class 1 is the highest class and is limited to good-quality RCTs. Class 2 includes moderate-quality RCTs and good-quality cohort or case-control studies. Class 3 is the lowest class and is given to low-quality RCTs, moderate- to low-quality cohort or case-control studies, and treatment series and other noncomparative designs. Differences in ratings were reconciled via consensus or the inclusion of a third reviewer as needed.

Data Abstraction

Data were abstracted from studies by a member of the methods team and checked for accuracy by a second member. Information was recorded about the study population, design, and results. Key elements of each included study are presented in the Summary of Evidence tables for each topic. Complete abstraction tables are available upon request.

Synthesis

The final phase of the evidence review is the synthesis of individual studies into information that the clinical investigators and the methods team use to develop recommendations. This synthesis is described for each topic in the section titled "*Evaluation of the Evidence*," following the Recommendations and preceding the Evidence Summary.

Identification of Subtopics and Synthesis

For each monitoring, thresholds, or treatment topic, the clinical investigators identified important subtopics or clinical questions. The studies in each topic were reviewed to determine if quantitative synthesis—meta-analysis—was feasible. This involved determining if the patient populations, specifics of the intervention, and the outcomes were similar enough across several studies that the study results could be combined. The result of this assessment is included in the Quality of the Body of Evidence table for each subtopic. For this edition, we did not identify any topics for which quantitative synthesis was appropriate according to current standards. For this reason, the evidence was synthesized qualitatively.

Quality of the Body of Evidence

Assessing the quality of the body of evidence involves four domains: the aggregate quality of the included individual studies, the consistency of the results across studies, whether the evidence provided is direct or indirect, and the precision of the estimates of the outcomes. The criteria and ratings are outlined below, and more detailed definitions are given in **Appendix G** (Supplemental Digital Content 1, http://links.lww.com/PCC/A774). In addition, the number of studies and number of included subjects are considered. Based on these, an overall assessment is made as to whether the quality of the body of evidence is high, moderate, low, or insufficient. The assessment of the body of evidence for each subtopic is included in a summary table in each section following the recommendations.

Criteria

Quality of Individual Studies: This identifies the quality of the individual studies. It details how many studies 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), or low (no one conclusion is more frequent). It is 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 outcomes are clinical rather than intermediate outcomes. Evidence is labeled as direct, indirect, or mixed.

Precision: Precision is the degree of certainty surrounding the effect estimate for a given outcome. Precision is rated high, moderate, or low. How this is determined depends on the type of analysis used in a specific study but may include consideration of the width of CIs, other indicators of variance, or the magnitude of *p* values used to determine statistical significance.

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.
- Moderate: Moderate confidence that the evidence reflects the true effect. Further research may change the confidence in the estimate of effect and may change the estimate.

- 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.
- Insufficient: Evidence is unavailable or does not permit a conclusion.

A determination of quality of the body of evidence requires a judgment about the relative importance of the criteria, and these may vary across topics and subtopics. The following general examples are provided to illustrate the variations that are possible but are not intended as exhaustive decision rules. If two or more class 1 studies demonstrate contradictory findings for a particular topic, the overall quality of the body of evidence may be assessed as low because there is uncertainty about the effect. Similarly, class 1 or 2 studies that provide indirect evidence may only constitute low-quality evidence overall. In some cases, the body of evidence may be a single study, but the rating may vary. A single study may constitute a high-quality body of evidence if it is a large, multisite, class 1 RCT; a moderate-quality body of evidence if it is a single-site, class 2 study with a sizable sample and moderate precision; or insufficient evidence if the sample is small and the precision of the estimate of effect is low.

Applicability

Applicability is the extent to which research findings are useful for informing recommendations for a broader population (usually the population that is the target of the recommendations). What is important to consider when assessing applicability will vary depending on the topic, and the assessment is context specific. Consequently, there is currently no generally accepted universal rating system for applicability. Common considerations focus on the characteristics of the patient population (e.g., to which patients are the results applicable?) and the settings for care delivery (e.g., where could a similar result be expected?). Even if the patient population meets the inclusion criteria established for the review, there may be specific characteristics that affect applicability. The characteristics of the setting in which a study was conducted may also be important to consider. For example, a study conducted in a Veterans Administration (VA) Medical Center may or may not be applicable to other settings, depending on how similar the Veterans are to the population of interest or how similar the context of the VA is to the care setting of interest. Additional characteristics to be considered may include the geographic location (e.g., country, state, urban, or rural) and the type of hospital (e.g., level of trauma center). The geographic area and type of hospital are considered because it is possible that the patients, practice patterns, and available services are different across environments. In this edition, we consider the applicability of individual studies in the "*Quality of the Body of Evidence and Applicability* section" immediately following the recommendations.

Phase II: Development of Recommendations

Inclusion of Recommendations

Class 1, 2, or 3 studies constitute the evidence on which the recommendations are based. Under our current methods, identification of evidence is necessary but not sufficient for the development of recommendations. No recommendations were made without a basis in evidence.

Once evidence was identified, whether it could be used to inform recommendations was based on the quality of the body of evidence and consideration of applicability. Given this, there were cases in which evidence was identified, but the quality was low and applicability concerns restricted our ability to translate the evidence into recommendations. Even if a recommendation was not made, the evidence was included for future consideration because in the future, new studies may be added, resulting in changes in the assessment of the quality of the body of evidence.

Level of Recommendation

Recommendations in this edition are designated as level I, level II, or level III. The level of recommendation is determined by the assessment of the quality of the body of evidence, rather than the class of the included studies. The levels were primarily based on the quality of the body of evidence as follows:

- Level I recommendations were based on a high-quality body of evidence.
- Level II recommendations were based on a moderate-quality body of evidence.
- Level III recommendations were based on a low-quality body of evidence.

Applicability could result in a level III recommendation (e.g., a "moderate-quality body of evidence" with significant applicability concerns). In this edition, applicability alone was not used to downgrade a recommendation. However, given the lack of standards and developed methods in this area, we cited applicability issues that were identified and discussed by the clinical investigators.

"Insufficient" was used in cases where there were no studies identified or because the body of evidence had major quality limitations. If the evidence was insufficient, no recommendations were made.

Recommendation Review and Revision

Preliminary Topic Reviews. After completion of the literature review, identification of new studies, quality assessment, and data abstraction, the methods team sent drafts for each topic to two clinical investigators. The clinical investigators read the included studies and the draft recommendations, provided input, and suggested additional studies for consideration. Methods team members incorporated the input, acquired and reviewed new studies, and provided the clinical investigators with new publications and a revised summary of the evidence for each topic.

Clinical Investigator Review Meeting. In a day-long meeting in 2016, each topic was presented and discussed by the group. Based on these discussions, the methods team revised the draft guidelines.

Review of Complete Draft. The complete draft of all topics and the other sections of the guidelines (e.g., Methods; Appendices, Supplemental Digital Content 1, http://links.lww.com/PCC/A774) was sent to all clinical investigators for review and

comment. Phone conferences and e-mail exchanges occurred through April 2018 to answer questions, discuss the draft, and finalize the document.

Peer Review

After revisions were made based on input from the clinical investigators, the complete, revised Third Edition and an Executive Summary were sent to the journal *Pediatric Critical Care Medicine* for peer review. A comprehensive peer review was also conducted by members of the American Association of Neurological Surgeons/Congress of Neurological Surgeons Joint Guidelines Review Committee, in collaboration with the clinical investigators and methods team, to facilitate publication in the journal *Neurosurgery*.

MONITORING

ICP Monitoring

Recommendations

Strength of Recommendations: Weak

Levels I and II

There was insufficient evidence to support a level I or II recommendation for this topic.

Level III

To Improve Overall Outcomes. III.1. Use of ICP monitoring is suggested.

Changes From Prior Edition. There are no content changes from the Second Edition to the recommendations. Three new class 3 retrospective observational studies were added to the evidence base for this topic (17–19).

Introduction

Secondary injury to the brain after severe TBI is a result of a pathophysiologic cascade of events that reduces perfusion of surviving neural tissue, oxygen and metabolite delivery, and clearance of metabolic waste and toxins. Brain swelling resulting from vasogenic and or cytotoxic edema, occurring within the closed compartment of the skull, leads to intracranial hypertension, cerebral herniation syndromes, further focal ischemic injury, and brainstem compression. Sustained elevation of ICP thus represents a key pathophysiologic variable in the occurrence of secondary brain injury phase following TBI (20–22).

Since the late 1970s, significant improvements in both survival and functional outcome after severe TBI have been achieved using intensive care management protocols that center on the measurement of ICP and medical and surgical treatment of intracranial hypertension (23). Tilford et al (24) demonstrated that a PICU with higher occurrence of ICP monitoring in severely brain injured children, accompanied by specific ICP-directed medical interventions, resulted in a trend toward lower mortality than two comparison ICUs. Similarly, Tilford et al (23) demonstrated improved outcomes after severe TBI in an era during which the overall rates of ICP monitoring in these patients increased. Attempts to evaluate the independent benefit of direct ICP measurement to improve outcomes, per se, are confounded by the numerous therapeutic interventions that have been introduced simultaneously with increased ICP monitoring and have not been subjected individually to controlled trials. These confounders include protocol-driven prehospital care, tracheal intubation and oxygenation, aggressive treatment of systemic hypotension and hypovolemia, osmolar treatment of cerebral edema, rapid cranial CT imaging to detect mass lesions, and improved enteral and parenteral nutrition, among others.

Several studies demonstrate an association between intracranial hypertension and/or systemic hypotension and poor outcome after severe TBI (25–27). It is less clear, however, whether intracranial hypertension or reduced cerebral perfusion secondary to intracranial hypertension is the primary mechanism of secondary injury. CPP equals mean arterial blood pressure (MAP) minus mean ICP (28) and is the most readily available correlate of global cerebral perfusion (29–32). The relative value of ICP monitoring as a means of evaluating and manipulating CPP, versus avoidance of cerebral herniation events, is also unclear (33).

The lack of controlled trials on ICP monitoring limited the strength of the recommendations contained in the previous edition of the Guidelines for the Management of Pediatric Severe TBI (34). This dearth of strong evidence in children is associated with mixed adoption of guidelines-directed management in the United States and abroad (35–37). In addition, a single prospective controlled study carried out in South America in predominantly adult patients found no difference in outcome when comparing ICP monitoring-directed therapy or clinical-radiologic–directed therapy (38). Although the data in this study are not separable by age subgroup, the study did recruit patients more than 12 years old, and its results have therefore likely informed ongoing debate regarding the evidence for ICP monitoring in severe TBI and levels of adoption at individual centers. A 2007 survey of U.S. neurosurgeons and nonneurosurgeons caring for such patients found about 60% agreement and conformity with guidelines recommendations (35). In the United Kingdom in 2006, only 59% of children presenting with severe TBI underwent ICP monitoring, with only half of clinical units caring for such children using monitoring technology (36, 37). The use of monitoring in children less than 2 years old with severe TBI may be even less likely. Keenan et al (39) observed use of ICP monitoring in only 33% of patients in this young age group at multiple centers in the state of North Carolina. There is also significant variability in the use of various interventions for the treatment of intracranial hypertension at different centers (24).

Because a monitor is required to have an objective measure of ICP for directed critical care therapies, the outcome benefits of monitoring are considered to be supported inferentially.

Evaluation of the Evidence

Quality of the Body of Evidence. Studies included for this topic address the question about whether the information derived from the ICP monitor to inform treatment decisions improves outcomes for pediatric patients with TBI. Three large class 3 studies—two using patients as the unit of measure (17, 19) and one using hospitals as the unit of measure (18)—provided low-quality

TABLE 1. Intracranial Pressure Monitoring: Quality of the Body of Evidence

Components of Overall Quality: Class 3 Studies								
Topic	No. of Studies Study Design	Recommendation	Meta-Analysis Possible (Yes or No[a])	Total No. of Subjects (*n*)	Consistency (High, Moderate, Low)	Directness (Direct or Indirect)	Precision (High, Moderate, Low)	Quality of Evidence (High, Moderate, Low, or Insufficient)
Use of ICP monitoring (patients as unit of measure)	2 retrospective	III.1.	No	6,191	Low	Direct	Moderate	Low
Use of ICP monitoring (hospitals as unit of measure)	1 retrospective	III.1.	NA	4,667[b]	NA	Direct	Moderate	Low
Association of elevated ICP with outcomes	1 randomized controlled trial 2 prospective 10 retrospective 3 treatment series	III.1.	No	945	Moderate	Indirect	Low	Low

ICP = intracranial pressure, NA = not applicable.

[a]Meta-analysis to synthesize results is only possible if several studies address the same criteria/question, and other design criteria are met.

[b]Probable overlap of patients across Bennett et al (18, 19).

n indicates sample size.

direct evidence to support the recommendation. One RCT (40), two prospective studies (41, 42), 10 retrospective studies (30, 43–51), and three treatment series (52–54) provided indirect evidence that higher ICP is associated with poorer outcomes. The overall quality of the body of evidence is low (**Table 1**).

Applicability. The studies providing direct evidence (17–19) reported multicenter data from large samples in the United States. The findings were inconsistent, in that two (17, 18) suggested better outcomes for patients who are monitored and the third (19) suggested no benefit. The small observational studies and treatment series were conducted in the United States, Israel, United Kingdom, Spain, Lithuania, Switzerland, and Sweden (30, 40–54). There were no major applicability concerns.

Summary of the Evidence. Three class 3 studies provided direct evidence to support the recommendation (17–19). Sixteen class 3 studies from the Second Edition provided indirect evidence that patients with lower ICP have better outcomes (30, 40–54) (**Table 2**).

Evidence Synthesis

Are Children With Severe TBI at Risk of Intracranial Hypertension?. A number of small studies demonstrated a occurrence of intracranial hypertension in children with severe TBI (42, 43, 47, 49, 51–54). Some of these studies identified other clinical factors that, in combination with severe TBI in a child, are indicative of a high occurrence of intracranial hypertension. In these patients, "diffuse cerebral swelling" on CT scan is 75% specific for the presence of intracranial hypertension (54). In a study of 56 brain injured patients (39 of whom suffered from severe TBI), 32% of children had an initial ICP measurement greater than 20 mm Hg, but 50% had ICP max greater than 20 mm Hg at some point during their intensive care course (52). Intracranial hypertension (ICP > 20 mm Hg) may also be significantly more prevalent in children with severe TBI who do not demonstrate spontaneous motor function (80%) than those who do (20%) (42). These studies suggested that children presenting with severe TBI are at notable risk for intracranial hypertension. No specific markers have been identified which reliably determine the presence or absence of intracranial hypertension without monitoring in this population, and thus reliable noninvasive methods to detect intracranial hypertension are not currently available.

Are ICP Data Useful in Managing Pediatric Severe TBI?. Fifteen studies involving 857 pediatric patients demonstrated an association between intracranial hypertension (generally > 20 mm Hg) and poor neurologic outcome or death (30, 40–44, 46–54). Only one small study of 48 patients failed to demonstrate a clear association between intracranial hypertension and poor outcome (45), but in this study, children with higher peak ICP were immediately and successfully treated with decompressive craniectomy. These studies suggest that ICP is an important prognostic variable. It also plays a strong role both independently and as a component of CPP in directing the management of pediatric severe TBI patients.

Does ICP Monitoring and Treatment Improve Outcome?. Three recent retrospective studies using large patient populations provide direct evidence for the recommendation for this topic—two using patients as the unit of analysis (17, 19) and one using hospitals as the unit of analysis (18). Alkhoury and Kyriakides (17) and Bennett et al (18) suggest that improved clinical outcomes were associated with the use of ICP monitoring for the control of intracranial hypertension. Alkhoury and

TABLE 2. Intracranial Pressure Monitoring: Summary of Evidence

Class 3 Studies			
Reference Type of Trauma Center Geographic Location	**Study Design *n* Age (yr) Outcomes**	**Data Class**	**Results**
Use of information from ICP monitors to inform treatment: recommendation III.1.			
Bennett et al (19)[a] Multisite (30 children's hospitals participating in two national databases) United States	Retrospective registry review *n* = 3,084 (1,002 with ICP monitoring; 2,082 without) Age: mean, 7.03; range, NR Primary: composite of mortality, discharge to hospice or poor functional survival (placement of both a new tracheostomy and a new GT; mortality; poor functional survival)	Class 3 ICP-monitored group had greater treatment intensity than nonmonitored group. Unmeasured differences between the ICP and non-ICP groups may have contributed to the subsequent treatment intensity.	No ICP vs ICP Composite 484 patients (15.7%) had primary outcome. 241 (11.6%) vs 243 (24.3%) Mortality 197 (9.5%) vs 185 (18.5%) Poor functional survival 55 (5.5%) vs 43 (2.1%) Mortality and poor functional survival rates were higher for ICP-monitored group. With propensity matching weights to adjust for patient-level differences and clustering by hospital, no significant difference in functional survival for no ICP monitor group vs ICP monitor group (OR, 1.31; 95% CI, 0.99–1.74) ICP monitoring not significantly associated with hospital mortality but was associated with the composite outcome including mortality, discharge to hospice, or either tracheostomy or GT placement. The ICP-monitored group had longer hospital LOS, more mechanical ventilation days, more days of osmolar therapy, more days of inotropes or pressors, and more days of pentobarbital.
Alkhoury and Kyriakides (17)[a] Level I or level II trauma centers Multiple states (National Trauma Data Bank) United States	Retrospective *n* = 3,107 Age: ICP monitor group: mean, 8.8 No ICP monitor group: mean, 8.4; range, NR Mortality, hospital LOS, ICU LOS, ventilator days	Class 3 Differential loss to follow-up; groups different at baseline	Mortality ICP monitoring was associated with a reduction in mortality only for patients with a GCS score of 3 (OR, 0.64; 95% CI, 0.43–1.00). Monitoring of ICP was performed in only 7.7% of patients who met recommended monitoring criteria. LOS ICP monitoring group had a longer hospital stay than other groups: 21.0 vs 10.4 d; $p < 0.001$. Longer ICU stay: 12.6 vs 6.3 d; $p < 0.001$ Ventilator days 9.2 vs 4.7; $p < 0.001$
Bennett et al (18)[a] Multisite (36 children's hospitals participating in the Pediatric Health Information System database) United States	Retrospective GCS NR Head Abbreviated Injury Score at least 3 *n* = 4,667 Age: mean, NR; range, 0–18 Mortality or severe disability rates per hospital, ICP	Class 3 Blinding not specified; differential loss to follow-up not specified	Mortality or severe disability Hospitals with higher standardized ICP monitoring rates had lower rates of mortality or severe disability ($p < 0.001$ for the slope of poor outcomes by hospital monitoring rate). 55% of patients (2586/4,667) had ICP monitoring. ICP monitoring independently associated with ages 1 yr old and older (OR, 3.1; 95% CI, 2.5–3.8) vs age < 1 yr old. Adjusted logistic model indicated that 12.7% (95% CI, 7.7–20.4) of the total variance in ICP monitoring was between-hospital variance not explained by identified patient factors.

(*Continued*)

TABLE 2. (*Continued*). Intracranial Pressure Monitoring: Summary of Evidence

Class 3 Studies			
Reference Type of Trauma Center Geographic Location	**Study Design *n* Age (yr) Outcomes**	**Data Class**	**Results**
Association of elevated ICP with outcomes (indirect evidence supporting the need for ICP monitoring)			
Grinkeviciūte et al (45) PICU Kaunas, Lithuania	Retrospective *n* = 48 Age: mean, 10.6; range, 2.4 mo to 18 yr Survival, dichotomized GOS at 6 mo postinjury, ICP, CPP	Class 3 No control for confounders Indirect evidence Association of ICP with outcomes	Survival 47 (97.9%) for children admitted to the PICU GOS 43 (89.6%) favorable outcome ICP and CPP Differences in peak ICP (22.2 vs 24.6 mm Hg, respectively) in groups with favorable vs unfavorable outcomes were not statistically significant; also, no difference was seen between groups in minimum CPP. There was no difference in ICP maximum in groups with good (22.2 mm Hg) vs poor (24.6 mm Hg) outcomes.
Jagannathan et al (46) PICU, University of Virginia Health System Charlottesville, VA	Retrospective *n* = 96 Age: mean, 15.1; range, 3–18 ICP	Class 3 Unclear if analysis of ICP monitoring controlled for confounders Indirect evidence Association of ICP with outcomes	ICP ICP control achieved in 82/96 (85%) overall. 20/23 (87%) achieved ICP control with external ventricular drain. Of three not achieving ICP control, two died and one had craniectomy. Refractory ICP was associated with 100% mortality; the method used to control ICP had no correlation with mortality. Death was associated with refractory raised ICP, $p < 0.0001$, but not with ICP maximum, irrespective of the surgical or medical methods(s) used for successful reduction of ICP.
Adelson et al (40) Multisite multinational hospitals Pittsburgh, PA	Randomized controlled trial *n* = 75 48 in multicenter study 27 in single-center study Age: mean, 6.89; range, 0–13 Mortality, GOS-E at 3 and 6 mo postinjury	Class 3 No control for confounders (class 2 for hypothermia trial) Indirect evidence Association of ICP with outcomes	Mortality 8 of 48 deaths (17%) GOS-E ICP of 20 was most sensitive and specific for good outcome. The percent time with ICP < 20 mm Hg differed significantly in the good (90.8% ± 10.8%) vs poor (68.6% ± 35.0%) outcome groups, $p < 0.05$. Mean ICP was lower in patients who had a good outcome versus those with a poor outcome (good, 11.9 mm Hg; poor, 24.9 mm Hg); $p = 0.036$.
Wahlström et al (50) Neuro-ICUs at university hospitals Umea, Sweden	Retrospective *n* = 41 Age: median, 8.8; range, 3 mo to 14.2 yr Survival, dichotomized GOS at median 12 mo postinjury, ICP	Class 3 No control for confounders Indirect evidence Association of ICP with outcomes	Survival 38 (93%) GOS 80% favorable outcomes ICP ICP in three nonsurvivors was significantly higher than in 38 survivors (mean, 43 ± 26 vs 13 ± 4 mm Hg). Relationship between ICP and outcome in survivors was not statistically analyzed.

(*Continued*)

TABLE 2. (*Continued*). Intracranial Pressure Monitoring: Summary of Evidence

Class 3 Studies			
Reference Type of Trauma Center Geographic Location	**Study Design *n* Age (yr) Outcomes**	**Data Class**	**Results**
Cruz et al (43) Federal University of São Paulo, and Clean Field Hospital São Paulo, Brazil	Retrospective *n* = 45 Age: Favorable outcomes: 6 Unfavorable outcomes: 6.3; range, 1–12 Mortality, modified dichotomized GOS at 6 mo postinjury, ICP	Class 3 No control for confounders Indirect evidence Association of ICP with outcomes	Mortality 2 (4.4%) GOS 37 favorable 8 unfavorable ICP ICP peaked on day 4 in both groups. ICP was significantly higher on days 2–5 in children with unfavorable vs favorable outcomes, $p = 0.02$. Daily mean ICP values ranged between 15 and 21 mm Hg on days 2–5 in the favorable outcome group and between 19 and 26 mm Hg on days 2–5 in the unfavorable outcome group. Uncontrolled ICP > 40 mm Hg occurred in the two children who died. 4.4% died; 13.3% had severe disability. Higher ICP for days 1–5 was significantly associated with decreased cerebral O_2 extraction and worse clinical outcome, $p \leq 0.02$.
Pfenninger and Santi (49) Pediatric intensive care Bern, Switzerland	Retrospective *n* = 51 Age: mean, 8.1; range, 1 mo to 16 yr Mortality, GOS at 6 to 12 mo postinjury, ICP	Class 3 No control for confounders Indirect evidence Association of ICP with outcomes	Mortality 14 (27.5%) died GOS 14 (27.5%) dead (GOS 1) 1 (2%) permanent vegetative state (GOS 2) 1 (2%) severe disability (GOS 3) 35 (68.5%) good recovery (GOS 4–5) ICP ICP > 40 mm Hg was associated with higher mortality, $p < 0.001$. Thirteen of 16 patients with ICP 20–40 mm Hg had good outcomes or moderate disability. Three of three patients with ICP < 20 mm Hg had good outcomes or moderate disability. Moderate to severe intracranial hypertension (mean sustained ICP ≥ 20 mm Hg) was associated with poor outcome, $p < 0.05$. 69% of monitored patients had sustained ICP > 20 mm Hg.
Chambers et al (30) Neurosurgical Centre at Newcastle General Hospital Newcastle, United Kingdom	Retrospective *n* = 84 Age: median, 10; range, 3 mo to 16 yr GOS at 6 mo postinjury, ICP, CPP	Class 3 No control for confounders; unclear if patient selection was unbiased Indirect evidence Association of ICP with outcomes	GOS Individual patient data NR. ICP and CPP Overall, thresholds of 35 mm Hg for ICP and 45 mm Hg for CPP were the best predictors of outcome. The receiver operating characteristic–defined cutoffs varied depending on the Marshall CT classification and ranged from 21 to 59 mm Hg. ICP maximum predictive of poor outcome was > 35 mm Hg.

(*Continued*)

TABLE 2. (*Continued*). Intracranial Pressure Monitoring: Summary of Evidence

Class 3 Studies			
Reference Type of Trauma Center Geographic Location	**Study Design *n* Age (yr) Outcomes**	**Data Class**	**Results**
White et al (51) Division of Pediatric Critical Care Medicine Washington, DC	Retrospective *n* = 136 *n* = 37 with ICP monitoring Age: Survivors: median, 6.8 Nonsurvivors: median, 7.7; range, 0–17 Survival at discharge, ICP	Class 3 No control for confounders for ICP analysis Indirect evidence Association of ICP with outcomes	Survival 104 (76%) survived ICP 14% of survivors and 41% of nonsurvivors had ICP > 20 mm Hg in the first 72 hr. Those with lower mean ICP were more likely to be survivors, $p < 0.005$. ICP maximum and ICP measured 6, 12, and 24 hr after admission were all significantly lower in survivors.
Downard et al (44) Neurosurgery and Emergency Medicine, Oregon Health & Science University and Department of Pediatrics, Emanuel Hospital and Health Center Portland, OR	Retrospective *n* = 118 Age: mean, 7.4; range, 0–15 Mortality, GOS at last recorded patient interaction, ICP	Class 3 Retrospective review Indirect evidence Association of ICP with outcomes	Mortality 33 (28%) died GOS 33 (28%) dead (GOS 1) 13 (11%) permanent vegetative state or severe disability (GOS 2–3) 25 (21%) moderate disability (GOS 4) 47 (40%) good recovery (GOS 5) ICP In a stepwise logistic regression analysis, mean ICP > 20 mm Hg in the initial 48 hr was significantly associated with an increased risk of death.
Michaud et al (48) Level 1 trauma center, Harborview Medical Center Seattle, WA	Retrospective *n* = 75 *n* = 51 with ICP monitoring Age: mean, 8.2; range, 3 mo to 16 yr Mortality, GOS at hospital discharge, ICP	Class 3 Retrospective review Indirect evidence Association of ICP with outcomes	Mortality 25 (33%) died GOS 25 (33%) dead 4 (5%) vegetative state 14 (19%) severe disability 9 (12%) moderate disability 23 (31%) good recovery ICP 94% of children with ICP maximum < 20 mm Hg vs 59% with ICP maximum > 20 mm Hg survived, $p = 0.02$. 48% of children with ICP elevation > 1 hr survived compared with 89% of children with ICP elevated for < 1 hr. Outcome was also better in children with ICP elevation for < 1 hr. No statistically significant relationship was found between peak ICP and degree of disability.
Barzilay et al (52) PICU, The Chaim Sheba Medical Center Tel Aviv, Israel	Treatment series *n* = 56 *n* = 41 TBI Age: mean, 6.2; range, NR Mortality, dichotomized GOS at hospital discharge, ICP	Class 3 Uncontrolled series Indirect evidence Association of ICP with outcomes Mixed pathologies	Mortality 15 (27%) died GOS 15 (27%) died 17 (30%) poor recovery 24 (43%) good recovery ICP For children with severe TBI, ICP maximum was 16.9 ± 3.1 in survivors ($n = 32$) and 53.7 ± 10.8 in nonsurvivors ($n = 9$); $p < 0.01$.

(*Continued*)

TABLE 2. (*Continued*). Intracranial Pressure Monitoring: Summary of Evidence

Class 3 Studies			
Reference Type of Trauma Center Geographic Location	**Study Design *n* Age (yr) Outcomes**	**Data Class**	**Results**
Kasoff et al (47) Department of Neurosurgery New York	Retrospective *n* = 25 Age: mean, 8.8; range, 3 mo to 17 yr Mortality, ICP	Class 3 Selection not specified (25 cases selected over a 3-yr period) Indirect evidence Association of ICP with outcomes	Mortality 5 (20%) died ICP Mean of peak ICP in patients who died (*n* = 5) was 81 mm Hg (range, 55–120 mm Hg). Mean of peak ICP was 18.7 mm Hg (range, 10–30 mm Hg) in patients who did not require additional treatment for ICP; no deaths; no statistical analysis presented. Children with elevated ICP had a lower survival rate than children with normal ICP; no statistical analysis presented.
Alberico et al (41) Medical College of Virginia Hospital pediatric service Richmond, VA	Prospective *n* = 100 Age: mean, 13.39; range, 0–19 Mortality, dichotomized GOS at 3 mo and 1 yr, ICP	Class 3 No control for confounders Indirect evidence Association of ICP with outcomes	Mortality 24 (24%) died GOS 43 (43%) good outcome ICP 70% good outcome in children with ICP < 20 mm Hg with treatment vs 8% good outcome in children with ICP refractory to treatment (> 20 mm Hg), $p < 0.05$ Reducible ICP was significantly associated with better outcome than nonreducible ICP.
Esparza et al (53) Pediatric Neurosurgery Madrid, Spain	Treatment series *n* = 56 Age: mean, 7.6; range, 3 mo to 14 yr Mortality, GOS (timing unclear), ICP	Class 3 Uncontrolled series Indirect evidence Association of ICP with outcomes	Mortality 18 (32%) died GOS 18 (32%) died 0 vegetative state 1 (1.8%) severe disability 2 (3.6%) moderate disability 35 (62.5%) good recovery ICP Thirteen of 13 patients (100%) with ICP > 40 mm Hg had poor outcome (severe disability, vegetative, or dead), and all the patients with poor outcome died. Four of 14 patients (≈28%) with ICP > 20–40 mm Hg had poor outcome. Two of 29 patients (≈7%) with ICP 0–20 mm Hg had poor outcome. Outcomes: 93% good, 7% poor for patients with ICP maximum ≤ 20 mm Hg 71% good, 29% poor for patients with ICP maximum > 20 to 40 mm Hg 0% good, 100% poor for patients with ICP maximum > 40 to 60 mm Hg 0% good, 100% poor for patients with ICP maximum > 60 mm Hg (no significance test reported)

(*Continued*)

TABLE 2. (*Continued*). Intracranial Pressure Monitoring: Summary of Evidence

Class 3 Studies			
Reference Type of Trauma Center Geographic Location	**Study Design *n* Age (yr) Outcomes**	**Data Class**	**Results**
Shapiro and Marmarou (54) Albert Einstein College of Medicine New York	Treatment series $n = 22$ Age: range, 3 mo to 15 yr Mortality, outcomes (not specified), PVI, ICP	Class 3 Uncontrolled series Indirect evidence Association of ICP with outcomes	Mortality 5 (23%) died Outcome Four of 17 survivors were severely disabled. Thirteen of 17 had a good outcome or were moderately disabled. PVI and ICP Two of the five deaths were due to uncontrolled ICP. Sixteen of 22 patients had PVI measured before and after therapy. Drainage increased PVI and decreased ICP in 14 of 16. 86% of children had ICPs exceeding 20 mm Hg. ICP could be controlled in 14 of the 16 children whose pressure-volume index was measured, and in those patients, there were no deaths.
Bruce et al (42) Children's Hospital of Philadelphia Philadelphia, PA	Prospective $n = 85$ $n = 40$ with ICP monitoring Age: mean, 7.1; range, 4 mo to 18 yr Mortality, dichotomized GOS at 6 mo, ICP	Class 3 No control for confounders Indirect evidence Association of ICP with outcomes	Mortality 8 (9%) died GOS 8 (9%) died 3 (3.5%) persistent vegetative state 74 (87.5%) good recovery or moderate disability ICP Of those who had ICP monitoring ($n = 40$): level of ICP related to outcome: ICP < 20 ($n = 9$): 67% good recovery/moderate disability; 11% severe disability/persistent vegetative state; 22% died ICP $> 20 \leq 40$ ($n = 17$): 88% good recovery/moderate disability; 6% severe disability/persistent vegetative state; 6% died ICP > 40 ($n = 14$): 57% good recovery/moderate disability; 7% severe disability/persistent vegetative state; 36% died

CPP = cerebral perfusion pressure, GCS = Glasgow Coma Scale, GOS = Glasgow Outcome Scale, GOS-E = Glasgow Outcome Scale Extended, GT = gastrostomy tube, ICP = intracranial pressure, LOS = length of stay, NR = not reported, OR = odds ratio, PVI = pressure-volume index, TBI = traumatic brain injury.

[a]New study.

n indicates sample size.

Kyriakides (17) found that the use of ICP monitoring versus no ICP monitoring was associated with a reduction in mortality in more severely injured patients but also showed monitoring of ICP was performed in only 7.7% of patients who met recommended monitoring criteria (17). Interestingly, the ICP monitoring group had a longer hospital stay, longer ICU stay, and more ventilator days. In another retrospective study of 36 institutions, using the Pediatric Health Information Systems database, Bennett et al (18) showed that hospitals with higher standardized ICP monitoring rates had better patient outcomes with lower rates of mortality or severe disability. However, a subsequent study by Bennett et al (19), using a propensity-weighted effectiveness analysis that linked two national databases (n = 3,084; 1,002 with ICP monitoring and 2,082 without), reported no significant difference in functional survival between groups, no significant association between monitoring and hospital mortality, but an association between monitoring and higher mortality, discharge to hospice, or either tracheostomy or gastrostomy tube placement (19). The ICP-monitored group had greater treatment intensity than the nonmonitored group, and

authors caution that the findings could be due to unmeasured differences between the groups that may have contributed to the subsequent treatment intensity.

Multiple studies contribute indirect evidence to support the recommendation for this topic. For example, two studies of combined treatment strategies suggest that improved clinical outcomes are associated with successful control of intracranial hypertension (41, 46). A prospective observational study of 100 children with severe TBI treated with varying combinations of hyperventilation, diuretics, CSF drainage, sedation, pharmacologic paralysis, and barbiturates reported that children whose ICP was successfully lowered had better 1-year outcomes than children whose ICP was uncontrollable (but worse than those without intracranial hypertension) (41). A retrospective review of a prospectively acquired TBI database showed that reduced survival and worsened outcomes in children with severe TBI were associated with intracranial hypertension refractory to treatment, rather than peak ICP per se (46). In this study, successful control of ICP, irrespective of treatment modality (osmolar therapy, CSF drainage, decompression, etc), was deemed to be important.

The decision to insert and use any monitoring device depends on understanding the data and information derived from the monitor that permits targeted evidence-based care. Because there are no imaging or other biomarkers that indicate a patient with intracranial hypertension, it is recommended that ICP is measured to determine if intracranial hypertension is present. Given that much of present care is predicated on prevention and treatment of elevated ICP, detection of elevated ICP with monitoring is considered to be more capable of allowing for timely delivery and accurate titration of treatment than without the use of an ICP monitor. Although they represent only class 3 evidence for long-term outcomes related to ICP monitoring, these studies support the association of successful ICP monitor–based management of intracranial hypertension with improved survival and neurologic outcome.

Indications From Adult Guidelines

Consistent with the recommendations in this edition, the Fourth Edition of the adult guidelines provides a level III recommendation to monitor ICP (14).

Advanced Neuromonitoring

Recommendations

Strength of Recommendation: Weak

Levels I and II

There was insufficient evidence to support a level I or II recommendation for this topic.

Level III

To Improve Overall Outcomes. III.1. If brain tissue oxygenation ($Pbro_2$) monitoring is used, maintaining a level greater than 10 mm Hg is suggested.

Note 1. There was insufficient evidence to support a recommendation for the use of a monitor of $Pbro_2$ to improve outcomes.

Note 2. Use of advanced neuromonitoring (brain oxygenation) should only be for patients with no contraindications to invasive neuromonitoring such as coagulopathy and for patients who do not have a diagnosis of brain death.

Changes From the Prior Edition. There are no content changes from the Second Edition to the recommendations. The notes are new to this edition. Two new class 3 treatment series were added to the evidence base for this topic (55, 56).

Introduction

Advanced monitoring systems provide information about cerebrovascular and metabolic function. In children with severe TBI, the addition to ICP monitoring of advanced neuromonitoring techniques such as microdialysis, electrophysiology assessments, and examination of cerebral autoregulation may help identify patients needing particular treatments (57). If treatment then prevents unwanted cerebral pathophysiologic processes and is shown to improve function and outcome, the use of these advanced monitoring systems may be warranted as part of optimal critical care (58, 59).

Evaluation of the Evidence

Quality of the Body of Evidence. Studies included for this topic addressed the use of advanced neuromonitoring methods to improve outcomes for children with severe TBI, and what threshold value should be targeted for measures of cerebrovascular and metabolic function. No studies meeting inclusion criteria were identified that evaluated the use of $Pbro_2$ monitoring and linked their use to improvements in outcomes. Four studies—three treatment series (55, 56, 60) and one prospective cohort (61)—constituted the evidence for the recommendation about a threshold, if $Pbro_2$ monitoring was used. The studies were small, with moderate consistency and low precision, reporting direct evidence. The overall quality of the body of evidence is low (**Table 3**).

Applicability. The included studies were small and conducted at single sites. They included a range of ages for pediatric patients. Two were conducted in the United States (56, 60) and two in South Africa (55, 61). The applicability of the evidence is limited.

Summary of Evidence

Four class 3 studies (55, 56, 60, 61), two new (55, 56) and two from the Second Edition, provided evidence to support the recommendation (60, 61). One prospective cohort (61) included patients from one of the treatment series (55) (**Table 4**).

Evidence Synthesis.

What Threshold Value Should Be Targeted for Measures of Cerebrovascular and Metabolic Function?

The four studies that focused on this question looked for an association between $Pbro_2$ levels and favorable or unfavorable outcome (55, 56, 60, 61).

Stippler et al (56) analyzed over 8,000 hours of monitoring of 46 children with severe TBI who were treated according to a protocol targeting $Pbro_2$ at 25 mm Hg. Overall levels were high and 30 mm Hg represented the highest combined sensitivity and

TABLE 3. Advanced Neuromonitoring: Quality of the Body of Evidence

Components of Overall Quality: Class 3 Studies								
Topic	No. of Studies Study Design	Recommen-dations	Meta-Analysis Possible (Yes or No[a])	Total No. of Subjects (*n*)	Consisten-cy (High, Moderate, Low)	Directness (Direct or Indirect)	Precision (High, Moderate, Low)	Quality of Evidence (High, Moderate, Low, or Insufficient)
Brain tissue O_2 monitoring thresholds	1 prospective 3 treatment series	III.1	No, different designs	114[b]	Moderate	Direct	Low	Low

[a]Meta-analysis to synthesize results is only possible if several studies address the same criteria/question, and other design criteria are met.
[b]The two articles by Figaji et al (55, 61) are assumed to include the same patients.
n indicates sample size.

TABLE 4. Advanced Neuromonitoring: Summary of Evidence

Class 3 Studies			
Reference Type of Trauma Center Geographic Location	Study Design *n* Age (yr) Outcomes	Data Class	Results
$Pbro_2$ monitoring thresholds: recommendation III.1.			
Stippler et al (56)[a] Pediatric Neurotrauma Center, University of Pittsburgh Pittsburgh, PA	Treatment series *n* = 46 Age: mean, 9.4; range, 0.1–16.5 Mortality, dichotomized GOS at 6 mo postinjury, ICP, CPP	Class 3 Uncontrolled series	Mortality 2 deaths (4.3%) during acute hospitalization GOS 70% of patients had favorable outcomes ICP There was no significant difference in ICP during the first 6 d postinjury between patients with favorable vs unfavorable outcomes. CPP (with protocol targeting maintenance of $Pbro_2$ > 25 mm Hg) A $Pbro_2$ of 30 mm Hg was associated with the highest combined sensitivity (20.0%)/specificity (80.7%) for favorable neurologic outcome at 6 mo. $Pbro_2$ alone was not independently associated with outcome. High, rather than the expected low, values of $PbrO_2$ were observed in some patients with refractory intracranial hypertension and low CPP.
Figaji et al (55)[a] Red Cross War Memorial Children's Hospital Cape Town, South Africa	Treatment series *n* = 28 (appear to be part of the cohort for Figaji et al [61]) Age: mean, 5.8; range, 9 mo to 11 yr GOS at 6 mo postdischarge, FIo_2, Pao_2, $Pbro_2$	Class 3 Uncontrolled series	GOS A greater delta $Pbro_2$/delta Pao_2 was associated with a lower probability of favorable outcome. Estimate: −1.839; 95% CI, 0.03–0.78; $p = 0.02$ GOS outcomes: GOS 1 (died) (*n* = 3, 12.5%) GOS 2 (*n* = 0) GOS 3 (*n* = 4, 16.7%) GOS 4 (*n* = 7, 29.2%) GOS 5 (*n* = 10, 41.7%) FIo_2, Pao_2, $Pbro_2$ Effect of increased FIo_2 on Pao_2 and $Pbro_2$: Induced hyperoxia significantly increased both Pao_2, $p < 0.0001$, and $Pbro_2$, $p < 0.0001$. When FIo_2 was increased, Pao_2 significantly increased ($p < 0.0001$) and $Pbro_2$ significantly increased ($p < 0.0001$). Normobaric hyperoxia increased $Pbro_2$, but the responses varied in patients.

(*Continued*)

TABLE 4. (*Continued*). Advanced Neuromonitoring: Summary of Evidence

Class 3 Studies			
Reference Type of Trauma Center Geographic Location	**Study Design *n* Age (yr) Outcomes**	**Data Class**	**Results**
Figaji et al (61) Red Cross Children's Hospital Cape Town, South Africa	Prospective $n = 52$ Age: mean, 6.5; range, 9 mo to 14 yr Mortality at 6 mo postinjury PCPC	Class 3 Unclear if outcome assessment was unbiased	$Pbro_2 < 5$ mm Hg for >1 hr or $Pbro_2 < 10$ mm Hg for >2 hr Mortality Adjusted OR, 26.8; 95% CI, 2.7–265; $p = 0.005$ PCPC Unfavorable: severe disability or death Adjusted OR, 27.4; 95% CI, 1.9–391; $p = 0.015$ Independent of other significant factors such as ICP, CT, low Pao_2, and CPP mortality
Narotam et al (60) Level II trauma center Creighton University Medical Center Omaha, NE	Treatment series $n = 16$ Age: mean, 14; range, 1.5–18 Mortality at 3 mo postinjury	Class 3 Uncontrolled series	Mortality Normal initial $Pbro_2$ (≥ 10 mm Hg) No patients died Mean initial $Pbro_2$ 10 survivors vs 6 deaths 16.07 ± 18.7 vs 6.76 + 6.69 mm Hg; $p = 0.247$ Mean final $Pbro_2$ Survivors vs nonsurvivors $Pbro_2$, 25.0 ± 11.57 vs 8.53 ± 11.0 mm Hg; $p = 0.01$

CPP = cerebral perfusion pressure, GOS = Glasgow Outcome Score, ICP = intracranial pressure monitoring, OR = odds ratio, $Pbro_2$ = brain tissue oxygen, PCPC = pediatric cerebral performance category.

[a]New study.

Different abbreviations such as $pBto_2/Pbto_2$ and $P_{ti}O_2$ are used to denote brain tissue oxygen and brain tissue oxygen tension; we use $PbrO_2$ for consistency, which may differ from what was used by the authors of the cited studies.

specificity for favorable outcomes. However, the sensitivity was low (20%), and the unexpected observations of high rather than low $Pbro_2$ in patients with intracranial hypertension and compromised CPP suggest the need for studies designed to understand what may be a complex relationship between $Pbro_2$ and outcome. Figaji et al (61) used a treatment threshold of 20 mm Hg and reported an association of poor outcome with $Pbro_2$ less than 10 mm Hg, which was even stronger for $Pbro_2$ less than 5 mm Hg. In another analysis of a subgroup of the studied patients, Figaji et al (55) reported that in patients whose $Pbro_2$ changed more in response to changes in Pao_2, outcomes were worse. Narotam et al (60) also reported an association between unfavorable outcome and $Pbro_2$ less than 10 mm Hg. Combined, this evidence suggests that if this advanced monitoring modality is used, it would be prudent to target the more conservative threshold of greater than 10 mm Hg. Although all these studies suggest that higher $Pbro_2$ levels are associated with better outcomes to some degree, the relationship appears complex and the studies were not designed to isolate the effect of treating to specific thresholds or to compare the utility of $Pbro_2$ to other measures.

Indications From Adult Guidelines

Due to insufficient evidence, there are no recommendations in the Fourth Edition of the adult guidelines regarding $Pbro_2$ monitoring or thresholds (14).

Neuroimaging

Recommendations

Strength of Recommendation: Weak

Levels I and II

There was insufficient evidence to support a level I or II recommendation for this topic.

Level III

To Improve Overall Outcomes. III.1. Excluding the possibility of elevated ICP on the basis of a normal initial (0–6 hr after injury) CT examination of the brain is not suggested in comatose pediatric patients.

III.2. Routinely obtaining a repeat CT scan greater than 24 hours after the admission and initial follow-up is not suggested for decisions about neurosurgical intervention, unless there is either evidence of neurologic deterioration or increasing ICP.

Changes From the Prior Edition. Recommendation III.1. is new to this edition. Two new class 3 studies—one retrospective observational study (62) and one treatment series (63)—were added to the evidence base for this topic.

Introduction

CT of the head is the current preferred imaging technique for rapid detection of intracranial injury, signs of mass effect, and/

or cerebral edema for trauma victims with severe TBI. Acute CT imaging is universally performed in high-income countries during initial evaluation, and detection of intracranial injury is common (62–75%) among these severely injured patients (64, 65).

The Rotterdam head CT score grades severity of injury and increasing scores are associated with greater mortality (66). Risk of mortality increases with Rotterdam scores in children in a similar pattern to adults (67).

Although an abnormal head CT has been an indication to monitor ICP, a question remains regarding the risk of intracranial hypertension in patients with a normal head CT. In the Second and Third Editions of the adult TBI guidelines, ICP monitoring was indicated for patients with a normal initial head CT if two or more features were present: age more than 40 years old, unilateral or bilateral motor posturing, or systolic blood pressure (SBP) less than 90 mm Hg (68, 69). The First and Second Editions of the Pediatric TBI Guidelines referenced this recommendation (1, 70). However, for the Fourth Edition of the adult TBI guidelines, this recommendation was removed due to lack of evidence meeting current standards (14). No decision rule regarding CT and indications for ICP monitoring has been endorsed for infants and children with severe TBI.

An initial CT is obtained acutely to evaluate intracranial injury, need for neurosurgical procedures, and for signs of intracranial hypertension; however, routine repeat CT imaging is more controversial. Repeating a CT scan in children with severe TBI is usually considered when there is 1) no evidence of neurologic improvement; 2) persistent or increasing ICP; or 3) an inability to assess neurologic status (e.g., sedation, paralytic agents) (71).

Evaluation of the Evidence

Quality of the Body of Evidence. Studies included for this topic addressed the questions about whether initial CTs should be used to rule out intracranial hypertension, and whether routine repeated CT scans, after the initial scan, should be used to make decisions about neurosurgical intervention. The overall quality of the body of evidence is low and is based on one new class 3 treatment series (63), one new class 3 retrospective study (62), and one class 3 retrospective study from the Second Edition of these guidelines (72) (**Table 5**).

Applicability. The recommendations are supported by three small, uncontrolled studies (62, 63, 72). Applicability is considered limited.

Summary of Evidence. Three class 3 studies—two new (62, 63) and one from the Second Edition—provide evidence to support the recommendations (72) (**Table 6**).

Evidence Synthesis

Use of CT to Rule Out Intracranial Hypertension. Bailey et al (63) conducted a retrospective chart review of moderate to severe pediatric TBI cases to evaluate factors associated with ICP monitoring and to determine to what extent normal ICP (< 20 mm Hg) can be predicted by normal initial head CT scans ($n = 299$). ICP monitors were placed in 13% of children (9/68) with normal initial head CTs (Rotterdam and Marshall 1) and 31% (30/98) of those with Marshall 2 (diffuse injury, open cisterns, and midline shift 0 mm to 5) scores. Seven of nine children (78%) with an initial normal head CT but who were unable to localize pain when examined by a pediatric neurosurgeon after initial resuscitation developed ICP greater than 20 mm Hg during the first 24 hours of pressure monitoring. This series of nine patients constitutes a highly selected and uncontrolled sample, providing low-quality evidence to support the recommendation to not exclude the possibility of intracranial hypertension based on a normal initial head CT.

Use of Repeated CT Scans to Make Decisions About Neurosurgical Interventions. Bata and Yung (62) conducted a retrospective review of children with mild, moderate, and

TABLE 5. Neuroimaging: Quality of the Body of Evidence

Components of Overall Quality: Class 3 Studies								
Topic	No. of Studies Study Design	Recommendation	Meta-Analysis Possible (Yes or No[a])	Total No. of Subjects (*n*)	Consistency (High, Moderate, Low)	Directness (Direct or Indirect)	Precision (High, Moderate, Low)	Quality of Evidence (High, Moderate, Low, or Insufficient)
Use of initial CT to rule out intracranial hypertension	1 treatment series (subset of a retrospective review)	III.1.	NA	9	NA	Direct	NA	Low
Use of repeated CT scans to make decisions about neurosurgical interventions	2 retrospective	III.2.	No	73 severe	Moderate	Direct	Low	Low

NA = not applicable.

[a]Meta-analysis to synthesize results is only possible if several studies address the same criteria/question, and other design criteria are met.

n indicates sample size.

TABLE 6. Neuroimaging: Summary of Evidence

Class 3 Studies			
Reference Type of Trauma Center Geographic Location	**Study Design *n* Age (yr) Outcomes**	**Data Class**	**Results**
Use of initial CT to rule out intracranial hypertension: recommendation III.1.			
Bailey et al (63)[a] Primary Children's Medical Center Salt Lake City, UT	Treatment series subset of a retrospective review *n* = 9 Age: ICP monitor: median, 7 No ICP monitor: median, 6.7; range, NR Early intracranial hypertension with normal initial head CT (Marshall I)	Class 3 Extrapolated a subset of nine patients, resulting in a highly selected sample without control for confounders	Early intracranial hypertension Of nine patients with a Marshall score of I who had ICP monitoring, seven had early intracranial hypertension. This was not significantly different from those with radiographic pathology meeting Marshall 2 criteria.
Use of repeated CT scans to make decisions about neurosurgical interventions: recommendation III.2.			
Bata and Yung (62)[a] Women's and Children's Hospital North Adelaide, SA, Australia	Retrospective *n* = 71 33 severe Age: median, 10 yr; range, NR Neurosurgical procedures resulting from repeat CT, change in management or need for further imaging resulting from repeat CT	Class 3 No control for potential confounders	36 had routine repeated CTs. 35 had clinically indicated repeat CTs. Neurosurgical procedures Five patients required surgical intervention (two severe had routine repeat CT; two severe and one moderate had clinically indicated repeat CT). Medical management Of the 33 severe cases, 10 had change in medical management following repeat CT. OR for delayed ICP monitoring or EVD was not significantly different between patients with worse repeat head CT vs those with stable radiologic lesions: ICP monitoring OR, 2.48; 95% CI, 0.38–16.29; *p* = 0.31 EVD insertion OR, 3.6; 95% CI, 0.21–61; *p* = 0.40
Figg et al (72) Level 1 trauma center Grand Rapids, MI	Retrospective *n* = 40 Age: mean, 9.6; range, 2 mo to 17 yr Urgent neurosurgical procedures resulting from serial CT scans	Class 3 No control for potential confounders	115 repeat CT scans conducted 87 routine (76%) 24 for increased ICP (21%) 4 for neurologic change 3%) Neurosurgical procedures Five patients (4.3%) had a surgical intervention based on findings from the serial CT scans; however, all five scans were ordered due to clinical indicators (ICP or neurologic status), not as routine follow-up. Findings from repeat scans after the admission and initial follow-up study No change: 61 (53%) Improvement: 39 (34%) Worsening: 15 (13%)

EVD = external ventricular drain, ICP = intracranial pressure, NR = not reported, OR = odds ratio.

[a]New study.

n indicates sample size.

severe TBI treated over a decade. They evaluated whether routine head CT scans altered surgical or MM. Among 1,675 admissions with head trauma, 71 met criteria for the analysis (33 severe). Of five patients who had progression of intracranial injury demonstrated on repeat imaging, two occurred in patients who were reimaged without worsening signs and symptoms of intracranial injury. Both had severe TBI. The other three repeat CTs were obtained because of signs and symptoms of worsening injury. The likelihood of having delayed ICP monitoring or an external ventricular drain (EVD) after initial trauma evaluation was not significantly greater in subjects with progression of intracranial injury versus those with stable radiologic lesions.

Figg et al (72) retrospectively reviewed 40 pediatric patients treated from January 1990 to December 2003 for severe TBI, and examined whether serial CT scans led to urgent neurosurgical operative intervention. One hundred fifteen serial CT scans were ordered (76% routine follow-up, 21% increased ICP; 3% neurologic change). Results of these scans showed no change (53%), improvement (34%), and worsening (13%). Five patients (4.3%) had a surgical intervention supported by results of the serial CT scan (one evacuation of epidural hematoma; one evacuation of a subdural hematoma; one burr hole; and three for additional EVDs). All five scans were ordered based on a clinical indicator (ICP or neurologic status), not as routine follow-up.

Both reports by Bata and Yung (62) and Figg et al (72) were studies conducted at a single center. They lacked consistent criteria for routine reimaging; time elapsed after injury or initial CT imaging also varied. Thus, the quality of evidence is low to support the recommendation against use of serial CT scans to make decisions about neurosurgical interventions.

Indications From Adult Guidelines

The adult guidelines do not include neuroimaging as a topic (14).

THRESHOLDS

Thresholds for Treatment of Intracranial Hypertension

Recommendations

Strength of Recommendation: Weak

Levels I and II

There was insufficient evidence to support a level I or II recommendation for this topic.

Level III

To Improve Overall Outcomes

III.1. Treatment of ICP targeting a threshold of less than 20 mm Hg is suggested.

Changes From Prior Edition. There are no content changes from the Second Edition to the recommendations. Two new class 3 retrospective observational studies were added to the evidence base for this topic (73, 74), and one class 3 study from the Second Edition was removed (53).

Introduction

In children with severe TBI, mortality is often due to refractory sustained increases in ICP, defined as intracranial hypertension. Because management of severe TBI in the PICU is largely focused on the management of raised ICP and preservation of perfusion as represented by CPP (MAP minus the mean ICP [28]), at present, preventing intracranial hypertension is central to current neurocritical care of these children. Prevention of severe intracranial hypertension is also thought to be important to avoid cerebral herniation events leading to a cascade of often fatal sequelae. Brief increases in ICP that return to normal in less than 5 minutes are believed to be insignificant, although some have challenged that belief in adult patients (75). However, sustained increases of greater than or equal to 20 mm Hg for greater than or equal to 5 minutes likely warrant treatment (76). Based in large part on adult studies, an ICP treatment threshold of 20 mm Hg has been used in most centers for decades.

Normal values for MAP and hence CPP are lower in children, particularly in infants and young children, but optimal ICP in the postinjury period is undefined. It has been shown in anesthetized children without TBI that the lower CPP limit of autoregulation of cerebral blood flow (CBF) is similar in young children versus older children—and does not decrease below ≈60 mm Hg (77). Thus, young children have less autoregulatory reserve than older children. For example, the difference in CPP between normal and the lower limit of autoregulation is smaller in infants and young children than it is in older children. This suggests the possible need to set a lower ICP therapeutic target to maintain adequate perfusion for infants and young children when compared with older children or adults with TBI.

Although an ICP threshold of 20 mm Hg is generally used, an even lower threshold may be physiologically appropriate for infants and young children. It should also be recognized that some of the studies defining the ICP threshold used therapies that are no longer routinely recommended such as aggressive hyperventilation or moderate hypothermia. Finally, in light of the heterogeneity of the pathology and pathophysiology in pediatric TBI, ICP management may need to be individualized in some cases.

Evaluation of the Evidence

Quality of the Body of Evidence. Studies included for this topic addressed the question about the target threshold for treating intracranial hypertension to produce the best outcomes. The evidence consists of 10 small (30, 40, 43, 45, 47, 49, 51, 73, 74, 78) and two somewhat larger class 3 observational studies providing direct evidence (41, 44). The consistency is moderate and precision low, rendering a low overall quality of evidence (**Table 7**).

Applicability. The included studies were conducted in Spain, Switzerland, United States, United Kingdom, Brazil, and Lithuania. Ten (30, 40, 43, 45, 47, 49, 51, 73, 74, 78) of the twelve (30, 40, 41, 43–45, 47, 49, 51, 73, 74, 78) have small samples and most have other design flaws that taken together, call into question their applicability.

Summary of Evidence. Twelve class 3 studies, two new (73, 74) and 10 from the Second Edition (30, 40, 41, 43–45, 47, 49, 51, 78), provide evidence to support the recommendations (**Table 8**).

TABLE 7. Threshold for Treatment of Intracranial Hypertension: Quality of the Body of Evidence

Components of Overall Quality: Class 3 Studies								
Topic	No. of Studies Study Design	Recommendation	Meta-Analysis Possible (Yes or No[a])	Total No. of Subjects (*n*)	Consistency (High, Moderate, Low)	Directness (Direct or Indirect)	Precision (High, Moderate, Low)	Quality of Evidence (High, Moderate, Low, or Insufficient)
Target intracranial pressure threshold to improve outcomes	3 prospective 9 retrospective	III.1.	No	649[b]	Moderate	Direct	Low	Low

[a]Meta-analysis to synthesize results is only possible if several studies address the same criteria/question, and other design criteria are met.
[b]Patients in Mehta et al (73) are a subset of the sample in Miller Ferguson et al (74).
n indicates sample size.

TABLE 8. Threshold for Treatment of Intracranial Hypertension: Summary of Evidence

Class 3 Studies			
Reference Type of Trauma Center Geographic Location	Study Design *n* Age (yr) Outcomes	Data Class	Results
Target ICP threshold to improve outcomes: recommendation III.1.			
Miller Ferguson et al (74)[a] PICU of a tertiary children's hospital Pittsburgh, PA	Retrospective *n* = 85 Age: mean, 5.1; range, not reported Dichotomized GOS at 6 mo postinjury (1–2 unfavorable, 3–5 favorable) Note: article (p. 446) indicates "favorable 1–2, unfavorable 3–5"	Class 3 Selection of patients for ICP monitoring at discretion of neurosurgery	Outcome by threshold (> 14, > 20, > 30 mm Hg). GOS No significant difference in outcomes across three estimates utilizing three different thresholds
Mehta et al (73)[a] Pediatric Neurotrauma Registry Pittsburgh, PA	Retrospective *n* = 22 Age: median, 6.1 mo; range, 0–2 yr Dichotomized GOS 6 mo postinjury (favorable 3–5; unfavorable 1–2); ICP; CPP; physiologic variables Subset of 85 patients in Miller Ferguson et al (74) Note: article (p. 415) indicates "favorable [GOS: 1–2] and unfavorable [GOS: 3–5] outcomes." This is transposed from the generally accepted order (e.g., GOS 1 = dead).	Class 3 Small sample size	Outcome by threshold (< 15 mm Hg, < 20 mm Hg) GOS No significant difference between outcome groups in daily mean ICP over first 7 d. No significant difference between number of hourly readings of ICP > 20 mm Hg between outcome groups.
Grinkeviciūte et al (45) Kaunas University of Medicine Kaunas, Lithuania	Prospective *n* = 48 Age: mean, 10.6; range, 2.4 mo to 18 yr Survival, dichotomized GOS at 6 mo postinjury	Class 3 No control for confounders. Insufficient power to detect outcome	Survival 97.9% for children admitted to the PICU GOS No significant difference in peak ICP in groups with favorable vs unfavorable outcomes (22.2 vs 24.6 mm Hg, respectively) Five patients were described as having poor outcomes.

(*Continued*)

TABLE 8. (*Continued*). Threshold for Treatment of Intracranial Hypertension: Summary of Evidence

Class 3 Studies			
Reference Type of Trauma Center Geographic Location	**Study Design *n* Age (yr) Outcomes**	**Data Class**	**Results**
Adelson et al (40) Multicenter study ($n = 6$)[b]	Randomized controlled trial of moderate hypothermia vs normothermia plus medical management Post hoc analysis of relationship between ICP and outcome $n = 47$ Age: mean, 6.89; range, 0–13 Dichotomized GOS at 3 and 6 mo	Class 3 No control for confounders in ICP analysis	GOS Mean ICP was lower in children with good (11.9 ± 4.7 mm Hg) vs poor (24.9 ± 26.3 mm Hg; $p < 0.05$) outcome. Percent time with ICP < 20 mm Hg differed significantly in the good (90.8% ± 10.8%) vs poor (68.6% ± 35.0%; $p < 0.05$) outcome groups. ICP > 20 mm Hg was the most sensitive and specific for poor outcome.
Cruz et al (43) Federal University of São Paulo, and Clean Field Hospital São Paulo, Brazil	Prospective $n = 45$ Children with ICP < 15 mm Hg were excluded Age: Favorable Outcome: mean, 6 Unfavorable Outcome: mean, 6.3; range, 1–12 Dichotomized GOS at 6 mo postinjury	Class 3 No control for confounders	GOS Daily mean ICP values ranged between 15 and 21 mm Hg on days 2–5 in the favorable outcome group and between 19 and 26 mm Hg on days 2–5 in the unfavorable outcome group. ICP was significantly higher ($p \leq 0.02$) on days 2–5 in children with unfavorable vs favorable outcomes. 82% of the patients had favorable outcome. ICP peaked on day 4 in both groups. Uncontrolled ICP > 40 mm Hg occurred in the two children who died.
Pfenninger and Santi (49) University Children's Hospital Bern, Switzerland	Retrospective $n = 26$ with ICP monitoring and critical care management; 51 total Age: mean, 8.1; range, 1 mo to 16 yr Dichotomized GOS at 6 to 12 mo postinjury	Class 3 No control for confounders, potential selection bias in children who received ICP monitoring	GOS Mean sustained ICP ≥ 20 mm Hg was associated with poor outcome ($p < 0.05$).
Chambers et al (30) Neurosurgical Centre at Newcastle General Hospital Newcastle, United Kingdom	Retrospective $n = 84$ Age: median, 10; range, 3 mo to 16 yr Dichotomized GOS at 6 mo postinjury	Class 3 No control for confounders; unclear if patient selection was unbiased	GOS Threshold of ICP over 35 mm Hg was the best predictor of poor outcome. The receiver operating characteristic–defined cutoffs varied depending on the Marshall CT classification and ranged from 21 to 59 mm Hg.
White, 2001 (51) Johns Hopkins Hospital PICU database and the Pediatric Trauma Registry	Retrospective $n = 37$ with ICP monitoring; 136 total Age: Survivors: median, 6.8 Nonsurvivors: median, 7.7; range, 0–17 Mortality	Class 3 No control for confounders for ICP analysis, potential selection bias in patients who received ICP monitoring	Mortality 14% of survivors and 41% of nonsurvivors had ICP > 20 mm Hg in the first 72 hr. Patients with lower mean ICPs more likely to survive ($p < 0.005$). No other threshold was specifically examined. ICP maximum and ICP measured at 6, 12, and 24 hr after admission were significantly lower in survivors.

(*Continued*)

TABLE 8. (*Continued*). Threshold for Treatment of Intracranial Hypertension: Summary of Evidence

Class 3 Studies			
Reference Type of Trauma Center Geographic Location	**Study Design *n* Age (yr) Outcomes**	**Data Class**	**Results**
Downard et al (44) Oregon Health Sciences University trauma registry and Legacy Emanuel Hospital and Health Center Portland, OR	Retrospective *n* = 118 Age: mean, 7.4; range, 0–15 Mortality	Class 3 Primary objective was CPP thresholds; treatments varied according to physician preference.	Mortality In a stepwise logistic regression analysis, mean ICP > 20 mm Hg in the initial 48 hr was significantly associated with an increased risk of death ($p = 0.001$).
Kasoff et al (47) Westchester County Medical Center New York	Retrospective *n* = 25 Age: mean, 8.8; range, 3 mo to 17 yr Mortality	Class 3 No control for confounders, selection bias unclear	Mortality Mean of peak ICP in patients who died (*n* = 5) was 81 mm Hg (range, 55–120 mm Hg). Mean of peak ICP was 18.7 mm Hg (range, 10–30 mm Hg) in patients who did not require additional treatment for ICP and there were no deaths; no statistical analysis was presented.
Alberico et al (41) Medical College of Virginia Hospital pediatric service Richmond, VA	Prospective *n* = 100 Age: mean, 13.39; range, 0–19 GOS at 1-yr postinjury	Class 3 No control for confounders	GOS 70% good outcome in children with ICP < 20 mm Hg with treatment vs 8% good outcome in children with ICP refractory to treatment (> 20 mm Hg), $p < 0.05$
Pfenninger et al (78) University Children's Hospital Bern, Switzerland	Retrospective *n* = 24 Age: mean, 6.6; range, 3 mo to 14 yr Mortality; GOS (follow-up time not specified)	Class 3 No control for confounders	Mortality ICP > 40 mm Hg was associated with higher mortality ($p < 0.001$) GOS 13 of 16 patients with ICP 20–40 mm Hg had good outcome or moderate disability. Three of three patients with ICP < 20 mm Hg had good outcome or moderate disability.

CPP = cerebral perfusion pressure, GOS = Glasgow Outcome Scale, ICP = intracranial pressure.

[a]New study.

[b]1) Children's Hospital of Pittsburgh, Pittsburgh, PA; 2) University of California, Davis, Sacramento, CA; 3) Jackson Memorial Hospital and Children's Hospital of Miami, Miami, FL; 4) Primary Children's Hospital, Salt Lake City, UT; 5) Pennsylvania State University Hershey Medical Center, Hershey, PA; and 6) Harborview Medical Center, Seattle, WA.

Evidence Synthesis

What Is the Target Threshold to Produce the Best Outcomes?. Two retrospective studies assessed patient outcomes across different thresholds for ICP (73, 74). The 22 patients in Mehta et al (73), who were under the age of 2 years old, were a subset of the 85 pediatric patients in Miller Ferguson et al (74). Miller Ferguson et al (74) associated thresholds of greater than 14, 20, and 30 mm Hg with outcome, and Mehta et al (73) used thresholds of less than 15 or 20 mm Hg (74). No significant difference was observed across thresholds in dichotomized Glasgow Outcome Scale (GOS) at 6 months postinjury in either study.

In a subanalysis of a RCT of hypothermia ($n = 47$), Adelson et al (40) instituted treatment for increased ICP at different thresholds according to age (≥ 15 mm Hg for 0–24 mo; ≥ 18 mm Hg for 25–96 mo; ≥ 20 mm Hg for 97–156 mo). They reported significantly lower mean ICP in children with good versus poor outcomes but did not report information about the effect of different thresholds by age on outcome.

Seven studies used the ICP threshold of 20 mm Hg as the indicator of intracranial hypertension (41, 44, 45, 47, 49, 51, 78). One prospective study reported no significant difference in 6-month postinjury GOS based on ICP levels for 48 patients (45). Two studies, one retrospective (49) ($n = 26$) and one prospective ($n = 100$) (41), reported significantly better GOS scores at 6 and 12 months postinjury for patients with lower ICP. The remaining four retrospective studies, including a total of 204 patients, reported higher mortality in patients with higher ICP. Methods to identify ICP and initiate treatment varied across studies.

In a prospective study of 45 pediatric patients, Cruz et al (43) used the ICP threshold of 15 mm Hg as the indicator of intracranial hypertension, and reported lower daily mean ICP values (days 2–5) in the favorable versus unfavorable outcome group using the GOS at 6 months postinjury. In a retrospective study of 84 pediatric patients, Chambers et al (30) reported that an ICP threshold of 35 mm Hg was the best indicator of poor outcome using the GOS at 6 months postinjury.

A methodologic concern with studies of ICP thresholds is whether the studies were conducted with an inherent bias for ICP less than 20 mm Hg as the a priori therapeutic target for some or all patients. In addition, variable statistical approaches were used to adjust for confounding variables in examining the association between ICP and outcome. Another important limitation was that there was no consistent approach to assessing the relationship between outcome and either the timing or duration of intracranial hypertension after TBI. Generally, mean or peak values, or ICP values within a given epoch were used. Consequently, the available evidence provides a weak level III recommendation.

Indications From Adult Guidelines

The Fourth Edition of the adult TBI guidelines provides a level III recommendation that suggests a combination of ICP values and clinical and brain CT findings may be used to make management decisions (14). This recommendation is also considered clinically relevant in pediatric patients.

Thresholds for CPP Recommendations

Strength of Recommendations: Weak

Levels I and II

There was insufficient evidence to support a level I or II recommendation for this topic.

Level III

To Improve Overall Outcomes. III.1. Treatment to maintain a CPP at a minimum of 40 mm Hg is suggested.

III.2. A CPP target between 40 and 50 mm Hg is suggested to ensure that the minimum value of 40 mm Hg is not breached. There may be age-specific thresholds with infants at the lower end and adolescents at or above the upper end of this range.

Changes From Prior Edition. There are no content changes from the Second Edition to the recommendations. Of the 15 included studies (30, 40, 44, 52, 60, 61, 73, 74, 79–85), four are new to this edition. One new class 2 (79) and three new class 3 retrospective observational studies were added to the evidence base for this topic (73, 74, 85).

Introduction

CPP—as defined by MAP minus the mean ICP (28)—is the pressure gradient driving CBF, which, in turn, in the normal state, is autoregulated and coupled with cerebral metabolic rate for oxygen ($CMRO_2$). Autoregulation refers to the mechanisms of changes in cerebral vascular resistance by which CBF is maintained over a wide range of increases or decreased in CPP (86). If autoregulation is disrupted after TBI, then a decrease in CPP may induce cerebral ischemia. With continuous monitoring of MAP and ICP, CPP can be followed and manipulated by interventions that attempt to avoid both regional and global ischemia. The optimal CPP for therapy remains unknown.

There are age-related differences in MAP, CBF, and $CMRO_2$ from infancy through adulthood. Because pediatric values are in general lower than adult values, we need to know whether there are age-specific thresholds or targets for CPP that should be used during critical care management of pediatric severe TBI.

There are three main limitations in comparing CPP data from various studies for the purpose of identifying whether low CPP is harmful, or whether there is an age-related "critical threshold" that should be targeted in treatment. First, there may be a problem with the measurement of CPP, which relates to position of zero calibration for ICP and MAP, ICP device used, and the practice of head elevation. Together, these differences may lead to a measurement difference of 5–10 mm Hg (related to the vertical distance between the two zeroing points). Second, the real-time numerical value of CPP not only reflects intracranial tissue and fluid dynamics but also the CPP level that is being targeted by those at the bedside. There is considerable variance in the referenced studies, with respect to their description of any ICP- or CPP-directed strategy (**Table 11**). Third, the CPP summary statistic that is used in the analysis is different in many of the studies (Table 11) and only one report describes excluding preterminal data; the rest of the reports do not discuss whether these data are included or excluded.

Taken together, caution should be applied when interpreting the results from the pediatric TBI CPP studies and applying the information to treatment strategies for TBI.

Evaluation of the Evidence

Quality of the Body of Evidence. Studies included for this topic addressed the questions about what are the minimum thresholds and target ranges for managing CPP; are ranges age-specific, and what is the target threshold for infants? Multiple class 3 studies provided low-quality evidence supporting a minimum target of 40 mm Hg and use of age-specific ranges (Table 11). Although one class 2 study provided data supporting use of age-specific ranges, it was not considered sufficient to make a level II recommendation (79). Evidence from two small class 3 studies was insufficient to make a recommendation specific to infants (73, 80) (**Table 9**).

Applicability. Twelve of the 15 studies were published since 2000 (30, 40, 44, 60, 61, 73, 74, 79, 81, 83–85). The body of evidence included multisite studies and use of registry data from multiple sites. Countries included the United States, United Kingdom, Israel, Germany, South Africa, and Switzerland. Although two studies focused on infants (73, 80), the remainder contained a range of ages. There are no major applicability concerns.

Summary of Evidence. Of the 15 studies summarized in the Evidence Tables, 13 provide evidence to support the recommendations for this topic: one new class 2 (79), two new class 3 (74, 85), and 10 class 3 studies from the Second Edition (30, 40, 44, 52, 60, 61, 81–84) (**Tables 10** and **11**).

TABLE 9. Cerebral Perfusion Pressure: Quality of the Body of Evidence

Topic	No. of Studies Study Design	Recommendations	Meta-Analysis Possible (Yes or No[a])	Total No. of Subjects (*n*)	Consistency (High, Moderate, Low)	Directness (Direct or Indirect)	Precision (High, Moderate, Low)	Quality of Evidence (High, Moderate, Low, or Insufficient)
Components of overall quality: class 2 study								
CPP threshold Mixed ages	1 retrospective	III.2.	NA	317	NA	Direct	Low	Low
Components of overall quality: class 3 studies								
CPP threshold Mixed ages	1 prospective 2 retrospective 9 treatment series	III.1. III.2.	No; different thresholds; different populations	836	Low	Direct	Low	Low
CPP threshold for infants < 2 yr old	1 retrospective 1 treatment series	None	No	39	Moderate	Direct	Low	Insufficient

CPP = cerebral perfusion pressure, NA = not applicable.

[a]Meta-analysis to synthesize results is only possible if several studies address the same criteria/question, and other design criteria are met.

n indicates sample size.

TABLE 10. Cerebral Perfusion Pressure: Summary of Evidence

Reference Type of Trauma Center Geographic Location	Study Design *n* Age (yr) Outcomes	Data Class	Results
Class 2 study			
CPP age-specific ranges: recommendation III.2.			
Allen et al (79)[a] 22 (of 46 designated) trauma centers in New York: 20 are level I centers and two level II New York	Retrospective *n* = 317 pediatric Age: 0–5: 55 6–11: 65 12–17: 197 Mortality at 14 d postinjury, CPP, hypotension, elevated ICP	Class 2 Relevant criteria for minimizing bias were met	Predefined CPP thresholds by age group 40 and 30 mm Hg for 0–5 yr 50 and 35 mm Hg for 6–11 yr 60 and 50 for 12 yr old and older CPP categories CPP-H: events above high threshold CPP-B: events between high and low threshold CPP-L: events below low threshold Mortality Rates of survival and relative risk of mortality at 14 d postinjury: Regarding age (0–11 vs 12–17 yr), there was a difference between survivors (*n* = 101) and nonsurvivors (*n* = 19) for CPP-B. For CPP-L, there was a significant difference in the 0- to 11-yr-olds, not present in 12- to 17-yr-olds. Refer to Tables 3 and 4 in the publication for specific data about relationship between mortality and CPP thresholds by age. Data suggest that CPP targets should be age specific: Above 50 mm Hg in 6- to 17-yr-olds Above 44 mm Hg in 0- to 5-yr-olds

(*Continued*)

TABLE 10. (*Continued*). Cerebral Perfusion Pressure: Summary of Evidence

Reference Type of Trauma Center Geographic Location	Study Design *n* Age (yr) Outcomes	Data Class	Results
Class 3 studies			
Minimum threshold and target ranges for managing CPP: recommendations III.1. and III.2.			
Miller Ferguson et al (74)[a] PICU of a tertiary children's hospital Pittsburgh, PA	Retrospective *n* = 85 Age: mean, 5.1; range, NR Dichotomized GOS at 6 mo postinjury (1–2 unfavorable, 3–5 favorable) Note: article (p. 446) indicates "favorable 1 to 2, unfavorable 3 to 5."	Class 3 Selection of patients for ICP monitoring at discretion of neurosurgery	Outcome by threshold (< 40, < 45, < 50, < 55, < 60 mm Hg during first 5 d after ICP monitor placement) GOS No significant difference in outcomes across five estimates utilizing five different thresholds.
Vavilala et al (85)[a] Five Pediatric Trauma Centers Seattle, WA; Pittsburg PA; Chicago, IL; Torrance, CA; Columbus, OH	Retrospective *n* = 236 Age: mean, 8.0; range, NR Dichotomized discharge GOS	Class 3 Outcome assessment not blinded, unclear if groups are similar, some, but not all key confounders controlled for	Discharge GOS (survivors only) Adjusted risk ratio (95% CI) Reference: any CPP ≤ 40 (no surgery) Operating room All CPP > 40 mm Hg 0.61 (0.58–0.64) ICU All CPP > 40 mm Hg 0.73 (0.63–0.84) CPP > 40 mm Hg was associated with favorable discharge GOS
Kapapa et al (83) (Location not cited)	Treatment series Analysis of CPP in relation to age-specific lower limit (up to 1 mo, > 40 mm Hg; 2 mo up to 1 yr, > 45 mm Hg; 1 yr up to 7 yr, > 50 mm Hg; > 7 yr, 55–60 mm Hg) *n* = 36 Age: mean, NR; range, 0–16 Dichotomized GOS at varied timepoints	Class 3 Uncontrolled series	GOS Patients with CPP values below the age-specific lower limit for just a single occurrence had a significantly worse outcome ($p = 0.013$).
Chaiwat et al (81) Level I pediatric trauma center Seattle, WA	Treatment series *n* = 36 patients (two inflicted TBI) Age: mean, 9.1; range, 0.8–16 Dichotomized GOS dichotomized at 6 mo postinjury	Class 3 Uncontrolled series	GOS On univariate analysis, CPP < 40 mm Hg during the first 72 hr had no association with poor outcome. When logistic regression was performed, using a number of factors, only impaired autoregulatory index remained an independent predictor of poor outcome.
Figaji et al (61) Cape Town, South Africa	Treatment series *n* = 52 Age: mean, NR; range, 9 mo to 14 yr Dichotomized GOS at ≥ 6 mo postinjury	Class 3 Uncontrolled series	GOS Median (interquartile range) for lowest CPP was significantly lower in patients with unfavorable outcome: 29 mm Hg (20–45 mm Hg) vs 44 mm Hg (35–51 mm Hg), $p = 0.023$ Patients with unfavorable outcome had more episodes of CPP < 40 mm Hg: 3 (0–10) vs 0 (0–1), $p = 0.03$ There was no difference in the number of episodes of CPP < 50 mm Hg.

(*Continued*)

TABLE 10. (*Continued*). Cerebral Perfusion Pressure: Summary of Evidence

Reference Type of Trauma Center Geographic Location	Study Design *n* Age (yr) Outcomes	Data Class	Results
Narotam et al (60) Level II trauma center Omaha, NE	Treatment series $n = 16$ Age: mean, 14; range, 1.5–18 Mortality, GOS at 3 mo postinjury	Class 3 Uncontrolled series	Mortality Mean CPP was 81.52 ± 16.1 mm Hg for survivors vs 50.33 ± 31.7 mm Hg for nonsurvivors ($p < 0.033$). GOS All survivors had good outcome.
Stiefel et al (84) Level I trauma center Philadelphia, PA	Treatment series $n = 6$ Age: mean, 12; range, 6–16 Mortality, discharge GOS	Class 3 Uncontrolled series	Mortality 1 in 6 died Mean daily CPP in survivors was 75.63 ± 11.73 mm Hg. GOS 4 of 6: 5 1 of 6: 3 1 of 6: 1
Adelson et al (40) Multicenter: Pittsburgh, PA; Sacramento, CA; Miami, FL; Salt Lake City, UT; Hershey, PA; Seattle, WA (level I pediatric trauma center)	Randomized controlled trial of hypothermia therapy Analysis of average CPP over the first 5 d of care $n = 102$ Age: mean age in two part study 6.89 and 6.95 yr Range: 0–13 Dichotomized GOS at 6 mo postinjury	Class 3 No control for confounders in CPP analysis (for hypothermia, this is a class 2 study)	GOS Average CPP was 69.19 ± 11.96 mm Hg for favorable vs 56.37 ± 20.82 mm Hg for unfavorable ($p = 0.0004$) outcome groups. Percent time with CPP > 50 mm Hg was 94.2% ± 16.9% for favorable vs 87.3% ± 29.5% for unfavorable ($p = 0.0001$). Mean CPP on day 1 was higher in the hypothermia group (70.75 mm Hg) than the normothermia group (64.84 mm Hg), $p = 0.037$. No significant differences between groups on days 2–5, and GOS was not assessed in relation to differences in CPP on day 1.
Chambers et al (30) Neurosurgical Centre at Newcastle General Hospital Newcastle, United Kingdom	Treatment series $n = 84$ Age: median, 10 yr; range, 3 mo to 16 yr GOS dichotomized at 6 mo postinjury	Class 3 Uncontrolled series	GOS Poor outcome in all eight cases with CPP < 40 mm Hg; more patients had good outcome than poor outcome when mean CPP was > 40 mm Hg.
Downard et al (44) OHSU and Legacy Emmanuel Hospital and Health Center (both are level I trauma centers with immediately available neurosurgical services) Portland, OR	Treatment series $n = 118$ Age: mean, 7.4; range, 0–15 Mortality; last recorded GOS in records at 3 mo or later, dichotomized	Class 3 Uncontrolled series	Mortality All children with mean CPP < 40 mm Hg died. GOS No significant difference in GOS when mean CPP was divided into deciles from 40 to > 70 mm Hg. More patients had a good outcome than poor outcome when mean CPP was > 50 mm Hg, but no statistical analysis.

(*Continued*)

TABLE 10. (*Continued*). Cerebral Perfusion Pressure: Summary of Evidence

Reference Type of Trauma Center Geographic Location	Study Design *n* Age (yr) Outcomes	Data Class	Results
Barzilay et al (52) Chaim Sheba Medical Center with PICU Tel Aviv, Israel	Treatment series *n* = 56 total *n* = 41 TBI Age: mean, 6.2; range, NR Survival at hospital discharge	Class 3 Uncontrolled series	Survival (TBI group) CPP was 65.5 ± 8.5 mm Hg for survivors vs 6.0 ± 3.9 mm Hg for nonsurvivors ($p < 0.01$). 32 patients (78%) survived (mean ICP maximum 16.9 ± 3.1 and CPP minimum 65.5 ± 8.5 torr) compared with nine patients (22%) who died (mean ICP maximum 53.7 ± 10.8 and CPP minimum 6 ± 3.9 torr) ($p < 0.01$).
Kaiser and Pfenninger (82) ICU, University Children's Hospital Bern, Switzerland	Treatment series *n* = 24 Age: mean, 6.3 yr; range, 1–14 Survival; GOS at 6–12 mo postinjury	Class 3 Uncontrolled series	Survival All survivors (*n* = 19) had minimum CPP > 50 mm Hg. Three of the five children who died also had CPP > 50 mm Hg. GOS 1, *n* = 5 2, *n* = 0 3, *n* = 3 4, *n* = 3 5, *n* = 13
CPP threshold for infants < 2 yr old: no recommendation			
Mehta et al (73)[a] Pediatric Neurotrauma Registry Pittsburgh, PA	Retrospective *n* = 22 Age: mean, 6.1 mo; range, 0–2 yr Dichotomized GOS at 6 mo postinjury (favorable 3–5, unfavorable 1–2), ICP, CPP, physiologic variables Subset of 85 patients in Miller Ferguson et al (74). Note: article (p. 415) indicates "favorable [GOS: 1–2] and unfavorable [GOS: 3–5] outcomes." This is transposed from the generally accepted order (e.g., GOS 1 = dead).	Class 3 Small sample size	Outcome by threshold (< 40, < 45, < 50 mm Hg during the first 7 d) GOS No difference in daily mean CPP between outcome groups Patients in favorable outcome group had significantly fewer hourly readings of CPP < 45 mm Hg than unfavorable group ($p = 0.046$). No difference between number of hourly readings of CPP < 40 or < 50 in patients with favorable or unfavorable outcomes
Barlow and Minns (80) Edinburgh, Scotland, United Kingdom	Treatment series *n* = 17 all inflicted TBI Age: mean, 5.1 mo; range, 1–20 mo A 6-point outcome scale assessed 3–122 mo postinjury (mean, 33 mo).	Class 3 Uncontrolled series	Outcome scale Lowest CPP correlated with poor outcome ($p < 0.0047$)

CPP = cerebral perfusion pressure, GOS = Glasgow Outcome Scale, ICP = intracranial pressure monitoring, NR = not reported, TBI = traumatic brain injury.
[a]New study.
n indicates sample size.

Evidence Synthesis

What Are the Minimum Threshold and Target Ranges for Managing CPP, and Are Ranges Age Specific?. A RCT of hypothermia (32° to 33°) therapy (a class 2 study for the evidence about hypothermia, but class 3 for the evidence about CPP) reported average CPP over the first 5 days of care as well as for the total 5 days of care (40). The authors used dichotomized GOS outcome (good in 28 cases, 14 hypothermia patients and 14 normothermia patients; poor in 40 cases, 18 hypothermia patients and 22 normothermia patients) assessed at 6 months after injury to examine differences in CPP. The average CPP for all 5 days was higher in the good outcome group (good outcome

TABLE 11. Summary of Treatments, Cerebral Perfusion Pressure Target, and Cerebral Perfusion Pressure Statistics Used in Studies

Variations in Treatment and Measurement of CPP						
	Treatments Used					
Reference	Hyperventilation	Induced Hypothermia	Barbiturate Coma	Decompressive Craniectomy	CPP Target Strategy	CPP Statistic Used Time Period
Adelson et al (40)	NO	YES	YES	YES	Age-related 45 mm Hg	Mean CPP Days 1–5
Allen et al (79)[a]	Threshold	Threshold	Threshold	Threshold	Threshold	Number of events below minimum, above maximum, or between thresholds Any time during ICU stay
Barlow and Minns (80)	Threshold	Threshold	Threshold	Threshold	Threshold	Lowest CPP Timing NR
Barzilay et al (52)	YES	YES	YES	NO	–	Lowest CPP Timing NR
Chaiwat et al (81)	–	–	–	–	–	Lowest CPP First 72 hr
Chambers et al (30)	Threshold	Threshold	Threshold	Threshold	Threshold	Minimum CPP Range: 6.3–173 hr; median: 41.2
Downard et al (44)	YES	NO	NO	YES	Age-related 45 mm Hg	Mean CPP First 48 hr
Figaji et al (61)	YES	YES	YES	YES	Age-related 45 mm Hg	Initial and lowest CPP Mean duration 123.7 ± 67.1 hr
Kaiser and Pfenninger (82)	YES	YES	YES	NO	–	Mean CPP Mean time of 9 d; range 1–15 d
Kapapa et al (83)	YES	YES	YES	YES	Age-related 40 mm Hg	Lowest CPP Any point during hospitalization with monitor
Mehta et al (73)[a]	NO	YES	YES	YES	ICP of 20 and CPP 50 mm Hg	Mean CPP Daily mean for first 7 d
Miller Ferguson et al (74)[a]	NO	YES	YES	YES	ICP of 20 and CPP 50 mm Hg	Mean CPP daily mean for first 5 d
Narotam et al (60)	YES	NO	NO	NO	ICP-related	Mean CPP Timing NR
Stiefel et al (84)	–	–	–	–	Age-related 40 mm Hg	Mean CPP From admission for at least 72 hr
Vavilala et al (85)[a]	YES	–	YES	YES	CPP > 40 mm Hg	Below or above threshold At any time in operating room or ICU

CPP = cerebral perfusion pressure, ICP = intracranial pressure monitoring, NR = not reported.

[a]New study.

In the studies that describe therapy, "YES" denotes use of therapy and "NO" denotes where treatment is not used. "Threshold" denotes where the study is aimed at defining a threshold about burden from CPP insult and outcome, rather than it being an intervention study. Dash indicates where no information is given in the report.

69.19 ± 11.96 mm Hg vs poor outcome 56.37 ± 20.82 mm Hg; $p = 0.0004$). In addition, the percent time with CPP greater than 50 mm Hg was higher in the good outcome group (good outcome 94.2% ± 16.9% vs poor outcome 87.3% ± 29.5%; $p = 0.0001$). In contrast, a recent retrospective study of 85 pediatric patients with severe TBI (mean age, 5.1 ± 0.8 yr) analyzed outcome in five threshold groups (< 40, 45, 50, 55, and 60 mm Hg). No significant difference across groups was found in the dichotomized GOS at 6 months postinjury.

Five treatment series found higher CPP associated with better outcomes and their findings were as follows (52, 60, 61, 80, 84). Barzilay et al (52) studied 41 consecutive TBI admissions to their PICU with coma for at least 6 hours before admission. Survivors had higher minimum CPP than nonsurvivors (65.5 ± 8.5 vs 6.0 ± 3.9 mm Hg; $p < 0.01$). All patients with head trauma were treated for 5 days with dexamethasone, and neither the timing nor duration of ICP and CPP derangements was specified. "Preterminal" data were not removed, resulting in the low average CPP for nonsurvivors. Figaji et al (61) studied prospectively 52 children with TBI and found median lowest CPP experienced during the course of monitoring was higher in those with better outcome. By using dichotomized GOS outcome assessed at least 6 months after injury, those with favorable outcome had higher lowest CPP median (interquartile range) of 44 mm Hg (35–51 mm Hg) versus 29 mm Hg (20–45 mm Hg) in comparison with those with unfavorable outcome ($p = 0.023$). Narotam et al (60) analyzed data from 16 children 1.5–18 years old (mean, 14 yr), 15 of whom had GCS less than or equal to 8. All 10 survivors had GOS 5 at 3 months. Mean CPP was higher in survivors (81.52 ± 16.1 mm Hg) than nonsurvivors (50.33 ± 31.7 mm Hg; $p = 0.033$). Stiefel et al (84) studied brain tissue oxygen monitoring in six patients (age, 6–14 yr old; GCS = 3–7) and found that mean daily CPP in the five survivors was 75.63 ± 11.73 mm Hg. Last, in a sample of TBI cases restricted to 17 young children with inflicted injury (age, 1–20 mo old; mean, 5.1 mo), Barlow and Minns (80) reported that lowest CPP during intensive care was associated with poorer outcomes in a 6-point scale 3–122 months (mean, 33 mo) after injury ($p = 0.0047$).

Four studies reported findings in relation to a threshold in CPP of 40 mm Hg (30, 44, 61, 81). In the study reported by Figaji et al (61), the authors found that more episodes of CPP less than 40 mm Hg were observed in those with unfavorable (3 [0–10]) versus favorable (0 [0–1]) outcome ($p = 0.0.03$); a more complex relationship between CPP and outcome involved data from autoregulation of CBF. Chambers et al (30) analyzed 84 children age 3 months to 16 years old (median, 10 yr) and examined minimum CPP in relation to dichotomized GOS at 6 months. Sixty-three out of 76 cases with CPP greater than 40 mm Hg had good outcome, and all eight cases with CPP less than 40 mm Hg had poor outcome ($p < 0.0001$; Fisher exact test). Downard et al (44) analyzed 118 pediatric TBI cases of children up to 15 years old (mean age, 7.4 yr; 99 cases with GCS = 3–8) and reported dichotomized GOS at 3 months or later in relation to CPP thresholds. Seventy-two out of 96 patients with CPP greater than 40 mm Hg had good outcome, whereas all 22 cases with CPP less than 40 mm Hg died. The difference in mortality was statistically significant ($p < 0.0001$, Fisher exact test). Chaiwat et al (81) analyzed 36 cases of TBI for predictors of poor outcome. ICP of greater than 20 mm Hg and CPP less than 40 mm Hg during the first 72 hours were not associated with outcome. However, on logistic regression, an estimate of impaired CBF autoregulation using Doppler ultrasonography—the autoregulatory index (ARI)—was an independent predictor of poor outcome (adjusted odds ratio [OR], 23.1; 95% CI, 1.9–279.0). Impaired ARI was an independent risk factor when the authors entered CPP less than 40 mm Hg, SBP less than fifth percentile for age and gender during the first 72 hours after TBI, low middle cerebral artery (MCA) velocity, and impaired ARI into the model (adjusted OR, 29.8; 95% CI, 1.7–521.4). Because ARI is calculated as the percent change in cerebrovascular resistance (CVR) per percent change in CPP, and CVR is defined as the ratio of CPP to MCA velocity, it is impossible to disentangle the relationship between outcome and CPP. ARI represents a research tool.

Five class 3 studies contain data concerning CPP threshold above 40 mm Hg (3, 5, 10, 12, 14). Two retrospective treatment series support the idea that there may be an age-related CPP threshold above 40 mm Hg. Kapapa et al (83) analyzed 16 children under 16 years old and reported dichotomized GOS in relation to age-specific lower limits in CPP (i.e., > 40 mm Hg, infants up to 1 mo old; > 45 mm Hg, infants 2 mo to 1 yr old; > 50 mm Hg, children between 1 and 7 yr old; 55–60 mm Hg, children > 7 yr old). The authors found that patients with CPP value below the age-specific lower limit for just a single occurrence had a significantly worse outcome ($p = 0.013$). Kaiser and Pfenninger (82) reported findings in 24 consecutive admissions to their PICU of patients with a GCS less than 8, average age 6.3 years (10 patients between 1 and 5 yr old), and showed that all survivors had CPP greater than 50 mm Hg ($p < 0.005$, Fisher exact test). Two studies did not observe a threshold above 40 mm Hg (44, 61). In the study reported by Figaji et al (61) (see above), the authors also reported outcome in relation to the number of episodes during monitoring that CPP was less than 50 mm Hg: there was no difference in the number of episodes in those with unfavorable (8 [2–18.5]) versus favorable (3 [0–8.8]) outcome ($p = 0.137$). Of note, two thirds of the children in this series were younger than 8 years old. As discussed above, in the study reported by Downard et al (44), 100% of children with mean CPP less than 40 mm Hg died when compared with only 25% of children who had a CPP greater than 40 mm Hg. The difference in mortality was statistically significant ($p < 0.0001$, Fisher exact test). Last, in the study of young children with abusive TBI reported by Barlow and Minns (80) (see above), only one infant in the series of 17 had lowest CPP greater than 50 mm Hg.

These studies, in aggregate, suggest that in the pediatric age range, there may be an age-related threshold between 40 and 50 mm Hg, with infants at the lower end and adolescents at the upper end of this range. Finally, studies specifically focused on assessment of the optimal upper limit for CPP management in pediatric TBI were lacking.

Indications From Adult Guidelines

The recent Fourth Edition of the adult guidelines does not further inform the pediatric guidelines for this topic (14).

TREATMENTS

Hyperosmolar Therapy

Recommendations

Strength of Recommendations: Weak

Level I

There was insufficient evidence to support a level I recommendation for this topic.

Level II

For ICP Control. II.1. Bolus HTS (3%) is recommended in patients with intracranial hypertension. Recommended effective doses for acute use range between 2 and 5 mL/kg over 10–20 minutes.

Level III

For ICP Control. III.1. Continuous infusion HTS is suggested in patients with intracranial hypertension. Suggested effective doses as a continuous infusion of 3% saline range between 0.1 and 1.0 mL/kg of body weight per hour, administered on a sliding scale. The minimum dose needed to maintain ICP less than 20 mm Hg is suggested.

III.2. Bolus of 23.4% HTS is suggested for refractory ICP. The suggested dose is 0.5 mL/kg with a maximum of 30 mL.

Safety Recommendation (applies to all recommendations for this topic). In the context of multiple ICP-related therapies, avoiding sustained (> 72 hr) serum sodium greater than 170 mEq/L is suggested to avoid complications of thrombocytopenia and anemia, whereas avoiding a sustained serum sodium greater than 160 mEq/L is suggested to avoid the complication of deep vein thrombosis (DVT).

Note. Although mannitol is commonly used in the management of raised ICP in pediatric TBI, no studies meeting inclusion criteria were identified for use as evidence for this topic.

Changes From Prior Edition. Recommendation II.1. is new to this Third Edition. It replaces the level II recommendation from the Second Edition suggesting the use of HTS in general, with doses ranging between 6.5 and 10 mL/kg. Recommendations III.2. is new to this Third Edition. The recommendation from the Second Edition to maintain serum osmolarity less than 360 mOsm/L was removed from this edition. The Safety Recommendation is new to this edition. One new class 2 prospective observational study (2) and five new class 3 studies—four retrospective observational (85, 87–89) and one treatment series (90)—were added to the evidence base for this topic.

Introduction

Hyperosmolar Therapy for Intracranial Hypertension. IV administration of hyperosmolar agents was shown to reduce ICP in 1919 (91). Mannitol was introduced into clinical use in 1961 (92). Despite widespread use of a number of osmolar agents (mannitol, urea, and glycerol) up until the late 1970s (93, 94), mannitol gradually became the agent of choice to manage ICP (93). Subsequently, HTS was introduced in the 1990s (95), and although both are currently used, HTS use has increased while mannitol use has decreased (96). Additionally, a goal of euvolemia rather than dehydration as a therapeutic target is achieved by assessing fluid balance, central venous pressure, urine output, blood urea nitrogen, serum creatinine, and clinical examination. The placement of a Foley catheter is also routinely used to quantify urine output and to avoid potential bladder rupture.

Mannitol. Mannitol is commonly used to manage raised ICP in pediatric TBI (96). Despite this fact, mannitol has not been subjected to contemporary controlled clinical trials versus placebo, other osmolar agents, or other therapies in children. Most of the investigations on the use of mannitol were carried out in the 1970s on mixed disease populations in both children and adults (93).

Mannitol can reduce ICP by two distinct mechanisms. Mannitol can reduce ICP by reducing blood viscosity. This effect is immediate and results from a viscosity-mediated reflex vasoconstriction (intact autoregulation) which allows CBF to be maintained despite a reduced level of cerebral blood volume (CBV) (97, 98). The effect of mannitol administration on blood viscosity is transient (< 75 min) (97). Mannitol administration also reduces ICP by an osmotic effect, which develops more slowly (over 15–30 min), due to the gradual movement of water from the brain parenchyma into the systemic circulation. The effect persists up to 6 hours and requires an intact blood-brain barrier (99, 100). Mannitol may accumulate in injured brain regions (101), where a reverse osmotic shift may occur—with fluid moving from the vascular compartment into the brain parenchyma, possibly increasing ICP. This phenomenon has been suggested to occur when mannitol is used for extended periods of time (102, 103).

Mannitol is excreted unchanged in urine, and a risk of the development of acute tubular necrosis and renal failure has been suggested with mannitol administration with serum osmolarity levels greater than 320 mOsm in adults (104–106). However, the literature supporting this finding is limited in scope and was generated at a time when dehydration rather than euvolemia was the therapeutic target.

HTS. In the initial description in 1919 of the reduction in ICP by IV administration of hyperosmolar agents, HTS was the agent used (91). Its use in the treatment of increased ICP, however, failed to gain clinical acceptance. Resurgence in interest in this treatment emerged in the late 1980s (107), leading to the studies providing current evidence.

Like mannitol, the penetration of sodium across the blood-brain barrier is low (108). Sodium thus shares both the favorable rheologic and osmolar gradient effects involved in the reduction in ICP. HTS has other theoretical beneficial effects including restoration of normal cellular resting membrane potential and cell volume (109, 110), stimulation of arterial natriuretic peptide release (111), inhibition of inflammation (108), and enhancement of cardiac output (112). Possible side effects of HTS include rebound in ICP, central pontine myelinolysis, renal impairment, subarachnoid hemorrhage, natriuresis, high urinary water losses, hyperchloremic acidosis, and masking of the development of diabetes insipidus (108).

Much higher levels of serum osmolarity (≈360 to 370 mOsm) may be tolerated in children when induced with HTS (87, 113) versus mannitol although this point remains controversial (35).

In 14 adults with severe TBI, Lescot et al (114) suggested important differences in the response of contused versus noncontused brain tissue to HTS, with reductions in the volume of noncontused brain but increases in the volume of contusions after treatment. Studies of regional effects of HTS or mannitol have not been carried out in pediatric TBI.

A second use of HTS is to treat hyponatremia due to cerebral salt wasting if it develops in pediatric patients after TBI (1). However, the focus of this guideline is on the use of hyperosmolar agents in the treatment of raised ICP.

Evaluation of the Evidence

Quality of the Body of Evidence. Studies included for this topic addressed the question of the effectiveness of HTS to improve outcomes and control ICP, and the subquestions about HTS versus other agents, mode of administration, effective dose ranges, and the risk of DVT and other complications. Two class 2 RCTs (95, 115), one class 2 prospective study (2), three class 3 retrospective studies (85, 88, 113), and one class 3 treatment series (90) provide evidence for treatment effects on intracranial hypertension for this topic. Two class 3 retrospective studies provide evidence for the Safety Recommendation (87, 89). There was insufficient evidence to support a recommendation about use of HTS to improve outcomes, or about the comparative effectiveness of agents. The overall quality of the body of evidence is moderate to low (**Table 12**).

Applicability. The evidence includes current studies; however, they are observational, class 3. The two class 2 RCTs were

TABLE 12. Hyperosmolar Therapy: Quality of the Body of Evidence

Topic	No. of Studies Study Design	Recommendations	Meta-Analysis Possible (Yes or No[a])	Total No. of Subjects (*n*)	Consistency (High, Moderate, Low)	Directness (Direct or Indirect)	Precision (High, Moderate, Low)	Quality of Evidence (High, Moderate, Low, or Insufficient)
Components of overall quality: class 2 studies								
Bolus hypertonic saline to control ICP monitoring	1 RCT 1 prospective	II.1.	No, different comparators	34	Moderate	Direct	Moderate	Moderate
Continuous infusion hypertonic saline to control ICP monitoring	1 RCT	III.1.	NA	35	NA	Direct	Low	Low
Components of overall quality: class 3 studies								
Continuous infusion hypertonic saline to control ICP monitoring	1 retrospective	III.1.	NA	68	NA	Direct	Low	Low to moderate
Bolus hypertonic saline to control refractory ICP monitoring	1 treatment series	III.2.	NA	32	NA	Direct	Low	Low
Bolus hypertonic saline vs mannitol to control refractory ICP monitoring	1 retrospective	No recommendation	NA	16	NA	Direct	Low	Insufficient
Hypertonic saline to improve overall outcomes	1 retrospective	No recommendation	NA	236	NA	Direct	Low	Insufficient
Risk of deep vein thrombosis with hypertonic saline	1 retrospective	Safety recommendation	NA	58	NA	Direct	Moderate	Low
Hypertonic saline complications/ upper limits	1 retrospective	Safety recommendation	NA	48	NA	Direct	Low	Low

ICP = intracranial pressure, NA = not applicable, RCT = randomized controlled trial.

[a]Meta-analysis to synthesize results is only possible if several studies address the same criteria/question, and other design criteria are met.

n indicates sample size.

from the 1990s (95, 115). With the exception of one (85), the studies were conducted at single centers with sample sizes less than 100. Six were conducted in the United States (2, 85, 87, 89, 95, 113), one in Australia (90), one in Switzerland (115), and one in Canada (88). The studies included a range of ages. The small sample sizes and single-center designs limit the applicability.

Summary of the Evidence

Of the nine studies summarized in the evidence table, two class 2 studies (2, 95) provided evidence to support recommendation II.1. One class 2 study (115) and one class 3 study (113) provided evidence to support recommendation III.1. One class 3 study (90) provided evidence to support recommendation III.2. There was insufficient evidence to support a recommendation for the use of HTS to improve outcomes. Two class 3 studies (87, 89) supported the safety recommendations for this topic (**Table 13**).

Evidence Synthesis

Bolus Administration of HTS to Control ICP. Fisher et al (95) carried out a double-blind randomized controlled crossover study comparing IV administration of 3% saline (513 mEq/L, 1,027 mOsm/L) and 0.9% saline (154 mEq/L, 308 mOsm/L) in 18 children with severe TBI. Bolus doses of each agent were equal and ranged between 6.5 and 10 mL/kg. During the 2-hour trial, HTS use was associated with an approximately 7 mEq/L increase in serum sodium concentration, lower ICP, and reduced need for other interventions. Concomitant therapies used for patient management in this study included thiopental, dopamine, mannitol, and hyperventilation. CSF drainage was not used.

More recently, Shein et al (2) carried out a prospective cohort study comparing the effects of bolus IV administration of 3% saline (3 mL/kg [range, 2–5 mL/kg] over 10–20 min), fentanyl, pentobarbital, or mannitol, on ICP and CPP in 16 children with severe TBI. The study featured use of a data acquisition system sampling every 5 seconds, and over 2.7 million timepoints were analyzed for values of ICP, MAP, and CPP. The response to these therapies (collectively, 362 doses) was assessed in real world use rather than a randomized comparison to treat ICP greater than 20 mm Hg for greater than

TABLE 13. Hyperosmolar Therapy: Summary of Evidence

Reference Type of Trauma Center Geographic Location	Study Design *n* Age (yr) Outcomes	Data Class	Results
Class 2 studies			
Bolus hypertonic saline to control ICP: recommendation II.1.			
Shein et al (2)[a] Children's Hospital University of Pittsburgh Pittsburgh, PA	Prospective *n* = 16 in analysis Age: mean, 44 mo; range, 34–124 mo ICP and CPP	Class 2 Differences in patients by treatment, limited control for confounding	Hypertonic saline vs other drugs for intracranial hypertension Decrease in ICP; increase in CPP Associated with a two-fold faster resolution of intracranial hypertension than either fentanyl or pentobarbital Adjusted hazard ratio, 2.171 (95% CI, 1.062–4.439) Hypertonic saline may be first-line treatment given favorable hemodynamics and resolution of intracranial hypertension. Comparison drugs: beneficial effects on ICP only Fentanyl: ICP decreased; CPP decreased. Highest rate of treatment failure rate Pentobarbital: ICP decreased; CPP no significant change Note: Mannitol not included due to limited use (seven doses out of 362 total; four out 196 analyzed)
Fisher et al (95) San Diego Children's Hospital San Diego, CA	RCT *n* = 18 Age: mean, 8.3; range, 0.6–14.5 ICP	Class 2 Randomization and allocation concealment methods not reported; crossover study lacking reporting on first-period comparison of baseline characteristics; small sample size	3% saline vs 0.9% During the 2-hr trial, hypertonic saline was associated with a lower ICP and reduced need for additional interventions (thiopental and hyperventilation) to control ICP. Serum sodium concentration increased ≈7 mEq/L after 3% saline.

(*Continued*)

TABLE 13. (*Continued*). Hyperosmolar Therapy: Summary of Evidence

Reference Type of Trauma Center Geographic Location	Study Design *n* Age (yr) Outcomes	Data Class	Results
Continuous infusion hypertonic saline to control ICP: recommendation III.1.			
Simma et al (115) Children's Hospital of Zurich Zurich, Switzerland	RCT $n = 35$ Age: mean, 87 mo; range, 12–173 mo ICP, CPP, need for other interventions, fluid requirements, ICU stay, and survival rate	Class 2 Not blinded, insufficient power	Hypertonic saline (1.7%) vs lactated Ringer's solution No difference between groups in survival rate and length of hospital stay Patients treated with hypertonic saline required fewer interventions than those treated with lactated Ringer's to maintain ICP control ($p < 0.01$). The hypertonic saline treatment group had shorter length of ICU stay ($p = 0.04$), shorter duration of mechanical ventilation ($p = 0.10$ not significant), and fewer complications than the lactated Ringer's-treated group ($p = 0.09$) for two or more complications, not significant, without p value reported for one complication).
Class 3 studies			
Continuous infusion hypertonic saline to control ICP: recommendation III.1.			
Peterson et al (113) San Diego Children's Hospital San Diego, CA	Retrospective $n = 68$ Age: mean, 7.8; range, NR ICP, 6-mo GOS score	Class 3 No control for confounders	3% hypertonic saline, continuous infusion Survival rate was higher than expected based on Trauma and Injury Severity Score (41 predicted, 58 actual). 53% had good outcome, 20.5% moderate, 10% severe, 1.5% vegetative, and 15% died; three died of uncontrolled ICP. No patients developed renal failure. Central pontine myelinolysis, subarachnoid hemorrhage, or rebound increases in ICP were not observed.
Bolus hypertonic saline to control refractory ICP: recommendation III.2.			
Piper and Harrigan (90)[a] John Hunter Hospital Newcastle, NSW, Australia	Treatment series $n = 32$ (4 [87.5%] with GCS ≥ 9) Age: mean, 14; range, 8 mo to 17 yr ICP, mortality, GOS, ICU LOS	Class 3 No control for confounding; differences across patients	All received 23.4% hypertonic saline infused over 10 min, maximum dose of 30 mL All-cause mortality 6% (2/32) at 7 d No deaths after 7 d GOS 48% 5 (normal life activities) 26% 4 (disabled but independent) 19% 3 (conscious but severely disabled) 0% 2 (persistent vegetative state) 6% 1 (deceased) ICP Mean ICP response to HTS (pre HTS ICP-ICP 60 min post) 10 mm Hg (range, 1–30; SD, 8) ICU LOS Mean 10 d (range, 2–25; SD, 6)

(*Continued*)

TABLE 13. (*Continued*). Hyperosmolar Therapy: Summary of Evidence

Reference Type of Trauma Center Geographic Location	Study Design *n* Age (yr) Outcomes	Data Class	Results
Bolus hypertonic saline vs mannitol to control refractory ICP: no recommendation			
Roumeliotis et al (88)[a] Pediatric tertiary care and trauma center Montreal, QC, Canada	Retrospective *n* = 16 Age: mean, 13 Interquartile range: 10–15 ICP, CPP, and serum sodium	Class 3 Limited control for confounding; 11 of 16 patients had cointerventions	ICP Both HTS and Mannitol produced a nonsignificant decrease in ICP in first 4 hr. CPP No change in CPP postbolus Serum sodium No significant change in serum sodium
Hypertonic saline to improve overall outcomes: no recommendation			
Vavilala et al (85)[a] Five pediatric trauma centers Seattle, WA; Pittsburg PA; Chicago, IL; Torrance, CA; Columbus, OH	Retrospective *n* = 236 Age: mean, 8.0; range, NR In-hospital mortality, discharge GOS	Class 3 Limited control for confounding, outcome assessors not blinded, impact of baseline characteristics, and missing data unclear	Discharge survival Hypertonic saline or mannitol used for high ICP in operating room (adjusted relative risk, 0.62; 95% CI, 0.42–0.93) Reference: neither used with high ICP (measured in prehospital, emergency department, operating room, ICU. Combined not significant) Note: frequency of each agent or results not reported separately
Risk of DVT with hypertonic saline: safety recommendation			
Webster et al (89)[a] Cincinnati Children's Hospital Cincinnati, OH	Retrospective DVT compared with no DVT; all given HTS the exposure is the bolus volume and sodium level *n* = 58 Age: median DVT = 8 No DVT = 4.5 Range: NR DVT, survival at 30 d, and GOS	Class 3 Potential confounding; measurement and detection concerns for DVT	DVT Cumulative total bolus volume of HTS (mL/kg) associated with DVT (OR, 1.6; 95% CI, 1.2–2.4; $p = 0.01$) Peak sodium level and 72-hr sustained sodium levels: associated with DVT ($p = 0.05$) Sustained sodium level of at least 160 mmol/L: associated with DVT ($p = 0.02$) Mortality 69% alive at 30 d postinjury Total bolus volume of HTS during the hospital stay was not significantly associated with survival ($p = 0.62$) GOS A favorable GOS was not associated with a higher cumulative total bolus volume of HTS administered. Odds of a favorable GOS of 4 or 5 were less for those subjects who maintained a sustained sodium of at least 160 mmol/L (OR, 0.1; 95% CI, 0.03–0.38; $p = 0.008$). The sample-average sustained sodium for the subjects with a discharge GOS of 1–3 was 160.1 mmol/L, and the sample-averaged sustained sodium for the subjects with a discharge GOS of 4–5 was 144.8 mmol/L, a difference of 15.3 mmol (95% CI, 9.3–21.3; $p \leq 0.01$).

(*Continued*)

TABLE 13. (*Continued*). Hyperosmolar Therapy: Summary of Evidence

Reference Type of Trauma Center Geographic Location	Study Design *n* Age (yr) Outcomes	Data Class	Results
Hypertonic saline complications/upper limits: safety recommendation			
Gonda et al (87)[a] Rady Children's Hospital San Diego, CA	Retrospective $n = 48$ TBI Out of 88 total Age: mean, 8; range, 3 wk to 19 yr Complications associated with hypernatremia for TBI group Mortality, GOS at discharge, ICP monitor duration for entire group (indirect evidence) Complications for subset of TBI patients (direct evidence)	Class 3 Control for some identified confounders	Complications with sustained peak serum sodium level (mEq/L) ≥ 170 Reference: < 170 ORs Multivariate (95% CI) Thrombocytopenia: 31.5 (7.0–194)/71.6 (6.8–1,807), $p < 0.001$ Neutropenia: 26.7 (4.1–530.5)/195 (0.8–64,053,150), $p = 0.146$ RBC transfusion: 33.6 (5.7–650.7)/22.8 (1.7–935.4), $p < 0.001$ Fresh frozen plasma transfusion: 9.5 (2.5–41.6)/3.9 (0.6–27.1), $p < 0.001$ Renal failure: 10.2 (2.1–76.3)/17.5 (1.0–540.7), $p < 0.009$ Acute respiratory distress syndrome: 12.5 (1.8–253.2)/7.7 (0.3–354.4), $p < 0.028$ Overall mortality[b] 15.9% (14/88), 7/88 due to cerebral herniation Overall Glasgow Outcome Score[b] < 3: 10 (17.2%) vs 14 (46.7%), $p = 0.005$ Overall ICP monitor duration[b] Mean 10.9 d (SD, ± 4.7) vs 19 d (SD, ± 12.1), $p < 0.001$

CPP = cerebral perfusion pressure, DVT = deep vein thrombosis, GOS = Glasgow Outcome Scale, HTS = hypertonic saline solution, ICP = intracranial pressure, LOS = length of stay, NR = not reported, OR = odds ratio, RCT = randomized controlled trial, TBI = traumatic brain injury.

[a]New study.

[b]Rates based on total sample size including non-TBI patients.

5 minutes. HTS administration was associated with a two-fold faster resolution of intracranial hypertension than either fentanyl or pentobarbital and was the only agent that also improved CPP. Mannitol use could not be assessed given that only seven doses were administered.

These two class 2 studies provide evidence to support the level II recommendation for bolus administration of HTS (3% solution) to treat intracranial hypertension (2, 95).

Continuous Infusion Administration of HTS to Control ICP. Simma et al (115) carried out an RCT of 1.7% HTS (sodium 268 mmol/L, 598 mOsm/L) versus lactated Ringer's solution (sodium 131 mmol/L, 277 mOsm/L) administered IV over the initial 3 days in 35 children with severe TBI. Patients treated with HTS required fewer interventions (including mannitol use) to control ICP than those treated with lactated Ringer's solution. Patients in the HTS treatment group also had shorter length of PICU stay ($p = 0.04$) and fewer complications than the lactated Ringer's-treated group ($p = 0.09$ for two or more complications, not significant for one complication). Due to design flaws and insufficient power, the evidence from this study is class 2. Two facets of this study precluded the clinical investigators from making a level II recommendation in favor of continuous infusion of HTS to control ICP: 1) the control group received infusion of lactated Ringer's, and 2) the HTS concentration that was used (1.7%) has limited clinical use in pediatric TBI.

Peterson et al (113) reported a retrospective class 3 study on the use of a continuous infusion of 3% saline (sodium 513 mEq/L, 1,027 mOsm/L) titrated to reduce ICP to less than or equal to 20 mm Hg in 68 infants and children with TBI. The mean daily doses of HTS over a 7-day period ranged between 11.76 and 26.94 mL/kg/d. There was no control group. Three patients died of uncontrolled ICP, and mortality rate was lower than expected based on Trauma and Injury Severity Score (ISS) categorization. No patient with a serum sodium concentration greater than 180 mEq/L had a good outcome. No patients developed renal failure. Concomitant therapies included sedation, NMB, mannitol, hyperventilation, and barbiturates. CSF drainage was used in three children. The mean daily dose of mannitol was between 0.83 and 2.16 g/kg/d. Rebound in ICP, central pontine myelinolysis, and subarachnoid hemorrhage were not seen.

These two studies provided the evidence to support the level III recommendation for continuous infusion of HTS (3%) to treat intracranial hypertension (113, 115).

Bolus Administration of HTS for Refractory ICP. Piper and Harrigan (90) reported a treatment series on the use of 23.4% saline to treat refractory intracranial hypertension in 32 infants and children with severe TBI. Refractory intracranial hypertension was defined as an ICP greater than 20 mm Hg for greater than 5 minutes and not responding to a stepwise protocol that included sedation, analgesia, head elevation, mild hyperventilation, mild hypothermia (36.5°C), NMB, and use of inotropic support to support age-appropriate CPP. Contraindication to the administration of 23.4% saline in this study was a serum sodium level of greater than 155 mmol/L. The dose of 23.4% saline was 0.5 mL/kg administered over a period of 10 minutes, with a maximum dose of 30 mL. The mean reduction in ICP with treatment was 10 mm Hg (range, 1–30 mm Hg), and the highest serum sodium level observed in any patient was 161 mmol/L. GOS greater than 3 was achieved in 74% of the patients. This study provided the evidence to support the level III recommendation for the use of 23.4% saline to treat refractory intracranial hypertension.

Use of Hyperosmolar Therapy to Improve Outcomes. There was insufficient evidence to support a recommendation for the use of hyperosmolar therapy to improve overall outcomes. A single study, Vavilala et al (85) assessed acute care clinical indicators associated with in-hospital mortality and discharge GOS score in a retrospective cohort study of 236 infants and children with severe TBI across five medical centers. The use of HTS or mannitol for high ICP in the operating room was associated with favorable outcome versus no hyperosmolar therapy. However, when the comparison included the emergency department (ED), operating room, and ICU, a significant effect was not observed.

Safety Recommendations

Two class 3 studies contributed evidence supporting the safety recommendations for this topic (87, 89). Webster et al (89) carried out a single-center case-control study of 58 infants and children with severe TBI treated with bolus and/or continuous infusion of HTS. Eight patients developed DVTs. There was no association between the volume of HTS administered during the initial 72 hours and DVT; however, a serum sodium level greater than or equal to 160 mEq/L sustained for 72 hours was significantly associated with DVT ($p = 0.02$). Gonda et al (87) reported a retrospective cohort study of 48 infants and children with severe TBI in which bolus and infusion treatment with 3% saline were used. A sustained level (defined as ≥ 72 hr) of serum sodium greater than or equal to 170 mEq/L was significantly associated with thrombocytopenia and the need for erythrocyte transfusion. In addition, although the association with renal failure was not significant ($p = 0.064$), this could indicate a trend toward harm that merits further study.

Indications From Adult Guidelines

The Fourth Edition of the adult TBI guidelines inform the pediatric guidelines in that class 2 and 3 studies comparing HTS to mannitol have been carried out and suggest that HTS may be more effective that mannitol with regard to ICP burden and ICP greater than 25 mm Hg, but no differences in mortality or long-term outcome were noted (14, 116, 117).

Analgesics, Sedatives, and NMB

Recommendations

Strength of Recommendations: Weak

Levels I and II

There was insufficient evidence to support a level I or II recommendation for this topic.

Level III

For ICP Control. III.1. With use of multiple ICP-related therapies, as well as appropriate use of analgesia and sedation in routine ICU care, avoiding bolus administration of midazolam and/or fentanyl during ICP crises is suggested due to risks of cerebral hypoperfusion.

Note 1. In the absence of outcome data, the specific indications, choice, and dosing of analgesics, sedatives, and neuromuscular blocking agents should be left to the treating physician.

Note 2. Based on guidance from the U.S. Food and Drug Administration, prolonged continuous infusion of propofol for either sedation or the management of refractory intracranial hypertension is not recommended.

Changes From Prior Edition. Recommendation III.1. is new to this Third Edition. The recommendation about the use of thiopental from the Second Edition has been removed and the study by de Bray et al (118) has been removed. Five new class 3 studies—two prospective (2, 119), two retrospective (85, 120), and one treatment series (3)—were added to the evidence base for this topic.

Introduction

In management of pediatric severe TBI requiring tracheal intubation and mechanical ventilation, analgesics and sedatives are needed for comfort and tolerance (121). Neuromuscular blocking agents are not needed routinely, except at the time of rapid sequence intubation or when severe acute lung injury mechanics pose a problem with supportive ventilation (122). This topic evaluates the use of these agents during ICU treatment in patients who are appropriately sedated, when needed specifically for management of ICP, and for optimizing cerebral perfusion.

In a mechanically ventilated patient, appropriate use of analgesia and sedation will treat any pain or distress and mitigate patient-ventilator dyssynchrony, both of which may result in episodic rise in CBV and raise ICP (123). Routine care (e.g., oral hygiene, tracheal tube suctioning) while the patient is awake or aware may also lead to unanticipated rises in ICP (124). Pediatric practice is currently limited in the choice of sedative/analgesics that are available. Practice is markedly different in adult than in pediatric neurocritical care; especially in the frequent use of propofol, which in pediatrics has a U.S. Food and Drug Administration warning (125). As

a consequence, given the relatively long half-life of the drugs that are administered, frequently the neurologic examination can be obscured.

Neuromuscular blocking agents may reduce ICP by either optimizing patient-ventilator interactions or by prevention of shivering.

Evaluation of the Evidence

Quality of the Body of Evidence. Studies included for this topic addressed the questions of the effectiveness of combinations of NMB, ketamine, fentanyl, midazolam, etomidate, and pentobarbital to control ICP for children with severe TBI. There was insufficient evidence to derive a recommendation about mixed NMB, ketamine, etomidate, or pentobarbital. The overall quality of the body of evidence is low (**Table 14**).

Applicability. For the question of the use of NMB, the two studies were conducted in multiple sites and sample sizes were moderate, indicating cautious confidence in their applicability. The remaining studies enrolled small samples and were conducted at single sites, indicating limited confidence in their applicability.

Summary of the Evidence

Two new class 3 studies provided evidence to support the recommendation (2, 3) (**Table 15**).

Evidence Synthesis

Use of Fentanyl and/or Midazolam for ICP Control. One small retrospective study found that in 31 pediatric patients who received high-dose fentanyl, low-dose midazolam, or high-dose fentanyl plus low-dose midazolam, there was an increase in ICP for all treatment conditions (3). It is unclear if the finding was due to other patient factors, and the study did not address use of sedation beyond the context of ICP. In a prospective observational study of 16 pediatric patients, fentanyl decreased ICP, but less effectively than HTS or pentobarbital (2). Furthermore, it decreased CPP, and had the highest treatment failure rate. This study suggests that in the setting of adequate analgesia/sedation, HTS might be preferable over fentanyl. Taken together, these studies provide the evidence to support the recommendation for this topic.

The findings from the studies by Welch et al (3) and Shein et al (2) should be interpreted cautiously given they included routine use of analgesia and sedation in ICU care. An ICP crisis could be caused by pain or anxiety in the absence of appropriate analgesia and sedation. In that setting, additional fentanyl and/or midazolam may reduce ICP. However, these two studies may indicate that these agents are ineffective at reducing ICP in patients receiving adequate analgesia and sedation. In that setting, they confer either lesser efficacy than other tier 1 choices such as HTS and/or reduce MAP, negating benefit on CPP. Alternatively, a tier 2 intervention such as pentobarbital may be required at that juncture of care (2).

Use of NMB for ICP Control. The NMB studies suggest differences between subjects who received a NMB agent and those who did not (85, 120). However, for reasons discussed in the "*Introduction* section," the studies evaluated also did not include the indication for a given dose of NMB.

TABLE 14. Analgesics, Sedatives, and Neuromuscular Blockade: Quality of the Body of Evidence

Components of Overall Quality: Class 3 Studies								
Topic	No. of Studies Study Design	Recommendations	Meta-Analysis Possible (Yes or No[a])	Total No. of Subjects (*n*)	Consistency (High, Moderate, Low)	Directness (Direct or Indirect)	Precision (High, Moderate, Low)	Quality of Evidence (High, Moderate, Low, or Insufficient)
Use of neuromuscular blockade (mixed)	2 retrospective	No recommendation	NA	326	Moderate	Direct	Low	Insufficient
Use of ketamine	1 prospective	No recommendation	NA	30	NA	Indirect	Low	Insufficient
Use of fentanyl and/or midazolam	1 treatment series	III.1.	NA	31	NA	Direct	Low	Low
Use of etomidate	1 treatment series	No recommendation	NA	8	NA	Direct	Low	Insufficient
Use of fentanyl or pentobarbital	1 prospective	III.1.	NA	16	NA	Direct	Low	Low

NA = not applicable.

[a]Meta-analysis to synthesize results is only possible if several studies address the same criteria/question, and other design criteria are met.

n indicates sample size.

TABLE 15. Analgesics, Sedatives, and Neuromuscular Blockade: Summary of Evidence

Class 3 Studies			
Reference Type of Trauma Center Geographic Location	**Study Design *n* Age (yr) Outcomes**	**Data Class**	**Results**
Use of NMB (mixed): no recommendation			
Chin et al (120)[a] 17 hospitals United States, Australia, and New Zealand	Retrospective (secondary analysis of data from an randomized controlled trial) *n* = 90 Group 1 NMB every day *n* = 31 Group 2 none or intermittent NMB *n* = 59 Age: mean, 9.5; range, NR GOS-E at discharge and 3, 6, and 12 mo postinjury; ICP; CPP; complications; ICU LOS	Class 3 Unclear allocation concealment; not blinded	GOS-E No significant difference ICP Increased number of daily ICP readings > 20 mm Hg (4.4 ± 1.1 vs 2.4 ± 0.5; *p* = 0.015) CPP No difference in frequency of low CPP Complications No significant difference ICU LOS Longer ICU and hospital LOS (*p* = 0.003 and 0.07) for group 1 Consistent administration of NMB was associated with ICH and increased ICU LOS. However, it was not associated with an increase in complications or improvement in GOS-E.
Vavilala et al (85)[a] Five pediatric trauma centers Seattle, WA; Pittsburg PA; Chicago, IL; Torrance, CA; Columbus, OH	Retrospective *n* = 236 Age: mean, 8; range, NR Discharge GOS	Class 3 Selection; blinding; differential loss to follow-up; baseline differences unclear; did not control for all relevant confounders	Discharge GOS Adjusted risk ratio (95% CI) All locations NMB monitored 1.13 (0.85–1.51) not significant No NMB given 1.37 (1.24–1.53) Reference: given, not monitored In OR NMB monitored 1.33 (0.93–1.9) not significant No NMB given 1.42 (1.28–1.58) Reference: given, not monitored In OR and ICU Adherence = NMB monitoring (all 112/121 OR patients received) Odds ratio: 18.8% overall; range, 0–32.1 ICU 3% (0–4.8) NMB monitoring does not have a significant effect on outcomes compared with using NMB without monitoring

(*Continued*)

TABLE 15. (*Continued*). Analgesics, Sedatives, and Neuromuscular Blockade: Summary of Evidence

Class 3 Studies			
Reference Type of Trauma Center Geographic Location	**Study Design *n* Age (yr) Outcomes**	**Data Class**	**Results**
Use of ketamine: no recommendation			
Bar-Joseph et al (119)[a] Meyer Children's Hospital, Rambam Medical Center Israel	Prospective Pre/post *n* = 30 5 (17%) not TBI Age: mean, NR; range, 6 mo to 18 yr ICP; CPP All elevated ICP (> 18 mm Hg) resistant to first-tier therapies received a single ketamine dose (1–1.5 mg/kg) Group 1: to prevent further ICP increase during a potentially distressing intervention Group 2: additional measure to lower ICP	Class 3 Selection bias; no control for confounders Indirect evidence Mixed severities; GCS NR; mixed pathologies	ICP and CPP Post ketamine administration Overall in both groups ICP decreased by 30% (from 25.8 ± 8.4 to 18.0 ± 8.5 mm Hg) ($p < 0.001$) After 65 ketamine administrations 61 ICP decreased 3 increase < 2 mm Hg 1 increase > 2 mm Hg CPP increased from 54.4 ± 11.7 to 58.3 ± 13.4 mm Hg ($p < 0.005$). Group 1 Mean ICP decreased from 25.2 ± 5.4 to 17.9 ± 5.5 mm Hg within the first 2 min of ketamine administration ($p < 0.001$) and during distressing activity increased slightly up to 19.6 ± 6.7 at minute 7 and then decreased again. Group 2 ICP decreased by 33% (from 26.0 ± 9.1 to 17.5 ± 9.1 mm Hg) ($p < 0.0001$) within 2 min following ketamine administration. Result contradicts prior concerns that ketamine increases ICP.
Use of fentanyl and/or midazolam: recommendation III.1.			
Welch et al (3)[a] Trauma PICU St. Louis Children's Hospital St. Louis, MO	Treatment series *n* = 31 8 (26%) abusive head trauma Age: mean, 8; range, 0–18 ICP, CPP, and MAP, difference between predrug and postdrug administration	Class 3 Uncontrolled series	AUC used to represent cumulative ICH exposure The mean change AUC, ICP increased after drug administration Overall Increase in ICP of 17 mm Hg; $p = 0.04$ Mean change in AUC for ICP All significant High-dose fentanyl: $p = 0.02$ Low-dose midazolam; $p = 0.006$ High-dose fentanyl plus low-dose midazolam; $p = 0.007$ Dosing of fentanyl and midazolam did not reduce the ICP. Age and postresuscitation GCS did not correlate with change AUC-ICH, time after injury significantly correlated with change AUC-ICH $r = -0.12$, $p = 0.02$

(*Continued*)

TABLE 15. (*Continued*). Analgesics, Sedatives, and Neuromuscular Blockade: Summary of Evidence

Class 3 Studies			
Reference Type of Trauma Center Geographic Location	**Study Design *n* Age (yr) Outcomes**	**Data Class**	**Results**
Use of etomidate: no recommendation			
Bramwell et al (126) Primary Children's Medical Center, PICU Salt Lake City, UT	Treatment series *n* = 8 Age: mean, NR; range, NR ICP	Class 3 Uncontrolled series	Etomidate administration resulted in a decrease in ICP vs baseline ($p < 0.05$) without change in MAP; thereby increasing CPP at each 5 min interval. At 6 hr after etomidate administration, adrenocorticotropic hormone stimulation tests showed adrenal suppression in four of the eight patients; however, no patient required treatment with steroids.
Use of fentanyl or pentobarbital: recommendation III.1.			
Shein et al (2)[a] University of Pittsburgh Pittsburgh, PA	Prospective *n* = 16 in analysis Age: mean, 44 mo; range, 34–124 mo Outcomes: ICP and CPP	Class 3 Inadequate control for confounders; small sample	Hypertonic saline vs other drugs for ICP Decrease in ICP; increase in CPP Associated with a two-fold faster resolution of ICH than either fentanyl or pentobarbital. Adjusted hazard ratio, 2.171 (1.062–4.439) Fentanyl ICP decreased but had highest rate of treatment failure rate Pentobarbital ICP decreased; CPP no significant change

AUC = area under the curve, CPP = cerebral perfusion pressure, GCS = Glasgow Coma Scale, GOS = Glasgow Outcome Scale, GOS-E = Glasgow Outcome Scale Extended, ICH = intracranial hypertension, ICP = intracranial pressure, LOS = length of stay, MAP = mean arterial pressure, NMB = neuromuscular blockade, NR = not reported, OR = operating room.

[a]New study.

Use of Ketamine for ICP Control. Traditionally, ketamine has been considered contraindicated in patients with raised ICP, with the concern that it increases CBF and might increase ICP further. This reasoning has been questioned in a variety of studies and systematic reviews, and the report by Bar-Joseph et al (119) adds to this evidence. However, a level III recommendation on ketamine was not made because the GCS score for patients was not indicated, precluding the ability to confirm that the inclusion criteria were met for the publication.

Use of Etomidate for ICP Control. Use of etomidate for ICP control is largely of historical interest because we now have other sedatives and analgesics available that do not suppress adrenal function (126). A single dose of etomidate is, however, commonly used for intubation in pediatric TBI (122).

Indications From Adult Guidelines

The clinical investigators do not believe that the recommendations about analgesics, sedatives, and NMB from the adult guidelines can be used to guide treatment decisions in children.

CSF Drainage

Recommendations

Strength of Recommendation: Weak

Levels I and II

There was insufficient evidence to support a level I or II recommendation for this topic.

Level III

For ICP Control. III.1. CSF drainage through an EVD is suggested to manage increased ICP.

Changes From Prior Edition. The recommendation from the Second Edition about use of lumbar drain (LD) was eliminated. One new class 3 treatment series was added to the evidence base for this topic (127).

Introduction

The EVD can be used not only to measure ICP in children following TBI but may also provide added therapeutic benefit of CSF drainage. CSF drainage through an EVD has frequently

TABLE 16. Cerebrospinal Fluid Drainage: Quality of the Body of Evidence

Components of Overall Quality: Class 3 Studies								
Topic	No. of Studies Study Design	Recommendations	Meta-Analysis Possible (Yes or No[a])	Total No. of Subjects[b] (*n*)	Consistency (High, Moderate, Low)	Directness (Direct or Indirect)	Precision (High, Moderate, Low)	Quality of Evidence (High, Moderate, Low, or Insufficient)
External ventricular drainage to reduce ICP and improve outcomes	1 retrospective 2 treatment series	III.1.	No, study designs differ	56	Moderate	Mixed	Low	Low
Lumbar drain to reduce ICP and improve outcomes	2 treatment series	No recommendation	No, samples differ	21	Moderate	Direct	Low	Insufficient

ICP = intracranial pressure.
[a]Meta-analysis to synthesize results is only possible if several studies address the same criteria/question and other design criteria are met.
[b]The total number of subjects 18 yr old or younger when the studies included mixed ages.
n indicates sample size.

been used in patients with intraventricular hemorrhage and hydrocephalus. With its ability to potentially decrease ICP with CSF drainage, an EVD has been used as a therapeutic device following TBI. Different techniques for CSF drainage, both intermittent and continuous, as well as route of drainage, EVD, or LD, have been reported in the pediatric literature as potentially associated with increased risk of complications from hemorrhage and malposition (46, 54, 127–129).

Evaluation of the Evidence

Quality of the Body of Evidence. Studies included for this topic addressed questions about the use of EVD and LD to reduce ICP and improve outcomes for children with severe TBI. One class 3 observational study (46) and two treatment series (54, 127) provided evidence to support the recommendation about EVD. Two class 3 treatment series were insufficient to support a recommendation about LD (128, 130). The studies were small with moderate consistency in the results and low precision of effect estimates. One study (127) provided indirect evidence because it included patients with mixed severities and ages. The overall quality of the body of evidence is low (**Table 16**).

Applicability. Three studies were conducted 20 years ago or more (54, 128, 130) and two were more recent (2008, 2011) (46, 127). Four of the five studies are treatment series (54, 127, 128, 130), and three of them had sample sizes greater than 25 (54, 128, 130). All were conducted at single sites. Four were conducted in the United States (46, 54, 128, 130) and one (the most recent) in Brazil (127). Age ranges varied. The study designs and conduct in single sites limited their applicability.

Summary of the Evidence

Three class 3 studies—one new (127) and two from the Second Edition (46, 54)—provided evidence to support the recommendation (**Table 17**).

Evidence Synthesis

EVD to Reduce ICP and Improve Outcomes. Refractory ICP contributes to mortality, therefore, controlling elevated ICP is an important factor in patient survival following severe pediatric TBI. In one study, Shapiro and Marmarou (54) retrospectively studied 22 children with severe TBI, defined as a GCS score of less than or equal to 8, treated with an EVD and CSF drainage. Parameters measured included ICP, pressure-volume index (PVI), mortality, and outcome. Draining CSF increased (improved) PVI and decreased ICP. Two neurologic deaths occurred in patients with refractory intracranial hypertension; however, the study did not report the ICP of the other three patients who died or the four survivors with severe disability. Consequently, the absolute influence of CSF drainage and ICP in this sample cannot be determined. In contrast, Jagannathan et al (46) retrospectively studied 96 children with severe TBI comparing management of ICP alone versus ICP along with surgery using either an EVD or operative treatment (evacuation of hematoma or decompressive craniectomy). ICP control was achieved in 82 patients (85%). Methods employed to achieve ICP control included maximal medical therapy (sedation, hyperosmolar therapy, and NMB) in 34 patients (35%), EVD in 23 patients (24%), and surgery in 39 patients (41%). In this study, refractory ICP resulted in 100% mortality but the authors concluded that it was unclear if controlling elevated ICP using CSF drainage was important in patient survival following severe pediatric TBI. More recently, Andrade et al (127) reported on 58 patients who were treated with CSF drainage using an EVD. Eleven (19%) were pediatric, and 44 (76%) were severe. Given the mixed ages and severity levels, the evidence is indirect, and the sample size is small, limiting the level of evidence about ICP control or outcomes. Complications of ventriculitis were seen in 8.3% of patients. The evidence from these studies supports recommendation III.1. about ICP control. The data presented about patient outcomes reported in

TABLE 17. Cerebrospinal Fluid Drainage: Summary of Evidence

Class 3 Studies			
Reference Type of Trauma Center Geographic Location	**Study Design *n* Age (yr) Outcomes**	**Data Class**	**Results**
External ventricular drain to reduce ICP and improve outcomes: recommendation III.1.			
Andrade et al (127)[a] Clinicas Hospital University of São Paulo Medical School São Paulo, Brazil	Treatment series $n = 58$ $n = 11, < 17$ years $n = 44$ Glasgow Coma Scale 4–8 Age: mean, 29; range, 4–65 Mortality, neurologic assessment, complications	Class 3 No control for confounders, enrollment criteria unclear Indirect evidence Mixed ages and severities	All patients treated with ventricular CSF drainage Mortality 3 of 11 Neurologic assessment Among patients < 17 yr old Favorable outcome 6 (54.5%) Unfavorable outcome 5 (45.5%) (not separated by severity) No significant difference in outcome, between groups separated by age (adults vs children), $p > 0.05$ Complications: not separated by age or severity Overall rate of infection (ventriculitis): 8.3% Infection did not contribute to clinical worsening or death, $p > 0.05$
Jagannathan et al (46) University of Virginia Health System Charlottesville, VA	Retrospective $n = 96$ $n = 23$ treated with CSF using EVD (other groups: craniectomy and medical management) Age: mean, 5.1; range, 3–18 Mortality, GOS at mean 2 yr, ICP, complications	Class 3 Control for confounders unclear for ICP, only patients with 2-yr follow-up included in analysis	Mortality 3 of 23 GOS No significant difference in mean or median GOS across treatment groups ICP Overall 20/23 (87%) achieved ICP control with EVD. Of three not achieving ICP control, two died, one had a craniectomy and then died. Refractory ICP was associated with 100% mortality; the method used to control ICP had no correlation with mortality. Complications Higher rate of meningitis ($p < 0.05$) in patients with drain (5/23, 22%) compared with patients treated with craniectomy (3/40, 7%)
Shapiro and Marmarou (54) Albert Einstein College of Medicine New York	Treatment series $n = 22$ Age: mean, NR; range, 3 mo to 15 yr Mortality, outcome (scale not specified), ICP	Class 3 Uncontrolled series	Mortality 5/22 Outcome 4/17 severe disabilities 13/17 good outcome or moderately disabled ICP Decreased 14/16 16 of 22 patients had PVI measured before and after therapy. Drainage increased PVI. Two of the five deaths were due to uncontrolled ICP.

(*Continued*)

TABLE 17. (*Continued*). Cerebrospinal Fluid Drainage: Summary of Evidence

Class 3 Studies			
Reference Type of Trauma Center Geographic Location	**Study Design *n* Age (yr) Outcomes**	**Data Class**	**Results**
LD to reduce ICP and improve outcomes: no recommendation			
Baldwin and Rekate (128) Children's Hospital and Medical Centers Arizona	Treatment series *n* = 5 Age: mean, NR; range, 8–14 Mortality, outcome (scale undefined), ICP	Class 3 Uncontrolled series	Mortality 2/5 Outcome One moderate disability, two good recovery ICP Decreased in 5/5 LD was added to an aggressive ICP control protocol that included EVD.
Levy et al (130) St. Joseph's Hospital and Phoenix Children's Hospital Arizona	Treatment series *n* = 16 Age: mean, NR; range, 1–15 Mortality, GOS at 6 mo postinjury, ICP	Class 3 Uncontrolled series	Mortality 2/16 GOS Eight good recovery; three moderate disability, three severe disabilities ICP Decreased in 14/16 Lumbar drainage was added to an aggressive ICP control protocol that included EVD.

CSF = cerebrospinal fluid, EVD = external ventricular drainage, GOS = Glasgow Outcome Scale, ICP = intracranial pressure, LD = lumbar drain, NR = not reported, PVI = pressure-volume index.

[a]New study.

n indicates sample size.

these studies were insufficient to determine the influence of EVD on outcomes.

LD to Reduce ICP and Improve Outcomes. The evidence was insufficient to support a recommendation about LD.

Indications From Adult Guidelines

In the adult guidelines, the level III recommendations for CSF drainage that might be additive to the pediatric recommendations include the following: the EVD system zeroed to the midbrain with continuous drainage of CSF may be more effective in lowering the ICP burden than intermittent drainage; and the use of CSF drainage to lower ICP in patients with an initial GCS less than 6 during the first 12 hours after injury may be considered (14).

Seizure Prophylaxis

Recommendations

Strength of Recommendation: Weak

Levels I and II

There was insufficient evidence to support a level I or II recommendation for this topic.

Level III

For Seizure Prevention (Clinical and Subclinical). III.1. Prophylactic treatment is suggested to reduce the occurrence of early (within 7 d) PTSs.

Note. At the present time, there is insufficient evidence to recommend levetiracetam over phenytoin based on either efficacy in preventing early PTS (EPTS) or toxicity.

Changes From Prior Edition. Recommendation III.1. is modified from the Second Edition of these guidelines, with phenytoin removed. The note regarding levetiracetam is new to this Third Edition. Three new class 3 studies—one prospective observational (131), one retrospective observational (132), and one treatment series (133)—have been added to the evidence base for this topic.

Introduction

PTSs are defined as occurring early, within 7 days of injury, or late, beyond 8 days of recovery (134). Risk factors associated with the occurrence of PTS include location of the lesion, cerebral contusions, retained bone and metal fragments, depressed skull fracture, focal neurologic deficits, loss of consciousness, GCS greater than 10, severity of injury, length of posttraumatic amnesia, subdural or epidural hematoma, penetrating injury, and age. Infants and children have lower seizure thresholds (135), adding to the challenge of recognition of subtle clinical seizures (132) in critically ill children. The occurrence of electrographic seizures (seizures detected by continuous electroencephalogram recording) following severe TBI is higher in children than adults, occurring in up to 70% of cases (136).

TABLE 18. Seizure Prophylaxis: Quality of the Body of Evidence

Components of Overall Quality: Class 3 Studies								
Topic	No. of Studies Study Design	Recommendation	Meta-Analysis Possible (Yes or No[a])	Total No. of Subjects (*n*)	Consistency (High, Moderate, Low)	Directness (Direct or Indirect)	Precision (High, Moderate, Low)	Quality of Evidence (High, Moderate, Low, or Insufficient)
New topic: levetiracetam for the prevention of early posttraumatic seizures	1 prospective 1 treatment series	None	NA	74	Low	Indirect	Low	Insufficient
Prophylactic treatment to reduce posttraumatic seizures	2 retrospective	III.1.	NA	469 (252 with severe traumatic brain injury)	Moderate	Mixed	Low	Low

NA = not applicable.

[a]Meta-analysis to synthesize results is only possible if several studies address the same criteria/question, and other design criteria are met.

n indicates sample size.

Evaluation of the Evidence

Quality of the Body of Evidence. Studies included for this topic addressed the questions about the use of levetiracetam or phenytoin to reduce PTSs. Indirect evidence from one treatment series (133) and one phase II trial (131) was insufficient to support a recommendation about levetiracetam. Two class 3 retrospective studies provide a low-quality body of evidence to support the recommendation about phenytoin (132, 137) (**Table 18**).

Applicability. Both studies supporting the recommendation were retrospective and conducted in single sites (132, 137). The studies addressing the use of levetiracetam, one single center (133) and the other in two centers (131), used small sample sizes and provided indirect evidence. Applicability is limited.

Summary of the Evidence

Of the four class 3 studies included in the evidence tables for this topic (131–133, 137), two provided evidence to support the recommendation (132, 137) (**Table 19**).

Evidence Synthesis

Use of Phenytoin to Prevent PTSs. Two single-center, class 3 retrospective studies reported use of prophylactic phenytoin to prevent EPTSs (132, 137). In a retrospective study with a sample of 275 patients (221 with severe TBI), for the 133 who received an antiepileptic drug, 126 received phenytoin or fosphenytoin (95%) (132). Of those, 2.4% had early seizures and 97.5% did not. Both clinical and electrographic seizures were included in this analysis. An older retrospective review including 194 patients (31 severe) found in the severe TBI group a significantly lower rate of PTSs in patients treated prophylactically with phenytoin than in those who were not treated prophylactically (137). These studies provide direct (137) and indirect (132) evidence to support the level III recommendation for this topic.

Use of Levetiracetam to Prevent PTSs. Two studies assessed the use of levetiracetam; one small treatment series ($n = 34$) to prevent EPTS (133) and one phase II trial ($n = 40$) to prevent long-term seizures measured at 2 years postinjury (131). Chung and O'Brien (133) found that 17% of treated patients had EPTS. Pearl et al (131) reported one case of posttraumatic epilepsy at 2 years postinjury. The small samples included mixed severities, providing indirect evidence considered insufficient to support a recommendation for this topic.

Indications From Adult Guidelines

The clinical investigators do not think that the recommendations about seizure prophylaxis from the adult guidelines can be used to guide treatment decisions in children.

Ventilation Therapies

Recommendations

Strength of Recommendations: Weak

Levels I and II

There was insufficient evidence to support a level I or II recommendation for this topic.

Level III

To Improve Overall Outcomes. III.1. Prophylactic severe hyperventilation to a $PaCO_2$ less than 30 mm Hg in the initial 48 hours after injury is not suggested.

III.2. If hyperventilation is used in the management of refractory intracranial hypertension, advanced neuromonitoring for evaluation of cerebral ischemia is suggested.

Changes From Prior Edition. There are no content changes from the Second Edition to the recommendations. The title was

TABLE 19. Seizure Prophylaxis: Summary of Evidence

Class 3 Studies			
Reference Type of Trauma Center Geographic Location	**Study Design *n* Age (yr) Outcomes**	**Data Class**	**Results**
Levetiracetam for the prevention of EPTSs: no recommendation			
Chung et al (133)[a] Nationwide Children's Hospital, PICU Columbus, OH	Treatment series $n = 34$ Age: median, 6 mo; range, 5 d to 16 yr Effect of levetiracetam on EPTSs, GCS, ICP monitoring	Class 3 Uncontrolled series Fifteen of the 69 patients underwent continuous electroencephalogram monitoring, which was not a standard practice. Indirect evidence Mixed severities	Early seizures 6/34 patients (17%) had clinical seizures despite levetiracetam prophylaxis. Note: This is higher than rate reported in the literature for patients who receive phenytoin prophylaxis (2–15%). EPTSs occurred in younger patients (median age, 4 mo; $p < 0.001$) and abusive head trauma patients ($p < 0.0004$). Initial GCS score for patients with seizures slightly higher (median, 9) than patients without seizures (median, 7), $p = 0.04$. GCS score for patients with and without seizures were 9 (mean, 7–12) and 7 (mean, 3–12), $p = 0.04$. Elevated ICP monitoring (of those monitored) for patients with and without seizures was 0/1 (0%) and 11/14 (79%), respectively.
Pearl et al (131)[a] (note: these are the results for children included in a larger study by Klein et al [138]) Children's National Medical Center, Washington, DC; and Mid-Atlantic Epilepsy and Sleep Center, Bethesda, MD	Prospective (phase II trial) $n = 40$ Age: mean, NR; range, 6–17 Effect of levetiracetam on posttraumatic epilepsy at 2 yr postinjury	Class 3 Unclear that selection was unbiased; no control for confounders Indirect evidence Mixed severities	Posttraumatic epilepsy 1 of 40 subjects (2.5%) developed posttraumatic epilepsy (defined as seizures > 7 d after trauma). In the adult subjects in the same study (Klein et al [138]), there were higher rates. Acute and chronic treatment with levetiracetam (55/kg/d) was safe and well tolerated in children 6–17 yr old with traumatic brain injury. No children discontinued treatment because of side effects.
Prophylactic phenytoin to reduce posttraumatic seizures: recommendation III.1.			
Liesemer et al (132)[a] Primary Children's Medical Center Salt Lake City, UT	Retrospective $n = 54$ moderate $n = 221$ severe Median age: 7.4 w/o seizures; 1.4 w/ seizures Range: NR Effect of phenytoin on EPTSs (within first 7 d)	Class 3 Selection process not specified; blinding and qualifications of outcome assessors not specified. Indirect evidence Mixed severities	Early seizures No seizures or impact seizure only vs EPTS: Received AED before seizure Yes 125 (52%) vs 8 (24%) No 116 (48%) vs 26 (76%), $p < 0.01$ AED treatment is protective Odds ratio, 0.2 (95% CI, 0.07–0.5) Completed AED course (7 d of treatment) 78 (32%) vs 8 (24%), $p < 0.01$ AED used Fosphenytoin or phenytoin: 123 (51%) vs 3 (9%) Phenobarbital: 2 (1%) vs 4 (12%) Both: 0 (0) vs 1 (3) 23/34 (68%) developed EPTS in the first 12 hr postinjury

(*Continued*)

TABLE 19. (*Continued*). Seizure Prophylaxis: Summary of Evidence

Class 3 Studies			
Reference Type of Trauma Center Geographic Location	**Study Design *n* Age (yr) Outcomes**	**Data Class**	**Results**
Lewis et al (137) Harbor University of California Pediatric Trauma Center Torrance, CA	Retrospective *n* = 31 severe *n* = 194 total Age: median, 6 yr; range, 3 mo to 15 yr GCS: 3–8 (31–16%); 9–15 (163–84%) Effect of prophylactic phenytoin on EPTS	Class 3 Control for confounders only in analysis of predictors of seizure, not for comparison of groups based on seizure prophylaxis	EPTS For children with GCS 3–8, treatment with prophylactic phenytoin was associated with a reduced rate of seizures (2/13, 15%) compared with patients not treated with prophylactic medication (9/17, 53%), $p = 0.04$ one-tailed Fisher; $p = 0.057$, two-tailed. Rate of seizures in total group of 194 was 9.3%.

AED = antiepileptic drug, EPTS = early posttraumatic seizure, GCS = Glasgow Coma Scale, ICP = intracranial pressure, NR = not reported.
[a]New study.

changed from "Hyperventilation" to "Ventilation Therapies." No new studies have been added to the evidence base for this topic.

Introduction

Patients with severe TBI are comatose and may lack both airway protective reflexes and normal ventilatory drive. Thus, airway protection and controlled mechanical ventilation and oxygenation are necessary. Hyperventilation has been used in the management of severe pediatric TBI for the rapid reduction of ICP since the 1970s (139). It reduces ICP by producing hypocapnia-induced cerebral vasoconstriction with a reduction in CBF and CBV. The use of hyperventilation was based on the assumption that hyperemia was common after pediatric TBI and it was thought to reduce ICP by reducing luxury perfusion (20). Subsequent pediatric studies, however, showed that hyperemia is uncommon (58, 140), that low (rather than high) CBF is associated with unfavorable outcome (58, 140), and that hyperventilation can produce hypoperfusion or ischemia (58, 140). Concerns have thus been raised about the safety of hyperventilation therapy (141, 142). After TBI, the CBF response to changes in $Paco_2$ can also be unpredictable (142). Hypocarbia has also been shown experimentally to reduce the buffering capacity of CSF, an effect which may increase vulnerability of the brain to abrupt increases in ICP in response to increases in $Paco_2$ (143). Thus, ventilation targeting normal arterial levels of Co_2 (35–45 mm Hg) is currently recommended.

Despite a prior recommendation in the 2003 guidelines against prophylactic hyperventilation, several subsequent reports suggested that it was still a commonly used therapy in children (36, 144). This trend, however, may be reversing based on a report of the pretrial survey of the ADAPT study (4).

Finally, although clinical studies are lacking on the topic of reversal of transtentorial herniation in children after TBI, titrating the use of hyperventilation to effect (i.e., reversal of pupillary dilation and resolution of Cushing's triad) is recommended as an integral component of the approach to the emergent treatment of transtentorial herniation, and this approach is supported by studies in adults (145, 146). The use of hyperventilation is addressed in the TBI treatment algorithm article which is a companion to these guidelines.

Evaluation of the Evidence

Quality of the Body of Evidence. Studies included for this topic addressed the use of hyperventilation to manage pediatric patients with severe TBI. One class 3 retrospective study (141) contributed indirect evidence, and one class 3 treatment series (139) contributed direct evidence, and together they provided a low-quality body of evidence to support the recommendations for this topic (**Table 20**).

Applicability. The studies supporting the recommendation about use of hyperventilation—one large (141) and one small (139)—were both conducted at single sites, which limited their applicability.

Summary of the Evidence

Two class 3 studies from the Second Edition provided evidence to support the recommendations (139, 141) (**Table 21**).

Evidence Synthesis

Use of Hyperventilation to Manage Severe TBI in Children. Of the two class 3 studies included as evidence for this topic, neither represented a comparison of hyperventilation to normal ventilation, or to any other therapy targeting control of ICP (139, 141). Similarly, there were no reports in children specifically addressing the effects of varying levels or duration of hyperventilation on ICP or outcome, or studies of the transient application of hyperventilation in the setting of impending herniation or ICP crisis. Last, neither study had a standardized protocol to assess $Paco_2$, measuring it only intermittently.

One report described the effects of hyperventilation on CBF and brain physiology, and reported GOS at 6 mo (139). Skippen et al (139) carried out a selected treatment series of 23 children (3 mo to 16 yr old) with isolated severe TBI. CBF was measured by Xenon-enhanced CT during $Paco_2$ adjustments to greater

TABLE 20. Ventilation: Quality of the Body of Evidence

Components of Overall Quality: Class 3 Studies								
Topic	No. of Studies Study Design	Recommendation	Meta-Analysis Possible (Yes or No[a])	Total No. of Subjects (*n*)	Consistency (High, Moderate, Low)	Directness (Direct or Indirect)	Precision (High, Moderate, Low)	Quality of Evidence (High, Moderate, Low, or Insufficient)
General use of hyperventilation	1 retrospective 1 treatment series	III.1. III.2.	No, different designs	487	Low	Mixed	Low	Low

[a]Meta-analysis to synthesize results is only possible if several studies address the same criteria/question, and other design criteria are met.
n indicates sample size.

TABLE 21. Ventilation: Summary of Evidence

Class 3 Studies			
Reference Type of Trauma Center Geographic Location	Study Design *n* Age (yr) Outcomes	Data Class	Results
General use of hyperventilation: recommendations III.1. and III.2.			
Curry et al (141) Harborview Level I Pediatric Trauma Center Seattle, WA	Retrospective *n* = 464 Age: mean, 8; range, 0–14 Prevalence of SH (SH, $Paco_2$ < 30 mm Hg) during the initial 48 hr and risk of inpatient mortality; association between SH and morality	Class 3 Unclear if outcome assessment methods unbiased Indirect evidence Although SH is associated with mortality, it is unclear to what extent SH was caused by intentional hyperventilation.	SH SH on initial measurement was more common in infants (≤ 2 yr) vs older children 30.8% vs 19.3%, respectively, $p = 0.02$. Prevalence of SH in the first 48 hr was similar between age groups, 58.9% for infants vs 58.0% for older children; $p = 0.91$. Mortality Mortality-adjusted odds ratio, 1.44; 95% CI, 0.56–3.73 for one episode of SH 4.18; 95% CI, 1.58–11.03 for two episodes of SH 3.9; 95% CI, 1.61–9.62 for ≥ 3 episodes
Skippen et al (139) British Columbia's Children's Hospital PICU Vancouver, BC, Canada	Treatment series *n* = 23 Age: mean, 11; range, 3 mo to 16 yr Ischemic threshold defined as < 18 mL/100 g/min CBF; GOS score at 6 mo (the association between hyperventilation and GOS was not assessed)	Class 3 Uncontrolled series	CBF measured at three levels of $Paco_2$: > 35, 25–35, < 25 mm Hg Areas of CBF below ischemic threshold 28.9%, 59.4%, and 73.1%, respectively (not compared statistically) Mean vasoreactivity 2.7% change in CBF per mm Hg change in $Paco_2$ (range, −2.3% to 7.1%) Frequency of regional cerebral ischemia increased significantly with hyperventilation. GOS Ten (52.2%) had good or moderate outcome; 10 (43.5%) were severe or vegetative; one (4.3%) died (no analysis).

CBF = cerebral blood flow, GOS = Glasgow Outcome Scale, SH = severe hypocarbia.
n indicates sample size.

than 35, 25–35, and less than 25 mm Hg. The ischemic threshold was defined as CBF less than 18 mL/100 g/min. However, the ischemic threshold in children is not known and may vary with the severity of tissue injury and patient age. Co_2 reactivity of CBF was also assessed. Management included CSF drainage and hyperosmolar therapy. As $Paco_2$ was reduced with hyperventilation, CBF decreased in almost all patients despite decreased ICP and increased CPP. A relationship between the level of hypocarbia and frequency of cerebral ischemia was observed. The frequency of regional ischemia was 28.9% during normocapnia and increased to 59.4% and 73.1% for $Paco_2$ 25–35 mm Hg and less than 25 mm Hg, respectively. However, no statistical analysis was done. Fifty-two percent had good or moderate outcome, 43.5% were severely disabled or vegetative, and 4.3% died.

Again, no statistical comparison of outcomes was conducted, and outcomes were not reported by hyperventilation treatment.

A second report examined the association between hypocarbia and outcome at hospital discharge in a large pediatric series of severe TBI victims who were all mechanically ventilated (141). Curry et al (141) carried out a retrospective cohort study of 464 patients less than 15 years old with an admission GCS score less than 9 and a head Abbreviated Injury Score greater than or equal to 3, and with a $Paco_2$ recorded in the first 48 hours of admission for the years 2000 to 2005. The authors examined the prevalence of SH ($Paco_2$, < 30 mm Hg) and its relationship with neurologic outcome before (375 patients) and after (89 patients) the publication of the 2003 Pediatric TBI Guidelines (147). They found a nonsignificant change in the prevalence of SH from 60% of patients before to 52% after ($p = 0.19$). Patients with one documented episode of SH, controlling for ED GCS score, lowest ED SBP, ISS, $Paco_2$ sampling frequency, and year of admission had adjusted ORs for mortality of 1.44 (95% CI, 0.56–3.73) for one episode of SH, 4.18 (95% CI, 1.58–11.03) for two episodes, and 3.93 (95% CI, 1.61–9.62) for greater than or equal to three episodes, compared with patients with mild or no hypocarbia. These findings, although retrospective, show an association of SH with poor outcomes. However, there might be other contributors to hypocarbia such as marked reduction in metabolic rates or acidosis from systemic shock. Furthermore, although SH was associated with mortality, it is unclear to what extent SH was caused by intentional hyperventilation. Thus, the evidence from this study is indirect, and the exact contribution of induced hyperventilation to poor outcome cannot be clearly defined from this study.

Indications From Adult Guidelines. The recent Fourth Edition of the adult guidelines does not further inform the pediatric guidelines for this topic (14).

Temperature Control/Hypothermia

Recommendations

Strength of Recommendation: Moderate

Level I

There was insufficient evidence to support a level I recommendation for this topic.

Level II

To Improve Overall Outcomes. II.1. Prophylactic moderate (32–33°C) hypothermia is not recommended over normothermia to improve overall outcomes.

Level III

For ICP Control. III.1. Moderate (32–33°C) hypothermia is suggested for ICP control.

Safety Recommendation 1. If hypothermia is used and rewarming is initiated, it should be carried out at a rate of 0.5–1.0°C every 12–24 hours or slower to avoid complications.

Safety Recommendation 2. If phenytoin is used during hypothermia, monitoring and dosing adjusted to minimize toxicity, especially during the rewarming period, are suggested.

Note: See the last paragraph of the "*Evidence Synthesis section*" for a discussion that explains the seemingly contradictory recommendations.

Changes From Prior Edition. Recommendations II.1. is modified with regard to timing from the Second Edition of these guidelines. Recommendation III.1 on the use of hypothermia for ICP control is now at a Level III (rather than a level II) given that none of the studies of higher class had ICP control as a primary outcome and given the safety concerns that were identified. A level II recommendation about rewarming rate from the Second Edition has been removed and replaced with the more specific safety recommendation. A level III recommendation about use of moderate hypothermia from the Second Edition has been removed. The safety recommendation about phenytoin is new. One class 3 treatment series from the Second Edition has been removed (148). Two new meta-analyses (149–152), three new RCTs—one class 1 (153), one class 2 (154), and one class 3 (155)—and three new secondary analyses of RCTs—one class 2 (156) and two class 3 (157, 158)—have been added to the evidence base for this topic.

Introduction

The definitions of hypothermia and hyperthermia vary. Posttraumatic hypothermia is often classified as a core body temperature less than 35°C, whereas a temperature greater than 38.0–38.5°C represents fever/pyrexia if it results from an altered thermoregulatory set point, and represents hyperthermia if it is imposed upon a normal set point. For simplicity, the term hyperthermia is used to reflect an elevated core body temperature throughout this topic. Experimental studies in animal models and clinical studies in children demonstrated that hyperthermia correlates with poor outcomes and it has been recommended that hyperthermia following TBI in children should be prevented (159, 160). However, no studies of the influence of hyperthermia on outcomes in children were identified for inclusion in this guideline.

There are compelling reasons to explore the rationale for the use of therapeutic hypothermia to limit secondary brain injury based on its role in decreasing cerebral metabolic demands, inflammation, lipid peroxidation, excitotoxicity, cell death, and acute seizures (161, 162). Clinical studies reviewed on temperature regulation for these guidelines addressed global functional outcome and its effect on ICP. The influence on outcomes of reduction of ICP following severe TBI in children remains to be determined. As discussed in other topics, the lowering of severely elevated ICP with respect to the treatment threshold may be a desirable outcome.

Evaluation of the Evidence

Quality of the Body of Evidence. Studies included for this topic compared hypothermia with normothermia in the treatment of severe TBI in pediatric patients, and considered its influence on mortality, neurologic outcome, and control of ICP. Two meta-analyses (149–152); five RCTs—one class 1 (153), three class 2 (40, 144, 154), and one class 3 (155); and three

secondary analyses—one class 2 (156) and two class 3 (157, 158) provide evidence for this topic. Findings are consistent across the meta-analyses and class 1 and 2 RCTs. The overall quality of the body of evidence is moderate (**Table 22**).

TABLE 22. Temperature Control/Hypothermia: Quality of the Body of Evidence

Topic	No. of Studies Study Design	Recommendation	Meta-Analysis Possible (Yes or No[a])	Total No. of Subjects (*n*)	Consistency (High, Moderate, Low)	Directness (Direct or Indirect)	Precision (High, Moderate, Low)	Quality of Evidence (High, Moderate, Low, or Insufficient)
Components of overall quality: meta-analyses								
Comparison of hypothermia and normothermia	Two meta-analyses Tasker et al (150) Crompton et al (149, Tasker and Akhondi-Asl [151], and Crompton and Sharma [152])	II.1.	NA	504[b]	High	Direct	High	Moderate
Components of overall quality: class 1 study								
Comparison of hypothermia and normothermia	1 RCT Adelson et al (153)	II.1. & Safety Rec. 1.	NA	77	NA	Direct	Moderate	High
Components of overall quality: class 2 studies								
Comparison of hypothermia and normothermia	4 RCTs		No	350	High	Direct	Moderate	Moderate
	Beca et al (154)	II.1. III.1.	NA	50	NA	Direct	NA	NA
	Adelson et al (40)	II.1. III.1.	NA	75	NA	Direct	NA	NA
	Hutchison et al (144)	II.1. III.1.	NA	225	NA	Direct	NA	NA
	Hutchison et al (156)	II.1.	NA	225 (2008 sample)	NA	Direct	NA	NA
Components of overall quality: class 3 studies								
Comparison of hypothermia and normothermia	1 RCT 2 retrospective	Safety recommendation 2	No	119	High for Empey et al (155) and Bourdages et al (157)	Mixed	Low	Insufficient
	Su et al (158)	No recommendation	NA	84	NA	Indirect	NA	NA
	Empey et al (155)	Safety recommendation 2	NA	19	NA	Indirect	NA	NA
	Bourdages et al (157)	No recommendation	NA	16	NA	Direct	NA	NA

NA = not applicable, RCT = randomized controlled trial.

[a]Meta-analysis to synthesize results is only possible if several studies address the same criteria/question, and other design criteria are met.

[b]The total number of subjects for two meta-analyses was calculated with sample sizes of included studies in Tasker et al (150), except for Adelson et al (40), for which the sample size from the original publication was used, and Salonia et al (163), which was included in Crompton et al (149) and not Tasker et al (150).

n indicates sample size.

Applicability. The meta-analyses and three of the RCTs are recent (149–155). Study sites were located in the United States, New Zealand, Australia, Canada, France, and the United Kingdom. Sample sizes for individual studies ranged from 16 to 225 patients, and ages ranged from 0 to 18 years. Applicability concerns are minimal.

Summary of the Evidence

Of the 10 studies included in the evidence tables, two new meta-analyses (one fair [150] and one poor quality [149, 151, 152]), three new RCTs (one class 1 [153], one class 2 [154], and one class 3 [155]), and three new secondary analysis (one class 2 [156] and two class 3 [157, 158]) were added to two class 2 RCTs (40, 144) from the Second Edition. Together they provided evidence to support the recommendations for this topic. Two new studies were reviewed and included in the evidence table (157, 158) but not used to support a recommendation (**Tables 23** and **24**).

TABLE 23. Temperature Control/Hypothermia: Summary of Evidence

Reference Type of Trauma Center Geographic Location	Study Design *n* Age (yr) Outcomes Hypothermia Protocol	Data Class	Results
Meta-Analyses			
Comparison of hypothermia and normothermia: recommendations II.1. and III.1.			
Tasker et al (150)[a] Recommendation II.1. Adelson et al (153) Adelson et al (40) Beca et al (154) Biswas et al (164) Hutchison et al (144) Li et al (165)	MA 7 RCTs *n* = 470 Age: 0–17 Mortality Protocol varied across studies	Fair-quality MA Duplicate review not specified; search not comprehensive; exclusions not specified; publication bias not assessed; conflict of interest NR	Mortality With conventional MA, no difference in mortality. With Bayesian MA, probability of reducing mortality with hypothermia compared with normothermia is 0.40 (with RR < 1 or RRR > 0). Probability of RRR of death > 20%, with hypothermia rather than normothermia, 0.28
Crompton et al (149, Tasker and Akhondi-Asl (151), and Crompton and Sharma (152)[a] Recommendation II.1. Adelson et al (153) Adelson et al (40) Beca et al (154) Biswas et al (164) Hutchison et al Salonia et al (163)	MA Eight pediatric studies 7 RCTs; 1 observational *n* = 454 Age: 3 mo to 18 yr Mortality, neurologic outcome, GOS Protocol varied across studies	Poor-quality MA Duplicate review not specified; extent of literature search unclear; exclusions not specified; quality of individual studies not assessed or reported; publication bias not assessed; conflict of interest NR	Mortality No significant difference (RR, 1.53; 95% CI, 0.92–2.54; *p* = 0.10) Neurologic outcome No significant difference; 10% decrease in favorable neurologic outcomes (RR, 0.90; 95% CI, 0.80–1.01; *p* = 0.06) GOS No significant difference; GOS scores decreased by 0.17 points (mean difference, −0.17; 95% CI, −0.64 to 0.31; *p* = 0.50)
Class 1 and 2 Studies			
Adelson et al (153)[a] 15 sites United States, New Zealand, and Australia Recommendation II.1. and safety recommendation 1	RCT Cool Kids Trial *n* = 77 Age: median, 10.9 IQR: 3.4–14.6 Hypothermia: median, 9.7; IQR, 4.2–14.5 Normothermia: median, 12.5; IQR, 3.3–14.8 Mortality, GOS and GOS-E at 3 mo, complications Hypothermia 32–33°C for 48–72 hr with slow rewarming; 0.5–1.0°C every 12–24 hr	Class 1 (Evidence for Safety Rec. #1.)	Hypothermia vs normothermia Mortality within 3 mo 6 (15%) vs 2 (5%), *p* = 0.15 GOS and GOS-E No significant difference for GOS (*p* = 0.90) or GOS-E (*p* = 0.73) Complications (acute nonserious infection and late nonserious infection): no difference, *p* = 0.0622. Decompressive craniotomy: 17 (45%) vs 7 (18%), *p* = 0.0220 Trial terminated early for futility

(*Continued*)

TABLE 23. (*Continued*). Temperature Control/Hypothermia: Summary of Evidence

Reference Type of Trauma Center Geographic Location	Study Design *n* Age (yr) Outcomes Hypothermia Protocol	Data Class	Results
Beca et al (154)[a] 8 PICUs Australia: Adelaide, Brisbane, Melbourne, Perth, Sydney New Zealand: Auckland Canada: Vancouver, BC Recommendations II.1. and III.1.	RCT Phase 2 trial *n* = 50 Hypothermia: *n* = 24 Normothermia: *n* = 26 Age: Hypothermia: mean, 11.0; IQR, 6.9–14.2 Normothermia: mean, 9.5; IQR, 5.2–13.8 Mortality, PCPC, PICU length of stay, hospital length of stay, and mechanical ventilation; ICP, MAP, CPP; complications Early hypothermia (32–33°C) for 72 hr with slow based on individual patient to maintain ICP and CPP (no > 0.5°C every 3 hr)	Class 2 Criteria met except blinding which was not possible or unclear; sample size likely not adequate	Hypothermia vs normothermia Mortality 3 (13%) vs 1 (4%), $p = 0.34$ Poor outcome (included death) 3 (12%) vs 4 (17%) PCPC at 12 mo 4 (17%) vs 3 (12%), $p = 0.70$ PICU length of stay (d) in survivors 12 vs 11, $p = 0.87$ Hospital length of stay (d) in survivors 48 vs 40, $p = 0.70$ Mechanical ventilation (d) in survivors 8 vs 10, $p = 0.77$ No predefined covariables were significant in the multivariable model. ICP, MAP, CPP ICP was lower by 1.8 mm during cooling (95% CI, 0.3–3.4; $p = 0.02$) No significant group difference in MAP or CPP during cooling, $p = 0.44$ and $p = 0.77$ No significant group difference in MAP, ICP, or CPP during rewarming, $p = 0.68$, $p = 0.59$, $p = 0.07$ Complications Net effect of hypothermia during cooling: Heart rate drop: 23.4 beats/min; 95% CI, 15.9–30.9; $p < 0.001$
Adelson et al (40) Multicenter United States Recommendations II.1. and III.1.	2 RCTs Total *n* = 75 2 samples/studies *n* = 48 (patients who met inclusion criteria, multicenter) *n* = 27 (patients who did not meet inclusion criteria, single center) Age: Sample 1: mean, 6.89; range, NR Hypothermia: mean, 6.92 Normothermia: mean, 6.86 Sample 2: mean, 6.95; range, NR Hypothermia: mean, 7.17 Normothermia: mean, 5.6 Mortality, 3 and 6 mo GOS, ICP, complications Hypothermia 32–33°C for 48 hr; slow rewarming 1°C every 3–4 hr, with slower rates for individual patients based on ICP	Class 2 Unclear reporting of randomization methods, allocation concealment methods, and attrition	Mortality and GOS No difference between groups in mortality or 3 and 6 mo GOS. ICP Overall, there was no statistical difference in mean ICP between the groups during the 5-d period, $p = 0.37$ except within the first 24 hr, when the ICP was reduced in the hypothermia group, $p = 0.024$. Complications No difference between groups in complication rates

(*Continued*)

TABLE 23. (*Continued*). Temperature Control/Hypothermia: Summary of Evidence

Reference Type of Trauma Center Geographic Location	Study Design *n* Age (yr) Outcomes Hypothermia Protocol	Data Class	Results
Hutchison et al (144) Multicenter Canada, France, and United Kingdom Recommendations II.1 and III.1.	RCT *n* = 225 Age: Hypothermia: mean, 9.8; range, NR Normothermia: mean, 10.2; range, NR Mortality, PCPC at 4–6 mo postinjury, ICP, complications Hypothermia 32.5°C for 24 hr; rewarming 0.5°C every 2 hr	Class 2 Some differences between groups on baseline prognostic factors	Mortality There were 23 deaths (21%) in the hypothermia group and 14 deaths (12%) in the normothermia group (relative risk, 1.40; 95% CI, 0.90–2.27; $p = 0.06$). Although this is not significant, it suggests that additional studies to rule out or confirm this potential harm are needed. PCPC No difference between groups on functional outcomes at 6 mo ($p = 0.14$) ICP ICP was lower during cooling and higher during warming in the hypothermia group at 16 hr ($p < 0.02$), 24 hr ($p < 0.01$), 48 hr ($p = 0.01$), and 72 hr ($p = 0.03$). Complications Significantly more episodes of hypotension ($p = 0.047$), and lower mean blood pressures and CPPs ($p < 0.001$) in hypothermia group

CPP = cerebral perfusion pressure, GOS = Glasgow Outcome Scale, GOS-E = Glasgow Coma Scale Extended, ICP = intracranial pressure, IQR = interquartile range, MA = meta-analysis, MAP = mean arterial pressure, NR = not reported, PCPC = Pediatric Cerebral Performance Category, RCT = randomized controlled trial, RR = risk reduction, RRR = relative risk reduction.

[a]New study.

n indicates sample size.

Evidence Synthesis

Influence of Hypothermia on Mortality and Outcome. Two meta-analyses, one moderate quality (150) and one poor quality (149, 151, 152), contributed to the evidence to support recommendation II.1. against the use of hypothermia to improve outcomes. Together they included seven RCTs ($n = 469$) (40: samples 1 and 2, 153, 154, 163–165). The review by Crompton et al (149) included one study (163) that reported an analysis using patients from another study included in the review (40). The Tasker et al (150) analysis of these studies found no significant difference in mortality between hypothermia and normothermia groups, using conventional methods. With Bayesian analysis, the probability of reducing mortality with hypothermia versus normothermia was 0.40. The analysis by Crompton et al (149) originally reported significantly higher mortality ($p = 0.03$), no difference in neurologic outcomes ($p = 0.06$), and no difference in GOS scores ($p = 0.50$) for hypothermia versus normothermia. However, after repeating the analysis to correct for "double counting" in patient numbers across the studies, there was no significant difference in mortality ($p = 0.10$) (151, 152).

Five RCTs—one class 1 (153) and four class 2 (40, 144, 154, 156)—were also used as evidence to support recommendation II.1. Both the publications by Hutchison et al (144, 156) reported on the same set of patients, with the earlier focusing on mortality and outcomes and the latter on the association between hypotension and outcomes. The five studies included 427 patients, randomized to either hypothermia or normothermia. Adelson et al (40), Beca et al (154), and Adelson et al (153) reported no difference between groups in mortality or outcomes (40, 153, 154). Hutchison et al (144) reported no difference between groups on outcomes overall and no significant difference in morality ($p = 0.06$), but characterized this as a nonsignificant trend toward increased mortality in the hypothermia group. This is one way to acknowledge the potential for harm that merits further study.

Both publications by Adelson et al (40, 153) reported no difference between groups in complications. Beca et al (154) found decreased heart rate for hypothermia patients with cooling. Hutchison et al (144) reported significantly more hypotension, pressor requirements, and lower blood pressures and CPPs in the hypothermia group; the 2011 analysis of that sample identified in the hypothermia group a significant association between

TABLE 24. Temperature Control/Hypothermia Summary of Evidence: Secondary Analyses

Study Topic Reference Type of Trauma Center Geographic Location	Study Design *n* Age (yr) Outcomes	Data Class	Results
Class 2 Study			
Secondary analysis of Hutchison et al (144) Hutchison et al (156) 17 trauma centers Canada, France, and United Kingdom Recommendation II.1.	Retrospective (secondary analysis of 2008 RCT) *n* = 225 Age: Hypothermia: mean, 9.8; range, NR Normothermia: mean, 10.2; range, NR Low systolic pressure, low mean arterial pressure, low CPP, and episodes of hypotension and unfavorable outcomes	Class 2 RCT was class 2. Blinding NR. Original publication (2008) reported baseline differences between groups on prognostic factors.	Hypothermia patients: association of ≥ 1 episodes of hypotension and unfavorable outcome from 25 to 72 hr, $p = 0.04$, but not from 0 to 24 hr after injury, $p = 0.24$. Hypothermia vs normothermia Hypotension: low systolic pressure Odds Ratio — 95% CI — *p* 0–24 hr: 1.25 (86–1.83) 0.24; 3.76 (1.29–11.01) 0.02 25–72 hr: 1.13 (1.00–1.27) 0.04; 1.69 (1.03–2.76) 0.04 0–72 hr: 1.11 (1.00–1.23) 0.04; 1.18 (1.02–1.37) 0.03 Hypotension: low mean arterial pressure Odds Ratio — 95% CI — *p* 0–24 hr: 1.18 (0.81–1.74) 0.39; 2.20 (1.32–3.68) 0.003 25–72 hr: 1.10 (0.98–1.23) 0.12; 1.14 (0.97–1.33) 0.10 0–72 hr: 1.08 (0.98–1.20) 0.12; 1.18 (1.02–1.36) 0.02 Low CPP Odds Ratio — 95% CI — *p* 0–24 hr: 1.08 (0.83–1.42) 0.57; 1.37 (1.00–1.86) 0.05 25–72 hr: 1.13 (1.02–1.26) 0.03; 1.16 (1.02–1.32) 0.03 0–72 hr: 1.09 (1.00–1.19) 0.05; 1.13 (1.02–1.26) 0.02
Class 3 Studies			
Secondary analysis of Hutchison et al (144) Bourdages et al (157)[a] Multicenter and university affiliated PICU in a level III trauma center Quebec, Canada No recommendation	Retrospective (ancillary study of 2008 RCT) *n* = 16 Age: mean, 12.7; range, 7.2–17.0 Hypothermia: mean, 13.5; range, 8.8–16 Normothermia: mean, 12.2; range, 7.2–17.0 Mortality, ARDS, pneumonia, septic shock, brain herniation, PICU LOS, ICP, CPP; complications	Class 3 RCT was class 2; this study was conducted in a single center; no power analysis; of 23 eligible patients, 16 were included.	Hypothermia vs normothermia Mortality: 3 (43%) vs 1 (11%) ARDS: 2 (29%) vs 0 Pneumonia: 3 (43%) vs 4 (44%) Septic shock: 2 (29%) vs 0 Brain herniation: 2 (29%) vs 1 (11%) (Statistical significance for parameters above NR.) PICU LOS (d): 11 (5–21) vs 15 (4–32) ICP, CPP No significant difference Complications Ventilator-free at 28 d: 17 (0–24) vs 13 (0–23) Holter results: -Arrhythmias: 5 (71%) vs 2 (22%), $p = 0.13$ -Minimum heart rate: 58 (51–83) vs 83 (64–104), $p < 0.01$ -Maximum heart rate: 111 (84–121) vs 137 (104–147), $p < 0.01$

(*Continued*)

TABLE 24. (*Continued*). Temperature Control/Hypothermia Summary of Evidence: Secondary Analyses

Study Topic Reference Type of Trauma Center Geographic Location	Study Design *n* Age (yr) Outcomes	Data Class	Results
Secondary analysis of Adelson et al (40)			
Su et al (158)[a] Children's Hospital of Pittsburgh Pittsburgh, PA No recommendation	Retrospective (analysis of data from a phase II RCT) *n* = 27 w/TBI 57 non-TBI controls Age: Hypothermia: mean, 6.78 Normothermia: mean, 6.96 Range for TBI patients: 7 wk to 16 yr Controls: mean, 0.73; range, 8 d to 11 yr Mean and peak CSF MBP	Class 3 RCT was class 2; this study selected 27 patients from the trial (hypothermia *n* = 14; normothermia *n* = 13) and compared CSF MBP to 57 controls. Indirect evidence Intermediate outcome	Mean and peak CSF MBP concentrations Hypothermia vs normothermia No significant difference between groups Mean 45.27 ± 7.48 vs 56.70 ± 12.44 Peak 69.38 ± 22.76 vs 90.33 ± 32.37 No significant difference between groups on days 1 or 2 before rewarming TBI vs non-TBI controls Concentrations in TBI patients were generally 400- to 500-fold greater than concentrations in controls (50.49 ± 6.97 vs 0.11 ± 0.01 ng/mL)
Empey et al (155)[a] Children's Hospital of Pittsburgh ICU Pittsburgh, PA Safety recommendation 2	RCT *n* = 19 Age: Hypothermia: median, 11.1; range, 2.1–14.7 Normothermia: median, 13.6; range, 2.5–16.2 Phenytoin levels; hypothermia measurements Moderate hypothermia (32 33°C for 48 hr; rewarming 1°C every 12–24 hr)	Class 3 (Evidence for Safety Rec. #2.) RCT was class 2; this study selected a subset of patients who received fosphenytoin or phenytoin. (Evidence for Safety Rec. #2) Indirect evidence Intermediate outcome	Phenytoin levels Elevated free phenytoin concentrations in the hypothermia group in the rewarming and posttreatment periods (temperature effect: $p = 0.051$; study period effect: $p = 0.023$; interaction: $p = 0.633$). The cumulative dose of fosphenytoin administered to each patient was not different between the groups (temperature effect: $p = 0.853$; study period effect: $p = 0.249$; interaction: $p = 0.660$). Hypothermia vs normothermia Albumin mean (SD): Day 1: 3.0 (0.7) vs 3.2 (0.5) Day 3: 2.4 (0.5) vs 2.4 (0.2) Day 7: 2.7 (0.4) vs 2.2 (0.3) Aspartate transaminase median (range): 41 (31–111) vs 60 (38–1303) Alanine transaminase median (range): 30 (23–88) vs 26 (11–530) Alkaline phosphatase median (range): 168 (66–288) 145 (70–382) Total bilirubin mean (SD): 0.6 (0.4) vs 0.7 (0.8) Serum creatinine mean (SD): 0.5 (0.2) vs 0.5 (0.2)

ARDS = acute respiratory distress syndrome, CPP = cerebral perfusion pressure, CSF = cerebrospinal fluid, ICP = intracranial pressure, LOS = length of stay, MBP = myelin basic protein, NR = not reported, RCT = randomized controlled trial, TBI = traumatic brain injury.

[a]New study.

n indicates sample size.

1 or more episodes of hypotension and unfavorable outcomes from 25 to 72 hours postinjury ($p = 0.04$), but not from 0 to 24 hours postinjury ($p = 0.24$) (156). The rewarming rate for patients in Hutchison et al (144) was faster than that of patients in Adelson et al (153) (0.5°C every 2 hr vs 0.5–1°C every 12–24 hr, respectively).

Influence of Hypothermia on Intracranial Hypertension. Three class 2 RCTs contributed evidence to support recommendation III.1. for the use of hypothermia to decrease ICP (40, 144, 154). Beca et al (154) reported significantly lower ICP during cooling for the hypothermia group ($p = 0.02$). Adelson et al (40) found that ICP decreased within the first 24 hours in the

hypothermia group, but no difference between groups over 5 days. Hutchison et al (144) found that ICP was significantly lower during cooling, but then higher during warming in the hypothermia group at 16 hours ($p < 0.02$), 24 hours ($p < 0.01$), 48 hours ($p = 0.01$), and 72 hours ($p = 0.03$). Although the evidence does not suggest a long-term benefit for ICP control with hypothermia, it does suggest that hypothermia produces an immediate decrease in ICP.

Safety Recommendations. Safety recommendation 1 cautions against rapid rewarming that may be a source of complications seen in previous work in which temperature was increased at a rate of 0.5°C every 2 hours (144). The current recommended parameters are based on the protocol used in the study by Adelson et al (153), which found no significant difference between hypothermia and normothermia groups for adverse events.

Safety recommendation 2 is based on the RCT by Empey et al (155) which demonstrated elevated free phenytoin levels on rewarming from hypothermia (rate 1°C per 12–24 hr) although the cumulative doses administered to children in both groups were similar.

Seemingly Inconsistent Recommendations. Furthermore, the published studies targeting the effect of hypothermia on long-term outcomes in pediatric severe TBI implemented it early after injury and did not specifically randomize patients with intracranial hypertension to hypothermia versus another second-tier therapy. It was used in a prophylactic manner. We did not identify studies comparing the efficacy of second-tier therapies implemented for refractory raised ICP. It would thus be premature to dismiss hypothermia in this setting based on the available evidence.

Indications From Adult Guidelines

The clinical investigators do not consider the recommendations about temperature control from the adult guidelines applicable to guide treatment decisions in children.

BARBITURATES

Recommendations

Strength of Recommendations: Weak

Levels I and II

There was insufficient evidence to support a level I or II recommendation for this topic.

Level III

For ICP Control. III.1. High-dose barbiturate therapy is suggested in hemodynamically stable patients with refractory intracranial hypertension despite maximal medical and surgical management.

Safety Recommendation. When high-dose barbiturate therapy is used to treat refractory intracranial hypertension, continuous arterial blood pressure monitoring and cardiovascular support to maintain adequate CPP are required because cardiorespiratory instability is common among patients treated with barbiturate coma.

Changes From Prior Edition .There are no content changes from the Second Edition to the recommendations (1). Two new class 3 studies—one retrospective observational (85) and one treatment series (166)—were added to the evidence base for this topic.

Introduction

High-dose barbiturates lower ICP by suppression of metabolism and alteration of vascular tone (167–169) causing improved coupling of regional blood flow to metabolic demands resulting in higher brain oxygenation (170), with lower CBF and decreased ICP from decreased CBV. Barbiturates may lower ICP when first-tier medical and surgical management have not resulted in adequate control. However, cardiorespiratory side effects are very common and potentially harmful, including decreased cardiac output, hypotension, and increased intrapulmonary shunt, resulting in lower CPP and hypoxia. Thus high-dose barbiturate therapy has been reserved for cases of intracranial hypertension resistant to first-tier medical and surgical care.

Diffuse brain swelling and generalized hyperemia after severe TBI are more common and more lethal (67) in young children compared with older children and adults (171–173). The rationale for treatment with barbiturate coma is based on the logic that uncontrolled ICP leads to ongoing secondary brain injury, and a higher risk of poor cognitive outcome or death. Near maximum reduction in cerebral metabolism and CBF occur when burst suppression is induced. Pentobarbital is the most commonly reported medication used in children and is dosed to achieve burst suppression, so continuous electroencephalogram monitoring is required to monitor optimal dosing. Although high-dose barbiturates are reserved for a high-risk group, their use in severe pediatric TBI care is not rare.

Evaluation of the Evidence

Quality of the Body of Evidence. Studies included for this topic addressed the influence of barbiturate therapy on outcomes and ICP. The evidence consists of one relatively large observational study (85) and three small treatment series (47, 166, 174). Although consistency and precision were moderate, the overall quality is low because the studies were rated class 3 (**Table 25**).

Applicability. Two of the included studies were over 25 years old (47, 174). Three were small and were conducted at single sites (47, 166, 174), whereas the larger study was conducted at multiple sites (85). All were conducted in the United States and included a range of ages from infants to teens. Applicability of these studies is limited.

Summary of Evidence

Four class 3 studies, two new (85, 166) and two from the Second Edition (47, 174), provided evidence to support the recommendation (**Table 26**).

TABLE 25. Barbiturates: Quality of the Body of Evidence

Components of Overall Quality: Class 3 Studies								
Topic	No. of Studies Study Design	Recommendations	Meta-Analysis Possible (Yes or No[a])	Total No. of Subjects (*n*)	Consistency (High, Moderate, Low)	Directness (Direct or Indirect)	Precision (High, Moderate, Low)	Quality of Evidence (High, Moderate, Low, or Insufficient)
High-dose barbiturates for refractory intracranial hypertension	1 retrospective 3 treatment series	III.1. Safety recommendation	No Due to study designs	310	Moderate	Direct	Moderate	Low

[a]Meta-analysis to synthesize results is only possible if several studies address the same criteria/question, and other design criteria are met.
n indicates sample size.

Evidence Synthesis

Influence of Barbiturate Therapy on Outcomes and ICP. Three treatment series (47, 166, 174) and one multicenter observational study provided data for this topic (85). The treatment series included a total of 74 patients who received barbiturate therapy for refractory intracranial hypertension. Mortality was 43%. Two of the three studies assessed 43 patients for function at various timepoints, and reported that 19 (44%) had poor outcomes (166, 174). They also reported that of the total 63 patients, ICP control was achieved in 24 (38%). When high-dose barbiturates were added to additional therapies, rates for control of refractory intracranial hypertension were 28% and 52%, respectively. The third study reported a steep decline in ICP for patients treated with pentobarbital compared with those not treated and those treated with mannitol (47). One study found a nonsignificant lower risk of death in patients with controlled intracranial hypertension (risk reduction, 0.2; 95% CI, 0.03–1.3), and significantly better median discharge Pediatric Cerebral Performance Category (PCPC) scores for that group ($p < 0.05$) (166). They reported significantly better PCPC scores at 3–12 months follow-up ($p < 0.05$), but the analysis excluded patients who died ($n = 14$), and used discharge PCPC as the follow-up score for seven patients without follow-up data.

Patient and disease characteristics, treatment variation, and the uncontrolled nature of these studies limited the ability to associate the findings with the intervention. Mellion et al (166) reported that among patients who had ICP controlled, high-dose barbiturate therapy was employed significantly later after TBI (76 vs 29 median hours) compared with children whose ICP remained uncontrolled. Kasoff et al (47) reported that more than 90% of treated patients received ionotropic infusions. In two studies, despite monitoring and infusion therapies, 80% of patients experienced episodes of hypotension or a fall in CPP below the goal level (47, 166). However, reports of both efficacy and toxicity information for all three studies are based on reports from single centers and relatively few patients.

An observational analysis of 236 patients treated at five pediatric trauma centers by Vavilala et al (85) studied adherence to a set of clinical indicators to the 2003 Pediatric Guidelines for severe TBI management. They tested the relationship between rates of adherence and in-hospital mortality and discharge GOS score. Ninety-four children (82%) developed high ICP (either ICP > 20 mm Hg or clinical signs of intracranial hypertension within the first 72 hr of admission). Cerebral edema based on radiologic imaging was present in 127 (53.8%). The estimated decrease in mortality was 78% (adjusted hazard ratio, 0.22; 95% CI, 0.18–0.25) when ICU patients received barbiturates for refractory ICP as recommended.

These studies provide data to support the recommendation for this topic. However, there is insufficient evidence to recommend use of a particular barbiturate agent or regimen over another to treat refractory intracranial hypertension.

Indications From Adult Guidelines

The recent Fourth Edition of the adult guidelines does not further inform the pediatric guidelines for this topic (14).

Decompressive Craniectomy

Recommendations

Strength of Recommendation: Weak

Levels I and II

There was insufficient evidence to support a level I or II recommendation for this topic.

Level III

For ICP Control. III.1. Decompressive craniectomy (DC) is suggested to treat neurologic deterioration, herniation, or intracranial hypertension refractory to MM.

Changes From Prior Edition. The specification in the recommendation from the Second Edition, ". . . with duraplasty, leaving the bone flap out . . ." has been removed, and for this edition, the recommendation is made specifically for ICP control. One class 3 RCT from the First Edition which was removed from the Second Edition was returned to this edition (176). Fourteen new class 3 studies—five retrospective comparisons (176–180) and nine treatment series (181–189)—were added to the evidence base for this topic.

TABLE 26. Barbiturates: Summary of Evidence

Class 3 Studies			
Reference Type of Trauma Center Geographic Location	Study Design *n* Age (yr) Mean (Range) Outcomes	Data Class	Results
High-dose barbiturates for refractory intracranial hypertension: recommendation III.1.			
Vavilala et al (85)[a] Five pediatric trauma centers Seattle, WA; Pittsburg PA; Chicago, IL; Torrance, CA; Columbus, OH	Retrospective *n* = 236 Age: mean, 8.0; range, NR In-hospital mortality	Class 3 Selection, blinding, differential loss to follow-up, and baseline differences unclear; did not control for all relevant confounders	Discharge survival In ICU: barbiturates used with high ICP: adjusted hazard ratio, 0.22 (95% CI, 0.18–0.26) Reference: no barbiturates used with high ICP (Also measured in OR: not significant; overall, ICU and OR combined: not significant)
Mellion et al (166)[a] Level I pediatric trauma center Salt Lake City, UT	Treatment series *n* = 36 Age: Controlled intracranial hypertension: median, 10.7; range, NR Uncontrolled intracranial hypertension: median, 6.4; range, NR Mortality; PCPC at discharge and follow-up (3–12 mo); ICP; harms including infections, impaired oxygenation, and CPP below target	Class 3 Uncontrolled series	Mortality 22 of 36 survived Survival more common in responders than nonresponders but not significant (relative risk of death, 0.2; 95% CI, 0.03–1.3) PCPC 19 with favorable outcome (PCPC less than 3) at 3 mo or longer after injury; three returned to normal function ICP 10 out of 36 (28%) had controlled refractory intracranial hypertension Of 14 deaths, 13 were without control of ICP No control of refractory intracranial hypertension was significantly associated with poor scores on PCPC ($p < 0.05$), but with dichotomized PCPC, function did not differ significantly between patients with and without controlled intracranial hypertension.
Pittman et al (174) Cardinal Glennon Memorial Hospital for Children Missouri	Treatment series *n* = 27 total *n* = 7 for outcomes Age: mean, 9.0; range, 2 mo to 15 yr Mortality; GOS at 1, 6, and 12 mo postinjury; ICP CPP	Class 3 Uncontrolled series	Mortality 6 of 27 GOS Good recovery: 3 Moderate disability: 2 Vegetative: 2 ICP 14/27 (52%) achieved ICP < 20 mm Hg Of 13 with persistently elevated ICP, six died (22%) CPP Outcome not related to CPP
Kasoff et al (47) Westchester County Medical Center New York	Treatment series *n* = 11 Age: mean, 8.8; range, 3 mo to 17 yr Mortality	Class 3 Uncontrolled series	Mortality 4/11 (36%) Hypotension (mean arterial pressure) < 80 mm Hg occurred in 9/11 (82%)

CPP = cerebral perfusion pressure, GOS = Glasgow Outcome Scale, ICP = intracranial pressure, NR = not reported, OR = operating room, PCPC = Pediatric Cerebral Performance Category.

[a]New study.

TABLE 27. Decompressive Craniectomy: Quality of the Body of Evidence

Components of Overall Quality: Class 3 Studies								
Topic	No. of Studies Study Design	Recommendation	Meta-Analysis Possible (Yes or No[a])	Total No. of Subjects (*n*)	Consistency (High, Moderate, Low)	Directness (Direct or Indirect)	Precision (High, Moderate, Low)	Quality of Evidence (High, Moderate, Low, or Insufficient)
Effect of DC vs medical management on ICP, mortality, and outcomes	1 randomized controlled trial 1 prospective 4 retrospective	No recommendation	No	161 (DC: 67; medical management: 94)	Low	Direct	Low	Insufficient
Effect of DC on ICP, mortality, and outcomes	16 treatment series	III.1.	No	190	Low	Direct	Low	Low
Outcomes of DC by mechanism of injury	1 retrospective	No recommendation	NA	37	NA	Direct	Low	Insufficient

DC = decompressive craniectomy, ICP = intracranial pressure, NA = not applicable.
[a]Meta-analysis to synthesize results is only possible if several studies address the same criteria/question, and other design criteria are met.
n indicates sample size.

Introduction

DC for TBI is a controversial procedure that has become more widely considered as a treatment option. Controversy results from its invasiveness without clearly defined indications, lack of an optimally specified surgical technique, variability in reported outcomes, and significant risk for complications (190, 191). DC may be performed solely to treat ongoing or refractory intracranial hypertension ("therapeutic DC"), or concomitantly with the removal of a mass lesion in order to either treat observed brain swelling or prophylaxis against anticipated swelling ("incidental DC"). For therapeutic DC, the timing of the procedure may be predicated on the neurologic examination, an episode of neurologic deterioration, the degree of initial ICP, or the resistance of intracranial hypertension to medical treatment. These two general categories of indication for DC are referred to using a variety of sometimes confusing terms in the literature (e.g., each has been referred to as either "primary" or "secondary") (192–194). This section focuses on therapeutic DC (often but not always referred to as "primary DC").

Published techniques for DC vary. Bone may be removed unilaterally or bilaterally and may include or exclude subtemporal decompression. Hemispheric craniectomies vary in recommended size (from relatively small to nearly complete subtotal) and circumferential or bifrontal craniectomies are also used (195). Management of the dura also varies, including no manipulation, simple scoring, or wide opening (with or without expansile duraplasty) (196, 197). There is no consistent relationship between choice of craniectomy and dural opening techniques. The design of a procedure for any individual patient often depends on the underlying pathology as demonstrated on CT imaging, or may be focused on creating the maximum possible compartmental expansion to increase compliance. Technique varies between surgeons and in response to clinical context.

Two RCTs treated refractory intracranial hypertension in adults with DC (198, 199). No similar trials are available for the pediatric population.

Evaluation of the Evidence

Quality of the Body of Evidence. Studies included for this topic addressed questions about the effect of DC on ICP control, mortality, and functional outcomes, and outcomes of DC in treating accidental versus abusive head trauma. Subtopics addressed were effect of timing of the procedure and complications. One poor-quality RCT (175), one poor-quality prospective study (200), and four poor-quality retrospective studies (176, 177, 179, 180) compared ICP, mortality, and outcomes for patients who received DC versus those who received MM. Sixteen poor-quality treatment series compared ICP before and after DC, and reported mortality and outcomes without comparators (181–189, 201–207). One moderate-quality retrospective study compared outcomes after DC between patients who sustained abusive head trauma injury with those sustaining other mechanisms of injury (178). The overall quality of the body of evidence for this topic is low (**Table 27**).

Applicability. Of the 23 included studies conducted in 14 different countries, all but one were single center; 18 had samples sizes less than 25 patients, and 16 did not have comparators. Applicability of the individual studies is questionable.

TABLE 28. Decompressive Craniectomy: Summary of Evidence

Class 3 Studies			
Reference Type of Trauma Center Geographic Location	**Study Design *n* Age (yr) Mean (Range) Outcomes**	**Data Class**	**Results**
Effect of DC vs MM on ICP, mortality, and outcomes: no recommendation			
Mhanna et al (177)[a] Metro Health Medical Center Cleveland, OH	Retrospective *n* = 34 DC = 17 MM = 17 Age: DC: mean, 10.2; range, NR MM: mean, 12.4; range, NR Mortality; GOS 4 yr postinjury (IQR, 1–6 yr)	Class 3 Selection of patients to receive DC was based on physician discretion; inadequate control for confounders; baseline differences between groups.	Mortality DC 5/17 vs control 3/17, $p = 0.34$ No significant difference between groups for mortality or GOS. GOS Median GOS score DC = 4 (IQR, 3–5) vs control 3 (IQR, 3–4), $p = 0.09$ Comparing patients who died or had a disability, there was a significant difference between the DC and control groups (71% [12/17] vs 100% [17/17], respectively; $p = 0.022$).
Thomale et al (180)[a] Campus Virchow Medical Center Germany	Retrospective *n* = 53 DC = 14 No DC = 39 Age: All patients: median, 8; range, 0–16 No DC: median, 7; range, 0–16 DC: median, 12; range, 1–16 GOS at 3, 6, and 12 mo (mean follow-up 5.2 ± 2.4 yr [range, 1–10.5]); ICU days	Class 3 No control for confounding; baseline differences between groups	GOS No significant difference in median GOS at 3, 6, and 12 mo ICU days Significantly greater days in ICU for DC group ($p = 0.026$) DC group had significantly lower initial GCS but comparable outcomes.
Rubiano et al (179)[a] Simon Bolivar Hospital Colombia	Retrospective DC = 16; 7 pediatric Control = 20; 5 pediatric Pediatric patients: Age: mean, 5.86; range, 1–15 Mortality; GOS 6 mo postinjury	Class 3 Controlled for confounders for total sample with mixed ages	Mortality for pediatric patients DC = 1/7 (14%) Non-DC = 2/5 (40%) GOS For pediatric patients: 1: DC 2/7 (14%); Non-DC 2/5 (40%) 2: DC 0; Non-DC 0 3: DC 0; Non-DC 3/5 (60%) 4: DC 2/7 (29%); Non-DC 0 5: DC 3/7 (57%); Non-DC 0 For total sample (all ages): mean GOS at 6 mo postinjury significantly higher in DC group than control group (unadjusted $t = 4.26$; $p = 0.0002$)

(*Continued*)

TABLE 28. (*Continued*). Decompressive Craniectomy: Summary of Evidence

Class 3 Studies			
Reference Type of Trauma Center Geographic Location	**Study Design *n* Age (yr) Mean (Range) Outcomes**	**Data Class**	**Results**
Josan and Sgouros (176)[a] Birmingham Children's Hospital United Kingdom	Retrospective *n* = 12 Early DC (< 24 hr) = 6 Non-DC = 6 Age: Early DC: mean, 13; range, 2–16 Non-DC: mean, 11.5; range, 7–15 Mortality; GOS 1 yr postinjury	Class 3 Small sample; baseline differences between groups; no control for confounding	Statistical analysis not performed. Mortality DC = 0/6 Non-DC = 2/6 (33%). One of whom received late DC at 9 d. GOS DC: 1: 0; 2: 0; 3: 0; 4: 2/6 (33%); 5: 4/6 (67%) Non-DC: 1: 2/6 (33%); 2: 0; 3: 1/6 (17%); 4: 0; 5: 3/6 (50%) More patients with better outcomes in DC group than non-DC group
Taylor et al (175) Royal Childrens' Hospital Melbourne, VIC, Australia	Randomized controlled trial *n* = 27 DC = 13 Medical = 14 Age: median, 120.9 mo; range, 13.6–176.4 mo One patient GCS = 11 in DC group GOS and HSUI 6 mo postinjury; ICP after randomization/surgery	Class 3 Allocation concealment, blinding, and adequate sample size unclear. Baseline differences NR. No intent-to-treat analysis	GOS and HSUI There was no significant difference between groups in GOS or HSUI 6 mo postinjury. MM: GOS Fav. 2, Unf. 12; HSUI Fav. 1, Unf. 1 DC: GOS Fav. 7, Unf. 6; HSUI Fav. 6, Unf. 37 ICP 48 hr after randomization or surgery Range (SD) DC 17.4 (3.4) vs MM 21.9 (8.5) Number of episodes > 20 mm Hg DC-107 vs MM-223 Number of episodes > 30 mm Hg DC-9 vs MM-29 There was no significant difference between groups in mean ICP 48 hr after randomization or surgery.

(*Continued*)

TABLE 28. (*Continued*). Decompressive Craniectomy: Summary of Evidence

Class 3 Studies			
Reference Type of Trauma Center Geographic Location	**Study Design *n* Age (yr) Mean (Range) Outcomes**	**Data Class**	**Results**
Cho et al (200) Taichung Veterans Hospital Taiwan (Republic of China)	Prospective *n* = 23 Group A: low ICP/medical = 6 Group B: high ICP/medical = 7 Group C: high ICP/DC = 10 Age: mean, 5.91 mo; range, 2–14 mo Group A: mean, 5.33 mo; range, 2–11 mo Group B: mean, 7.42 mo; range, 3–14 mo Group C: mean, 5.2 mo; range, 2–14 mo Mortality; dichotomized scores on COS measured between 6 mo and 6 yr postinjury (mean, 3.2 yr) (COS ranges from 1 [best] to 5 [worst]). COS 1 to 2 = good COS 3 to 5 = poor ICP	Class 3 No control for confounders; very small sample; no power calculation; significant differences in baseline ICP and Children's Coma Scale scores	Mortality Three patients died—all from group B. COS Mean COS for group B significantly worse than groups A or C (p = 0.0058) ICP In group C, DC lowered the mean ICP measurements from 54.9 to 11.9 mm Hg. Effect of medical treatment on ICP for groups A and B was NR, so group differences unknown. Although DC was performed based on ICP elevation alone, a mean of 32 mL of subdural blood was removed during the surgery, indicating that this sample includes both primary and secondary DC patients.
Outcomes of DC by mechanism of injury: no recommendation			
Oluigbo et al (178)[a] Children's Hospital and University of Colorado Denver/Aurora, CO	Retrospective *n* = 37 *n* = 14 abusive head trauma *n* = 23 other mechanisms Age: mean, 6; range, 9 wk to 15 yr Abusive head trauma: mean, 2.2; range, NR Accidental: mean, 8.4; range, NR Mortality; KOSCHI (scored same as GOS) at mean 23.9 mo (range, 1–94 mo)	Class 3 Outcome assessors not blinded; baseline difference in age for accidental trauma	Mortality 5 of 14: abusive head trauma, 35.7% ($p < 0.05$) 1 of 23: other mechanisms 4.3% OR = 12.2 (p = 0.02) for abusive head trauma KOSCHI poor outcome (score of 1, 2, or 3) Nonaccidental: 57.2% Other mechanisms: 30.4% Authors report no significant difference between groups for poor outcome and an OR for poor outcome of 3.04 for the abusive head trauma group.

COS = Children's Outcome Scale, DC = decompressive craniectomy, Fav. = favorable, GCS = Glasgow Coma Scale, GOS = Glasgow Outcome Scale, HSUI = Health State Utility Index, ICP = intracranial pressure, IQR = interquartile range, KOSCHI = King's Outcome Scale for Childhood Head Injury, MM = medical management, NR = not reported, OR = odds ratio, Unf. = unfavorable.

[a]New study.

n indicates sample size.

TABLE 29. Decompressive Craniectomy: Summary of Evidence

Treatment Series			
Reference Type of Trauma Center Geographic Location	**Study Design *n* Age (yr) Mean (Range) Outcomes**	**Data Class**	**Results**
Effect of DC on ICP, mortality, and outcomes: recommendation III.1.			
Pechmann et al (187)[a] University Medical Center Freiburg Germany	Treatment series *n* = 12 Age: mean, 8.5; range, 2–14 Mortality; GOS mean 3.3 mo (± 2 mo) postinjury; range, 3–83 mo; ICP; complications	Class 3 Small uncontrolled series	Mortality 1/12 (8%) GOS 1 = 1/12 (8%) 2 = 2/12 (17%) 3 = 2/12 (17%) 4 = 5/12 (42%) 5 = 2/12(16%) ICP Initial decrease of ICP < 20 mm Hg in all children. Three of 12 showed a secondary increase in ICP. Complications • Formation of hygroma (83%) • Aseptic bone resorption of the reimplanted bone flap (50%) • Posttraumatic hydrocephalus (42%) • Infection: secondary infection or dysfunction of ventriculoperitoneal shunt (25%) or cranioplasty (33%) • Epilepsy (33%) Due to complications, 75% of patients required further surgery in addition to cranioplasty with up to eight interventions.
Prasad et al (208)[a] All India Institute of Medical Sciences New Delhi, India	Treatment series *n* = 71 Severe = 36 Age: mean, 1.6; range, 1 mo to 3 yr Mortality; GOS-E; mean 19.6 mo (range, 2–42 mo); complications	Class 3 Small uncontrolled series	Mortality 18/36 severe (50%) GOS-E 7 to 8 for all who survived except 1 (reported for all severities) Complications (reported for all severities) Ventilator-associated pneumonia in 22 of 71 cases Late onset seizures in 2 Septicemia in 6 Wound infection in 7 Subdural hygroma in 11 Hydrocephalus in 13
Desgranges et al (183)[a] Hospital Femme Mere Enfant Lyon, France	Treatment series *n* = 12 Age: mean, 8; range, NR Mortality; ICP; complications (IBL); Mortality	Class 3 Small uncontrolled series	Mortality 4/12 (33%) ICP Before DC (*n* = 12) After DC (*n* = 12) 46 ± 18 mm Hg 10 ± 4 mm Hg DC induced significant decrease in ICP ($p = 0.0005$), mean arterial pressure ($p = 0.04$) between the immediate pre- and postoperative periods. Complications Median IBL during DC was 49% (17–349%) of EBV. Children with IBL ≥ 50% of EBV had higher preoperative ICP ($p = 0.03$) and INR ($p = 0.02$) than those with an IBL < 50% of EBV. Mortality IBL ≥ 50% IBL<50% 3/6 50% 1/6 (17%)

(*Continued*)

TABLE 29. (*Continued*). Decompressive Craniectomy: Summary of Evidence

Treatment Series			
Reference Type of Trauma Center Geographic Location	**Study Design *n* Age (yr) Mean (Range) Outcomes**	**Data Class**	**Results**
Khan et al (185)[a] University Hospital Karachi, Pakistan	Treatment series *n* = 25, 21 severe Age: mean, 6; range, 1–15 Mortality; dichotomized GOS at mean 5 mo (± 2 SD); complications (blood loss)	Class 3 Small uncontrolled series	Mortality (of entire sample *n* = 25) 9 patients died (36%) GOS (of entire sample *n* = 25) 16 had good outcome (GOS 4 [*n* = 6] and 5 [*n* = 10]). Complications Significantly greater mortality among patients with > 300 mL operative blood loss (*p* = 0.001)
Csókay et al (182)[a] 3 Children's Hospitals Hungary and Wales	Treatment series *n* = 8 Age: mean, 7.13; range, 1–12 Mortality; GOS at 1 yr postinjury; ICP; effect of timing	Class 3 Small uncontrolled series	Mortality 2/8 (25%) GOS Discharge: 1 = 2/8 (25%); 2 = 1/8 (12.5%); 3 = 1/8 (112.5%); 4 = 4/8 (50%); 5 = 0 1 yr: 1 = 2/8 (25%); 2 = 1/8 (13%); 3 = 0/8; 4 = 2/8 (25%); 5 = 3/8 (37%) ICP For six patients with pre- and postoperative ICP measures, the average preoperative ICP was 23.3 mm Hg compared with 15.3 mm Hg postoperative ICP (calculated from data provided in Tables 1 and 2). Timing At above 20 mm Hg, fast progression of ICP (within 15 min) can occur, limiting the time available to perform DC with a successful patient outcome.
Perez Suarez et al (189)[a] Nino Jesus Pediatric Children's Hospital Madrid, Spain	Treatment series *n* = 14 Age: mean, 5.5; range, 11 mo to 15 yr Mortality; GOS at 2 yr postinjury; ICP; complications	Class 3 Small uncontrolled series	Mortality 2/14 (14%) GOS 1 = 2/14 (14%) 2 = 0 3 = 0 4 = 7/14 (50%) 5 = 5/14 (36%) ICP In 13 patients, craniectomy initially decreased ICP to < 25 mm Hg. Complications: Hygroma 8/14 (57%) Infections 3/14 (21%) Aseptic resorption of bone flap 3/14 (21%)

(*Continued*)

TABLE 29. (*Continued*). Decompressive Craniectomy: Summary of Evidence

Treatment Series			
Reference Type of Trauma Center Geographic Location	**Study Design *n* Age (yr) Mean (Range) Outcomes**	**Data Class**	**Results**
Adamo et al (181)[a] Albany Medical Center Hospital New York	Treatment series *n* = 7 Age: mean, 13.86 mo; range, 2–24 mo Mortality; KOSCHI (scored same as GOS); complications	Class 3 Small uncontrolled series	Mortality All patients survived KOSCHI Discharge: 3a = 4/7 (57%); 3b = 3/7 (43%) 1 yr: 4a = 3/7 (43%); 4b = 1/7 (14%); 3b = 3/7 (43%) Complications 7/7 (100%) hydrocephalus 2/7 (29%) bone resorption
Jagannathan et al (203) University of Virginia Health System Virginia	Treatment series *n* = 23 Age: mean, 11.9; range, 2–19 Mortality; GOS 5 yr mean (range, 11–126 mo); ICP	Class 3 Small uncontrolled series	Mortality 7 (30%; one intraoperative; five postoperative; one in rehabilitation) Mortality primarily in patients with multisystem trauma. GOS Mean 4.2 (range, 1–5) *n* / Score: 9 / 5; 5 / 4; 1 / 3; 1 / 2; 7 / 1 ICP ICP control in 19/23 patients. High ICP associated with increased mortality.
Figaji et al (184)[a] Red Cross War Memorial Children's Hospital Cape Town, South Africa	Treatment series *n* = 12 Age: mean, 8.125; range, 5–12 Mortality; GOS at median 35 mo postinjury (range, 1–6 yr); ICP; complications	Class 3 Small uncontrolled series	Mortality 1/12 (8%) GOS 1 = 1/12 (8%) 2 = 0 3 = 0 4 = 6/12 (50%) 5 = 5/12 (42%) ICP Control of ICP and clinical improvement was seen in all but one patient. Mean sustained ICP reduction postcraniectomy was 53.5% (range, 39–61%) in both pre- and postoperative ICP monitoring patients. Complications 1/12 (8%) bone flap sepsis after replacement 1/12 (8%) slight subsidence of the flap at follow-up 2/12 (17%) asymptomatic subdural hygromas
Kan et al (204) Primary Children's Medical Center Utah	Treatment series *n* = 51 *n* = 6 for intractable ICP Age: mean, 6.6; range, NR Mortality; ICP	Class 3 Small uncontrolled series	Mortality Five of six patients died (83%). ICP Three of the four patients with postoperative ICP monitoring had ICP < 20 mm Hg.

(*Continued*)

TABLE 29. (*Continued*). Decompressive Craniectomy: Summary of Evidence

Treatment Series			
Reference Type of Trauma Center Geographic Location	**Study Design *n* Age (yr) Mean (Range) Outcomes**	**Data Class**	**Results**
Rutigliano et al (206) Level 1 regional trauma center Stoney Brook University Health Center New York	Treatment series *n* = 6 Age: mean, 14.5; range, 12–19 Mortality; FIM score at hospital discharge; ICP	Class 3 Small uncontrolled series	Mortality All patients survived. FIM 3: Independent 2: Assistance 1: Dependent ICP Five of the six patients had sustained postoperative ICP < 20 mm Hg. One had ICP elevations requiring a second surgery for debridement, with no subsequent ICP elevations.
Skoglund, 2006 (207) Neonatal ICU Sahlgrenska University Hospital Goteborg, Sweden	Treatment series *n* = 8 Peds (19 total) Age: Mean 12.6 Range: 7 to 16 Mortality; GOS at minimum 1 yr postinjury (range 1 to 6 yr). (ICP and effect of size of DC on outcome were also considered, but in only 9 patients, and ages not specified.)	Class 3 Small uncontrolled series	Mortality 1/8 (12.5%) GOS 1: 1 (12.5%) 2: 0 3: 3 (37.5%) 4: 1 (12.5%) 5: 3 (37.5%)
Figaji et al (201) Red Cross War Memorial Children's Hospital Cape Town, South Africa	Treatment series *n* = 5 Age: mean, 8; median, 6; range, 5–12 GOS at a range of 14–42 mo; ICP; complications	Class 3 Small uncontrolled series	GOS All patients had early clinical improvement after surgery and were GOS 4 or 5 at long-term follow-up (14–40 mo). ICP In the four patients with postoperative ICP monitoring, two had no ICP elevations and two had mild, easily controlled elevations. Complications 1 subdural hygroma 1 cerebrospinal fluid leak and bone flap sepsis
Messing-Jünger et al (186)[a] Heinrich University Hospital Dusseldorf, Germany	Treatment series (publication is comparative but seven pediatric patients in the sample were reported as a treatment series) *n* = 7 Age: mean, NR; range, 1–16 Mortality, GOS (follow-up time not specified)	Class 3 Small uncontrolled series	Mortality 2/7 (29%) died between 24 and 48 hr and showed signs of decerebration at admission. GOS (in 6 of 7 patients; 1 lost to follow-up) 1 = 2/7 (29%) 2 = 0 3 = 1/7 (14%) 4 = 1/7 (14%) 5 = 2/7 (29%)

(*Continued*)

TABLE 29. (*Continued*). Decompressive Craniectomy: Summary of Evidence

Reference Type of Trauma Center Geographic Location	Treatment Series Study Design *n* Age (yr) Mean (Range) Outcomes	Data Class	Results
Ruf et al (205) PICU Justus-Liebig University Medical Centre Giessen, Germany	Treatment series *n* = 6 Age: mean, 7.8; range, 5–11 Mortality; neurologic status at 6 mo posttrauma; ICP; complications	Class 3 Small uncontrolled series	Mortality All patients survived. Neurologic Status Normal: 3 Hemiparesis: 1 Spasticity: 1 In rehabilitation: 1 ICP ICP decreased to < 12 mm Hg in five patients. Sixth patient required contralateral subsequent DC, then ICP was maintained at ≤ 20 mm Hg. Complications 1 (late aseptic necrosis of bone flap: 1 patient)
Hejazi et al (202) Landeskrankenhaus Hospital Feldkrich, Australia	Treatment series *n* = 7 Age: mean, 8.6; range, 5.5–14 Mortality; GCS within 5 wk postinjury; ICP	Class 3 Small uncontrolled series	Mortality All patients survived. GCS All patients had a GCS of 15. ICP Decrease in ICP to < 20 mm Hg in all patients. Postoperative ICP rose to maximum 29 mm Hg in five patients.

DC = decompressive craniectomy, EBV = estimated blood volume, FIM = Functional Independence Measure, GCS = Glasgow Coma Scale, GOS = Glasgow Outcome Scale, GOS-E = Glasgow Outcome Scale Extended, IBL = intraoperative blood loss, ICP = intracranial pressure, INR = international normalized ratio, KOSCHI = King's Outcome Scale for Childhood Head Injury, NR = not reported.

[a]New study.

n indicates sample size.

Summary of the Evidence

Sixteen class 3 treatment series, nine new (181–189) and seven (201–207) from the Second Edition, provided evidence to support the recommendation (**Tables 28** and **29**).

Evidence Synthesis

Effect of DC on Mortality and Functional Outcomes. Although mortality and functional outcomes are reported in the treatment series in this report, they are not used to support a recommendation because 1) there are no comparators for mortality and outcomes in these studies and 2) comparative studies are available that address these outcomes. One class 3 RCT (175) and two class 3 retrospective studies (177, 180) reported no significant difference between DC and MM in mortality and/or functional outcomes. In a comparison of six patients treated with DC and six with MM, Josan and Sgouros (176) reported better survival and outcomes for the DC group, but a statistical analysis was not performed. In a retrospective pre-/post-DC comparison, Rubiano et al (179) found the mean GOS at 6 months postinjury to be significantly better in the DC group ($t = 4.26$; $p = 0.0002$). Cho et al (201) compared outcomes for three groups: A) Low ICP/MM ($n = 6$); B) High ICP/MM ($n = 7$); and C) High ICP/DC ($n = 10$). The mean Children's Outcome Scale for group B was significantly worse than for groups A and C ($p = 0.0058$), and the three mortalities occurred in group B—patients with high ICP who were treated with MM.

These studies varied in criteria for DC, selection criteria for inclusion in the study, the DC techniques used, and their outcome parameters. In addition, none of the investigations defined the study population to an extent adequate to allow rigorous inter-study comparisons. The lack of internal comparison groups or matched controls weakens the analyses that can be applied and preclude making a recommendation for this topic.

Effect of DC on ICP Control. The issue with respect to the efficacy of DC in lowering ICP is not the statistical significance of the change in ICP from prior to surgery to the postoperative state; it is in lowering severe or medically intractable ICP elevation with respect to the treatment threshold such that intracranial hypertension is no longer encountered (optimal outcome) or easily controlled following surgery.

Two comparative studies reported postsurgical decreases in ICP (175, 200). Although Taylor et al (175) reported more

episodes of ICP greater than 20 and greater than 30 mm Hg in the MM group (> 20 DC-107, MM-223; > 30 DC-9, MM-29), there was no significant difference between groups in mean ICP 48 hours after randomization or surgery. Cho et al (201) reported mean ICP decreased in the DC group from 54.9 mm Hg presurgery to 11.9 mm Hg postsurgery. Changes in ICP for the MM group were not reported, so a comparison between groups could not be made.

Eleven treatment series compared ICP before and after DC (182–184, 187, 189, 201–206). Two reported a decrease in mean ICP after DC; in Desgranges et al (183), the decrease was statistically significant and Csókay et al (182) did not provide a statistical analysis (182, 183). In the other nine studies, of 88 patients with postoperative ICP monitoring, the ICP dropped to acceptable levels in 77 patients (87.5%) (184, 187, 189, 201–206). Although these studies did not compare ICP between DC and MM groups, they provided weak and limited evidence that DC may be effective in lowering ICP to below the threshold for treatment in patients' refractory to MM, and are the evidence base to support the level III.1. recommendation. This limited conclusion would support choosing to perform DC for ICP control when intracranial hypertension is resistant to nonsurgical management and observed ICP levels are considered hazardous to the patient.

Outcomes of DC by Mechanism of Injury. One moderate-quality class 3 retrospective study compared outcomes of children with severe TBI, with and without abusive head trauma, all of whom received DC (178). Significantly, more patients with abusive injury died compared with those whose TBIs were sustained by other mechanisms ($p < 0.05$; OR, 12.2 [$p = 0.02$]). Outcome measured between 1 and 94 months with the King's Outcome Scale for Childhood Head Injury showed no significant difference between groups for poor outcome, and an OR of poor outcome of 3.04 for the abusive head trauma group. Given this is one relatively small study with internal validity concerns, it was considered insufficient to support a recommendation.

Effect of Timing of the DC Procedure. One small class 3 treatment series noted that the ICP in two of eight patients rose rapidly to greater than 25 mm Hg within 15 minutes of onset of increase, resulting in death in both cases (182). The report did not contain sufficient data to assess what characteristics of these patients might have been indications for very early DC.

Complications. Of nine class 3 treatment series that systematically assessed complications, two reported blood loss associated with mortality (181, 183–185, 187–189, 201, 205). In one, of 12 patients, one of six with intraoperative blood loss (IBL) less than 50% of estimated blood volume (EBV) died, whereas three of six with IBL greater than 50% of EBV died (183). The second study ($n = 25$; 21 severe) found significantly greater mortality in patients with greater than 300 mL operative blood loss ($p = 0.001$) (185).

Tables 7 and 8 contain cumulative frequencies for complications reported in the remaining seven studies (181, 184, 187–189, 201, 205). One of the studies reported complications for a total sample of 71 patients, 36 of which were severe; all patients in the other samples are severe (188). These data indicate a high occurrence of complications among patients who receive DC and suggest that potential complications should be taken into account when making decisions about DC as a treatment. As with the subtopic of timing of DC, there are insufficient data in these reports to assess patient characteristics that might be risk factors for complications. Of note, many of the nonsurgical complications listed are also associated with severe TBI, itself, and relevant data from comparison group is not always available (**Table 30**).

TABLE 30. Complications From Decompressive Craniectomy

Complication	Occurrence (Total *n* = 164)	Percent
Hygroma	32	19.5
Hydrocephalus	25	15
Ventilator-associated pneumonia	22	13.4
Aseptic bone resorption	12	7
Infection	10	6
Septicemia	6	3.7
Epilepsy/seizures	6	3.7
Infection or dysfunction of cranioplasty	4	2.4
Infection or dysfunction of ventriculoperitoneal shunt	3	2
Bone flap sepsis	2	1.2
Slight subsidence of flap	1	0.6

n indicates sample size.

Indications From Adult Guidelines

Because the findings of the literature review for pediatric TBI provide levels of evidence and recommendations specific to the pediatric population, the clinical investigators do not think that the recommendations about DC from the adult guidelines are required to guide treatment decisions in children (14).

Nutrition

Recommendations

Strength of Recommendations: Weak

Level I

There was insufficient evidence to support a level I recommendation for this topic.

Level II

To Improve Overall Outcomes. II.1. Use of an immune-modulating diet is not recommended.

Level III

To Improve Overall Outcomes. III.1. Initiation of early enteral nutritional support (within 72 hr from injury) is suggested to decrease mortality and improve outcomes.

Changes From Prior Edition. The level III recommendation from the Second Edition has been removed. Recommendation III.1. is new to this Third Edition. One new class 3 retrospective observational study was added to the evidence base for this topic (209).

Introduction

Similar to adults, children with severe TBI require energy to support recovery (210, 211). Although the exact mechanisms remain unclear, TBI causes an increase in metabolism, which thereby requires increased caloric support during the critical phase of injury. In addition, developing children have greater nutritional needs for normal growth and development. The decision to administer nutritional support, including the timing, the quantity, the manner, and the composition of such support, may have effects on short- and long-term outcome.

Hyperglycemia is a consistent stress response to severe illness or injury including severe TBI (212). Although treatment of hyperglycemia with insulin to achieve glucose control has been studied in critically ill and injured pediatric patients, initial studies found conflicting results. The first-reported randomized trial found significantly lower infection rates, length of stay, and mortality, but greater risk of hypoglycemia among pediatric patients treated with tight glucose control compared with those treated with insulin to achieve higher glucose targets (213). Subsequent studies among general pediatric critically ill and injured patients as well as cardiac surgical patients found no influence on mortality from tight control compared with higher glucose targets, but consistently reported greater rates of severe hypoglycemia with concern for harm (214–216).

Because mortality was lower among pediatric patients with critical illness and injury compared with adults, there remained a concern that studies had not enrolled a subset of sufficiently ill patients to demonstrate a benefit from tighter glucose control. The most recent report restricted enrollment to hyperglycemia patients treated with either mechanical ventilation or vasoactive medications and the primary outcome was the mean number of 28-day ICU-free days. The study was terminated early due to low probability of benefit and significantly greater rates of severe hypoglycemia (5.2% vs 2.0%) in the tight control group (215). Currently, there appears to be no benefit to targeting glucose concentrations lower than a range of 150–180 mg/d among pediatric critical care patients (215, 217).

Nevertheless, the severity and duration of posttraumatic hyperglycemia are consistently associated with worse outcomes that likely reflect worse injury and greater stress (218, 219). No studies of glucose control have focused solely on children with severe TBI. Currently, there are insufficient data to recommend for or against tight glucose control for children with severe TBI and persistent hyperglycemia.

Although enteral nutrition is preferred for critically injured patients, some may receive parenteral nutrition due to other abdominal injuries or concerns regarding aspiration risk. A recent large randomized clinical trial in general critically ill pediatric patients demonstrated increased rates of early infection and prolonged length of stay among patients treated with early initiation of parenteral nutrition (within 24 hr of ICU admission) compared with those with initiation of parenteral nutrition after 1 week of critical illness. Both groups received early initiation of enteral nutrition, which was increased in accordance to local guidelines. The study found that early enteral feeding was tolerated as well as IV micronutrients (trace elements, minerals, and vitamins) starting from day 2 and continuing until the enteral nutrition provided reached 80% of the caloric targets (220). Currently, most pediatric critical care providers attempt enteral nutrition in preference to parenteral in trauma patients unless there are severe injuries to the bowel.

TABLE 31. Nutrition: Quality of the Body of Evidence

Topic	No. of Studies Study Design	Recommendations	Meta-Analysis Possible (Yes or No[a])	No. of Subjects (*n*)	Consistency (High, Moderate, Low)	Directness (Direct or Indirect)	Precision (High, Moderate, Low)	Quality of Evidence (High, Moderate, Low, or Insufficient)
Components of overall quality: class 2 study								
Immune-modulating diet	One randomized controlled trial	II.1.	NA	40	NA	Direct	Low	Moderate
Components of overall quality: class 3 study								
New topic: timing of nutritional support	One retrospective	III.1.	NA	90	NA	Direct	High	Low

NA = not applicable.

[a]Meta-analysis to synthesize results is only possible if several studies address the same criteria/question, and other design criteria are met.

n indicates sample size.

TABLE 32. Nutrition: Summary of Evidence

Reference Type of Trauma Center Geographic Location	Study Design *n* Age (yr) Mean (Range) Outcomes	Data Class	Results
Class 2 Study			
Immune-modulating diet: recommendation II.1.			
Briassoulis et al (221) PICU University Hospital Athens, Greece	Randomized controlled trial $n = 40$ Age: mean, 120 mo; range, 72–126 mo IE: mean, 127 mo; range, NR Standard: mean, 112 mo; range, NR Hospital mortality; infection; LOS; metabolic indices	Class 2 Attrition NR; unclear if intention-to-treat analysis conducted	IE vs regular formula Mortality Survival: 80% vs 95%; no significant difference Infection Fewer positive gastric cultures in IE group ($p < 0.02$), but no significant difference in infections LOS 16.7 vs 12.2 d; no significant difference Length of mechanical ventilation 11 vs 8 d; no significant difference Metabolic indices The IE group was more likely to have positive nitrogen balance at 5 d (69% vs 31%; $p < 0.05$).
Class 3 study			
Timing of nutritional support: recommendation III.1.			
Taha et al (209) [a] Level 1 pediatric trauma center California	Retrospective $n = 109$; 90 analyzed (19 died before nutritional support) Age: median, 13; range, 8–18; under 8 excluded Effect of time of initiation on neurologic status at discharge (normal, disability, death) and ICU LOS	Class 3 Unclear if groups were similar at baseline; no control for confounders; outcome assessors not blinded.	Effect of timing on neurologic status Time to initiation/time to full caloric intake by discharge status (mean ± SD in days) Home: 1.51 ± 1.23/3.38 ± 3.32 Disability: 3.08 ± 2.70/6.99 ± 4.73 Coma/death: 1.88 ± 0.99/7.12 ± 6.44 Early initiation and achieving full caloric intake significantly related to more favorable discharge status ($p < 0.05$). Effect of timing on ICU LOS Early initiation and achieving full caloric intake significantly related to shorter ICU LOS ($p < 0.01$).

IE = immune enhancing, LOS = length of stay, NR = not reported.
[a]New study.

Evaluation of the Evidence

Quality of the Body of Evidence. Studies included for this topic addressed questions about the effect on overall outcomes of an immune-modulating diet and the timing of nutritional support. One small class 2 RCT provided moderate-quality evidence to support recommendation II.1. (221). One class 3 observational study provided low quality of evidence to support recommendation III.1. (209) (**Table 31**).

Applicability. The RCT supporting the level II recommendation was small, and conducted at a single site in Greece, limiting its applicability (221). The single-center study supporting the level III recommendation did not include infants (209). Due to its retrospective design, it is not known whether the observed positive results were because children do better if they were fed, or were fed because they were less severely injured. Thus, the applicability of this study is in question.

Summary of the Evidence

One class 2 study from the Second Edition (221) and one new class 3 study (209) provided evidence to support the recommendation (**Table 32**).

Evidence Synthesis

Immune-Modulating Diet. No new evidence has been found since the Second Edition of these guidelines that suggests best practice in the quantity, manner, and composition of nutritional support for pediatric patients with TBI. Briassoulis et al (221), a class 2 RCT, showed no difference in outcomes for children provided an immune-enhancing diet versus regular formula.

TABLE 33. Corticosteroids: Quality of the Body of Evidence

Components of Overall Quality: Class 3 Study								
Topic	No. of Studies Study Design	Recommendation	Meta-Analysis Possible (Yes or No[a])	Total No. of Subjects (*n*)	Consistency (High, Moderate, Low)	Directness (Direct or Indirect)	Precision (High, Moderate, Low)	Quality of Evidence (High, Moderate, Low, or Insufficient)
Use of corticosteroids to improve outcomes	One randomized controlled trial with two publications	III.1.	NA	25	NA	Direct	Low	Low

NA = not applicable.

[a]Meta-analysis to synthesize results is only possible if several studies address the same criteria/question, and other design criteria are met.

n indicates sample size.

Timing of Nutritional Support. The retrospective study by Taha et al (209) suggested that initiation of early (enteral) nutrition may reduce mortality and morbidity. Conducted in children 8–18 years old, the study found that when full caloric intake was achieved, a shortened length of ICU stay with improved outcomes at the time of discharge could be demonstrated. However, it is not known whether the children who were fed had better outcomes because they were fed, or if they were fed because they were less severely injured. Thus, the recommendation it supports is a weak level III.

Indications From Adult Guidelines

The clinical investigators do not think that the recommendations about nutrition from the adult guidelines can be used to guide treatment decisions in children.

Corticosteroids

Recommendations

Strength of the Recommendation: Weak

Levels I and II

There was insufficient evidence to support a level I or II recommendation for this topic.

Level III

To Improve Overall Outcomes

III.1. The use of corticosteroids is not suggested to improve outcome or reduce ICP.

Note: Recommendation III.1. is not intended to circumvent use of replacement corticosteroids for patients needing chronic steroid replacement therapy, those with adrenal suppression, and those with injury to the hypothalamic-pituitary steroid axis.

Changes From Prior Edition. The Level II recommendation from the Second Edition has been downgraded to Level III. The note about use of replacement corticosteroids is new to this edition. No new studies were added to the evidence base for this topic.

Introduction

Corticosteroids can restore altered vascular permeability (222), inhibit tumor-induced angiogenesis (223), decrease edema and CSF production (224, 225), and diminish free radical production (224). These effects provide a rationale for potential steroid benefit in neurologic diseases. This topic summarizes the clinical evidence for glucocorticoid administration as a therapy to improve outcome in pediatric severe TBI.

Treatment of refractory hypotension (i.e., shock) with corticosteroids was not addressed by the included studies. Studies of adult patients with critical illness–related corticosteroid insufficiency (CIRCI) due to major trauma (defined by change in baseline hydrocortisone with an adrenocorticotropic hormone stimulation test) did not demonstrate a mortality benefit with steroid therapy. However, steroid treatment was associated with increased risk of ventilator-associated pneumonia and significant fewer ventilator-free days, and current international guidelines recommend against treatment for adult patients with major trauma and CIRCI (226). Similar trials are lacking in children. However, children with known primary or secondary adrenal insufficiency and major trauma should receive corticosteroid replacement therapy to avoid acute adrenal insufficiency.

Evaluation of the Evidence

Quality of the Body of Evidence. Two reports of a single small class 3 RCT were included for this topic (227, 228). They each addressed the question of the use of corticosteroids to improve outcomes for children with TBI. Because of the small sample size, low precision and class 3 evidence, the overall quality of evidence is low (**Table 33**).

Applicability. Both reports are over 25 years old, and the dose of steroids is greater than the dose used for acute laryngotracheobronchitis (229) and below that used for reversal of vasodilatory septic shock (230). Thus, the relevance of the evidence is limited and applicability is a concern. Questions about randomization, blinding, sample size, and statistical analysis render the publications class 3. However, in adults, a large class 1 RCT, the Corticosteroid randomisation after significant head injury (CRASH) trial, provided strong evidence against the use of steroids for acute care of severe TBI. This evidence confirms the findings from the older trial, mitigating the applicability concerns (231).

TABLE 34. Corticosteroids: Summary of Evidence

Class 3 Study (Same Sample)			
Reference Type of Trauma Center Geographic Location	Study Design *n* Age (yr) Mean (Range) Outcomes	Data Class	Results
Use of corticosteroids to improve outcomes: recommendation III.1.			
Fanconi et al (227), Klöti et al (228) ICU Zúrich, Switzerland	Randomized controlled trial *n* = 25; 13 steroid, 12 placebo (Fanconi et al [228]) *n* = 24; 12/12 (Klöti et al [229]) (same patients) Age: Steroid group: mean, 7.5; range, 1.8–14.6 Placebo group: mean, 7.4; range, 1.4–15.8 GOS at 6 mo postinjury, ICP, CPP, duration of monitoring and intubation; free cortisol levels; and complications	Class 3 Randomization and allocation concealment methods not described; unclear if outcome assessors were blinded; unclear if sample size was adequate; did not use intent-to-treat analysis.	GOS, ICP, CPP, duration of intubation Steroid treatment resulted in no differences vs placebo in 6 mo GOS, ICP, CPP, duration of ICP monitoring, or duration of intubation Free cortisol levels Steroid treatment vs placebo significantly suppressed endogenous free cortisol levels from day 1 to day 6. Complications Steroid treatment resulted in a trend toward increased bacterial pneumonia (7/13 vs 2/12 vs placebo, respectively, $p = 0.097$).

CPP = cerebral perfusion pressure, GOS = Glasgow Outcome Score, ICP = intracranial pressure.

Summary of the Evidence

Two reports of one class 3 study provide evidence to support the recommendation (227, 228) (**Table 34**).

Evidence Synthesis

Dexamethasone and ICP/CPP. Fanconi et al (227) performed a randomized, prospective, placebo-controlled clinical trial on 25 pediatric patients with severe TBI using dexamethasone at 1 mg/kg/d for 3 days ($n = 13$) versus placebo ($n = 12$). Baseline characteristics did not differ between groups. Dexamethasone treatment did not influence ICP (mean of 14 mm Hg in both groups), CPP, number of interventions required, duration of intubation, or 6-month GOS versus placebo. However, steroid treatment versus placebo significantly suppressed endogenous free cortisol levels up to day 6. In addition, steroid treatment resulted in a trend toward increased bacterial pneumonia versus placebo (7/13 vs 2/12, respectively, $p = 0.097$). Limitations included use of the Richmond screw to assess ICP, fluid restriction, and the use of hyperventilation to a $PaCO_2$ of 25–30 mm Hg as part of standard care.

Klöti et al (228) reported on 24 of the same 25 patients from the study described above. Additional outcomes in this report included duration of ICP monitoring; steroid treatment produced no difference between groups. The small sample size for this trial limited the ability to make definitive conclusions regarding neurologic outcomes or complications. However, suppression of cortisol production by steroid treatment was clearly documented.

Indications From Adult Guidelines

There is class 1 evidence in the adult guidelines that the use of steroids is not recommended for improving outcome or reducing ICP (level I) (14). In adult patients with severe TBI, high-dose methylprednisolone was associated with increased mortality and is therefore contraindicated (231). As the CRASH trial's findings were similar to the small, older pediatric trial, they support the existing recommendation and lessen the concerns about the applicability of the older trials.

ONGOING AND FUTURE RESEARCH

Climbing the Mountain With No Top

As stated in the "*Methods* section" of this document, evidence-based guidelines rarely (if ever) contain enough data to fully populate a clinical protocol. This is certainly the case with the treatment of severe pediatric TBI. The goal is to position the guidelines in a dynamic process as illustrated in Figure 1.

Available evidence is used to generate treatment guidelines. The guidelines provide recommendations based on the available evidence and identify gaps that become the future research agenda. In the interim, those gaps can be filled by creating clinical protocols using consensus where evidence is lacking. Together the gaps and protocols provide structure and identify patient samples for the generation of new research. The new research populates the evidence base which can then be used to further develop the guidelines. It is a recursive cycle—a mountain with no top.

The primary goal of this team has been to generate evidence-based guidelines for the treatment of pediatric TBI. Secondary goals—as important—have been to include and train new clinical investigators and methodologists in the technology, and to generate strong research in response to gaps identified in the guidelines documents. For the Second Edition of these guidelines, 11 new

TABLE 35. Current Status of Pediatric Traumatic Brain Injury Guidelines

Topic	Recommendations	Direct/Indirect/ Treatment Series	Ongoing Research
ICP monitoring	To improve overall outcomes Level III 1. Use of ICP monitoring is suggested.	19 Studies All class 3 3 Direct: all retrospective 16 Indirect • 1 RCT • 2 Prospective • 10 Retrospective • 3 Treatment series	None known
Advanced neuromonitoring	To improve overall outcomes Level III 1. If $Pbro_2$ monitoring is used, maintaining a level > 10 mm Hg is suggested.	4 Direct studies All class 3 1 Prospective 3 Treatment series	ADAPT hypotheses • $Pbro_2$ monitoring is associated with favorable outcomes. • A threshold $Pbro_2$ value is associated with favorable outcomes.
Neuroimaging	To improve overall outcomes Level III 1. Excluding the possibility of elevated ICP on the basis of a normal initial (0–6 hr after injury) CT examination of the brain is not suggested in comatose pediatric patients. 2. Routinely obtaining a repeat CT scan >24 hr after the admission and initial follow-up is not suggested for decisions about neurosurgical intervention, unless there is either evidence of neurologic deterioration or increasing ICP.	3 Direct studies All class 3 2 Retrospective 1 Treatment series	None known
ICP thresholds	To improve overall outcomes Level III 1. Treatment of ICP targeting a threshold of < 20 mm Hg is suggested.	12 Direct studies All class 3 3 Prospective 9 Retrospective	None known
CPP thresholds	To improve overall outcomes Level III 1. Treatment to maintain a CPP at a minimum of 40 mm Hg is suggested. 2. A CPP target between 40 to 50 mm Hg is suggested to ensure that the minimum value of 40 mm Hg is not breached. There may be age-specific thresholds with infants at the lower end and adolescents at or above the upper end of this range.	15 Direct studies 1 Class 2, 14 class 3 1 Prospective 4 Retrospective 10 Treatment series	None known

(*Continued*)

TABLE 35. (*Continued*). Current Status of Pediatric Traumatic Brain Injury Guidelines

Topic	Recommendations	Direct/Indirect/ Treatment Series	Ongoing Research
Hyperosmolar therapy	For ICP control Level II 1. Bolus hypertonic saline (3%) is recommended in patients with intracranial hypertension. Recommended effective doses for acute use range between 2 and 5 mL/kg over 10–20 min. For ICP control Level III 1. Continuous infusion hypertonic saline is suggested in patients with intracranial hypertension. Suggested effective doses as a continuous infusion of 3% saline range from between 0.1 and 1.0 mL/kg of body weight per hour, administered on a sliding scale. The minimum dose needed to maintain ICP < 20 mm Hg is suggested. 2. Bolus of 23.4% hypertonic saline is suggested for refractory ICP. The suggested dose is 0.5 mL/kg with a maximum of 30 mL.	9 Direct studies 3 Class 2, 6 class 3 2 RCTs 1 Prospective 5 Retrospective 1 Treatment series	ADAPT hypotheses • Hyperosmolar therapies improve outcomes. • Hypertonic saline is more effective than mannitol for ICP control.
Analgesics, sedatives, and neuromuscular blockade	For ICP control Level III 1. With use of multiple ICP-related therapies, as well as appropriate use of analgesia and sedation in routine ICU care, avoiding bolus administration of midazolam and/or fentanyl during ICP crises is suggested due to risks of cerebral hypoperfusion.	6 Studies All class 3 1 Direct prospective 1 Indirect prospective 2 Direct retrospective 2 Direct treatment series	None known
CSF	For ICP control Level III 1. CSF drainage through an external EVD is suggested to manage increased ICP.	5 Studies All class 3 1 Direct retrospective 3 Direct treatment series 1 Indirect treatment series	ADAPT hypotheses • Continuous CSF drainage improves outcomes. • Continuous CSF drainage reduces other ICP therapies.
Seizure prophylaxis	For seizure prevention (clinical and subclinical) Level III 1. Prophylactic treatment is suggested to reduce the occurrence of early (within 7 d) PTS.	4 Studies All class 3 1 Direct retrospective 1 Indirect prospective 1 Indirect retrospective 1 Indirect treatment series	None known
Ventilation	To improve overall outcomes Level III 1. Prophylactic severe hyperventilation to a $Paco_2$ < 30 mm Hg in the initial 48 hr after injury is not suggested. 2. If hyperventilation is used in the management of refractory intracranial hypertension, advanced neuromonitoring for evaluation of cerebral ischemia is suggested.	2 Studies Both class 3 1 Indirect retrospective 1 Direct treatment series	ADAPT hypotheses • Prophylactic hyperventilation (Co_2 < 30 mm Hg) is associated with unfavorable outcomes. • Moderate hyperventilation is associated with favorable outcomes.

(*Continued*)

TABLE 35. (*Continued*). Current Status of Pediatric Traumatic Brain Injury Guidelines

Topic	Recommendations	Direct/Indirect/ Treatment Series	Ongoing Research
Temperature control	To improve overall outcomes Level II 1. Prophylactic moderate (32–33°C) hypothermia is not recommended over normothermia to improve overall outcomes. For ICP control Level III 1. Moderate (32–33°C) hypothermia is suggested for ICP control.	10 Studies 1 Class 1, 4 class 2, 3 class 3, 2 meta-analyses 2 Direct meta-analyses 5 Direct RCTs 1 Indirect RCT 1 Direct retrospective 1 Indirect retrospective	None known
Barbiturates	For ICP control Level III 1. High-dose barbiturate therapy is suggested in hemodynamically stable patients with refractory intracranial hypertension despite maximal medical and surgical management.	4 Direct studies All class 3 1 Retrospective 3 Treatment series	None known
DC	For ICP control Level III 1. DC is suggested to treat neurologic deterioration, herniation, or intracranial hypertension refractory to medical management.	23 Direct studies All class 3 1 RCT 1 Prospective 5 Retrospective 16 Treatment series	None known
Nutrition	To improve overall outcomes Level II 1. Use of an immune-modulating diet is not recommended. To improve overall outcomes Level III 1. Initiation of early enteral nutritional support (within 72 hr from injury) is suggested to decrease mortality and improve outcomes.	2 Direct studies 1 Class 2, 1 class 3 1 RCT 1 Retrospective	ADAPT hypotheses • Increased caloric intake is associated with favorable outcomes. • Early institution of feeding is associated with favorable outcomes. • Early glucose administration is associated with unfavorable outcomes. • A threshold value for hyperglycemia is associated with favorable outcomes.
Corticosteroids	To improve overall outcomes Level III 1. The use of corticosteroids is not suggested to improve outcome or reduce ICP.	1 Direct study Class 3 1 RCT with 2 publications	None known

ADAPT = Approaches and Decisions in Acute Pediatric TBI, CPP = cerebral perfusion pressure, CSF = cerebrospinal fluid, DC = decompressive craniectomy, EVD = external ventricular drain, ICP = intracranial pressure, $Pbro_2$ = brain tissue oxygen, PTS = posttraumatic seizures, RCT = randomized controlled trial.

TABLE 36. Roadmap to Future Research: Pediatric Traumatic Brain Injury[a]

Topic	Level of Recommendation	Overall Outcomes vs. Intermediate	Class of Studies	Direct vs Indirect Evidence	Number of Studies
ICP monitoring					
Advanced neuromonitoring					
Neuroimaging					
ICP thresholds					
Cerebral perfusion pressure thresholds					
Hyperosmolar therapy					
Analgesics, sedatives, neuromuscular block					
Cerebrospinal fluid drainage					
Seizure prophylaxis					
Ventilation therapies					
Temperature control					
Barbiturates					
Decompressive craniectomy					
Nutrition					
Corticosteroids					

ICP = intracranial pressure.
[a]Lighter cells indicate stronger body of evidence.
Full explanation of shading is provided in FUTURE DIRECTIONS section.

investigators joined the team, and multiple new studies have been generated by our team as well as by other members of the TBI clinical research community. As mentioned in the "*Introduction* section," one of the most important studies of pediatric TBI, designed and executed by a guidelines clinical investigator, is concluding—the ADAPT. We look forward to strong class 2 publications from this project that will address 12 a priori hypotheses across five guidelines topics (**Table 35**), as well as post hoc analyses of other topics and questions. ADAPT is an important example of the utilization of a strong research design (comparative effectiveness) to address questions that have eluded examination via RCTs. It is also an important demonstration that part of the value of a guideline is found in both the evidence-based recommendations and in highlighting what cannot be said due to lack of evidence; those gaps provide opportunities for innovation and direction for research capable of fully populating a clinical protocol with evidence-based recommendations.

Current Status

Table 35 outlines the current status of research for each of the topics in this edition in terms of target outcomes, level of recommendations, class and quantity of studies, and current research in progress with a design capable of generating class 2 evidence. Blank cells in the "Future Research" column are obvious target priorities, with a caveat. A blank cell may indicate that there is no longer a need for further research of that topic, or that the questions within the topic may require reconsideration and reframing; this is what the TBI community needs to determine as it develops agendas and priorities for future research. For example, the clinical research community may benefit from reconsideration of the question about the use of monitors to measure ICP and a reframing of that question in the context of goal-directed therapy. Indeed, for clinical environments that are fully resourced, goal-directed therapy might be an appropriate context in which all topics and questions are reconsidered, and new ones generated. Furthermore, for cells populated with studies from ADAPT, the direction of future research may be defined by the findings from those studies; however, the questions may remain unanswered).

FUTURE DIRECTIONS

Table 36 illustrates target priorities for future pediatric TBI research. The rows are the current topics. The columns are characteristics of a body of evidence used to quantify quality. The cells that intersect row and column are coded in shades of gray. The range of shades from dark to light indicates:

- Level III to II to I
- Intermediate outcomes to relevant patient outcomes
- Class 3 to 2 to 1
- Indirect evidence to direct evidence
- Smaller number of studies to larger number of studies
- Thus, the lighter the cell, the stronger the body of evidence for the topic and characteristic; the darker the cell, the greater the need for change in research approach.

The dominance of lighter cells (indicating higher quality) in the columns for "Overall Outcomes vs Intermediate" and

"Direct vs Indirect Evidence" is due in part to the criteria we used to include studies into the evidence base. We only included studies with intermediate outcomes when there were insufficient data for overall outcomes; similarly, we only included indirect evidence when direct evidence was lacking or scarce.

Table 36 illustrates that for 11 of 15 topics, only class 3 studies were included, and 12 topics had only level III recommendations. Clearly, the TBI clinical research community needs to continue to find innovative methods to generate high-quality class 2 and 1 studies. What Table 36 does not illustrate is the following:

1. *The integration of individual treatments in the context of goal-directed therapy.* Management of patients with TBI is not a function of the application of individual treatments. No treatment or management approach exists independent of other treatments and approaches, or independent of the ecology of the treatment setting. The design of meaningful and effective future research must be consistent with this clinical reality. Thus, although Table 36 points to areas for improvement, it creates an illusion of independence of treatments by illustrating treatment characteristics with independent cells.
2. *New topics for investigation, or the integration of more than one topic as a treatment "approach."* Which topics are complete? What new topics should be identified and included? How can the clinical reality of multiple treatments be accurately represented in research that integrates topics in ecologically valid designs?
3. *Consistency in data collection across studies.* Future research should include consistency in data collection across research projects, such as utilization of the Common Data Elements of the National Institutes of Health (232–235).

The clinical investigators and methods team recommend that the pediatric TBI research community systematically addresses these questions through creating a prioritized research agenda and advocating for additional high-quality research that can populate the evidence base for future guidelines designed to improve outcomes for children who sustain TBI.

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