

**Guidelines for the Acute Medical Management
of Severe Traumatic Brain Injury in Infants, Children, and Adolescents-Second Edition**

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The following endorse these Guidelines:

American Academy of Pediatrics-Section on Neurological Surgery
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European Society of Pediatric and Neonatal Intensive Care
Neurocritical Care Society
Pediatric Neurocritical Care Research Group
Society of Critical Care Medicine
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The information contained in this Guidelines document reflects the current state of knowledge at the time of its completion, December 5, 2011. In view of the fact that there will be future developments in both scientific information and technology, it is anticipated that these Guidelines will be periodically reviewed and updated. These Guidelines are published and distributed with the understanding that the Brain Trauma Foundation and the other organizations that have collaborated and supported their development are not engaged in rendering professional medical services. If medical advice or assistance is required, the services of a competent physician should be sought. The recommendations contained in these Guidelines may not be appropriate for use in all circumstances. The decision to adopt any particular recommendation contained in these Guidelines must be made by a treating physician with knowledge of all of the facts and circumstances in each particular case and on the basis of the available resources.

Chapter 1. Introduction

I. RECOMMENDATIONS

This is the second edition of the *Guidelines for the Acute Medical Management of Severe Traumatic Brain Injury in Infants, Children, and Adolescents*. The first edition was published in 2003, >8 yrs ago (1). Writing the initial guidelines was an exciting but humbling experience, because it quickly became apparent that, based on the available literature, it would be difficult to make recommendations above level III for most categories. Despite this challenge, the guidelines committee maintained its commitment to produce an evidence-based document and did not come to a consensus when crafting the recommendations. It was clear that one of the major contributions of the document would be to identify key gaps in the literature as targets for future research.

For the second edition we were optimistic that sufficient new studies about pediatric traumatic brain injury (TBI) had been generated since 2003 to support a document with higher level evidence and stronger recommendations than the first edition. Without question, several valuable new reports in pediatric TBI have been published since 2003, including randomized controlled trials of hypothermia, additional reports investigating and/or describing optimal cerebral perfusion pressure in children, brain tissue oxygen monitoring, nutrition, cerebrospinal fluid drainage, and the impact of hypocarbia, among others (2–12).

After rigorous application of the criteria for including studies that were prespecified by the guidelines committee, we found 27 new publications for the second edition. However, 25 publications that were included in the 2003 document failed to meet the more rigorous criteria in this second edition (Appendix A). Key reasons for excluding publications were 1) no clear specification of admission Glasgow Coma Scale score; 2) inclusion of patients with pathologies other than

severe TBI; 3) inclusion of adult patients without analysis of data by age; and 4) failure to include a relevant health outcome such as mortality or function or even an important surrogate outcome such as intracranial pressure. For example, a recent study by Bar-Joseph et al (13) on the use of ketamine as a sedative in pediatric brain injury could not be included as evidence because the admission Glasgow Coma Scale was not specified, and the sample included children with pathologies other than severe TBI.

It is important to distinguish between inclusion criteria and quality criteria. Publications were not excluded based on their quality. The purposes of the inclusion criteria were to 1) clearly define the target patient population; 2) identify the independent variables (treatments) and dependent variables (outcomes); 3) identify the scope of the treatment phases; and 4) use sample sizes and study designs capable of providing a baseline level of data (see “Methods” section). All publications meeting these criteria, regardless of their quality, were included in the final library and constitute the body of evidence. If a publication did not meet these criteria, regardless of its quality, it was excluded.

After identification as “included,” each study was then assessed for its quality based on the quality criteria provided in detail in the “Methods” section. The purpose of the quality criteria is to determine the potential for bias and uncontrolled confounding based on 1) study design; and 2) flaws in the conduct of the studies. Regardless of quality (class I, II, or III), all included studies were used as evidence. However, the level and strength of the recommendations were derived from the quality of the overall body of evidence used to address each topic.

We rated the quality of randomized controlled trials using predefined criteria designed to assess study design factors that are widely accepted as important indicators of internal validity: use of adequate randomization, allocation concealment, and blinding methods; similarity of compared groups at baseline; maintenance of comparable groups; use of an

intention-to-treat analysis; overall follow-up rate of $\geq 85\%$; and no differential loss to follow-up. We used separate predefined criteria to rate the quality of cohort and case-control studies designed to reflect the most important aspects of those study designs: nonbiased patient selection methods, identification and ascertainment of events, adequate sample size, follow-up rate of at least 85%, and use of adequate statistical methods to control for potentially confounding variables.

One of the major problems in crafting guidelines in many fields, and in particular in pediatric TBI, is the lack of Utstein-style^a data collection for key parameters in the published studies. This resulted in the inability to include otherwise valuable studies as evidence in this document. Lack of Utstein-style data collection also created other difficulties. For example, data on intracranial pressure were collected and/or reported by investigators in a number of manners such as peak value, mean value, or number of values greater than a given threshold. This lack of a systematic approach to data collection and reporting created important problems in a number of chapters for our committee to generate cogent recommendations. Until we have an Utstein-style template for pediatric TBI that is widely accepted and used to conduct research, we strongly encourage the TBI community to consider use of the inclusion and quality criteria specified in these guidelines when designing studies.

There are several new additions and/or modifications to the second edition: 1) The levels of recommendation were changed from “standard, guideline, and option” to “level I, level II, and level III,” respectively; 2) new chapters include Advanced Neuromonitoring and Neuroimaging with the focus of these additions on management

^aThe Utstein style is a set of guidelines for uniform reporting that has been used by the American Heart Association and other organizations for reporting of cases of cardiac arrest. The name derives from the location of a consensus conference held at the Utstein Abbey in Norway. This standardized approach has greatly facilitated research and registry development in the field of resuscitation medicine.

Table 1. Changes in recommendations from the first edition to the second edition

Chapter	First Edition	Second Edition
Cerebral Perfusion Pressure	Level II—A CPP >40 mm Hg in children with TBI should be maintained Level III—A CPP between 40 and 65 mm Hg probably represents an age-related continuum for the optimal treatment threshold; there may be exceptions to this range in some infants and neonates Level III—Advanced cerebral physiological monitoring may be useful to define the optimal CPP in individual instances	Level III—A minimum CPP of 40 mm Hg may be considered in children with TBI Level III—A CPP threshold 40–50 mm Hg may be considered; there may be age-specific thresholds with infants at the lower end and adolescents at the upper end of this range
Hyperosmolar Therapy	Level III—Hypotension should be avoided Level III—Hypertonic saline is effective for control of increased ICP after severe head injury; 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 <20 mm Hg should be used Level III—Mannitol is effective for control of increased ICP after severe TBI; effective bolus doses range from 0.25 g/kg of body weight to 1 g/kg of body weight Level III—Euvolemia should be maintained by fluid replacement; a Foley catheter is recommended in these patients to avoid bladder rupture Level III—Serum osmolality should be maintained below 320 mOsm/L with mannitol use, whereas a level of 360 mOsm/L appears to be tolerated with hypertonic saline, even when used in combination with mannitol	Level II—Hypertonic saline should be considered for the treatment of severe pediatric TBI associated with intracranial hypertension; effective doses for acute use range between 6.5 and 10 mL/kg Level III—Hypertonic saline should be considered for the treatment of severe pediatric TBI associated with intracranial hypertension; 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 <20 mm Hg should be used; serum osmolality should be maintained below 360 mOsm/L Footnote below recommendations: 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
Temperature Control	Level III—Extrapolated from the adult data, hyperthermia should be avoided in children with severe TBI Level III—Despite the lack of clinical data in children, hypothermia may be considered in the setting of refractory intracranial hypertension	Level II—Moderate hypothermia (32–33°C) beginning early after severe TBI for only 24 hrs duration should be avoided Level II—Moderate hypothermia (32–33°C) beginning within 8 hrs after severe TBI for up to 48 hrs' duration should be considered to reduce intracranial hypertension Level II—If hypothermia is induced for any indication, rewarming at a rate of >0.5°C per hour should be avoided Level III—Moderate hypothermia (32–33°C) beginning early after severe TBI for 48 hrs duration may be considered
Hyperventilation	Level III—Mild or prophylactic hyperventilation (Paco₂ <35 mm Hg) in children should be avoided Level III—Mild hyperventilation (Paco₂ 30–35 mm Hg) may be considered for longer periods for intracranial hypertension refractory to sedation and analgesia, neuromuscular blockade, cerebrospinal fluid drainage, and hyperosmolar therapy Level III—Aggressive hyperventilation (Paco₂ <30 mm Hg) may be considered as a second-tier option in the setting of refractory hypertension; cerebral blood flow, jugular venous oxygen saturation, or brain tissue oxygen monitoring is suggested to help identify cerebral ischemia in this setting Level III—Aggressive hyperventilation therapy titrated to clinical effect may be necessary for brief periods in cases of cerebral herniation or acute neurologic deterioration	Level III—Avoidance of prophylactic severe hyperventilation to a Paco₂ <30 mm Hg may be considered in the initial 48 hrs after injury Level III—If hyperventilation is used in the management of refractory intracranial hypertension, advanced neuromonitoring for evaluation of cerebral ischemia may be considered

Table 1.—Continued

Chapter	First Edition	Second Edition
Corticosteroids	Level III—The use of steroids is not recommended for improving outcome or reducing ICP in pediatric patients with severe TBI; despite two class II studies failing to show efficacy, the small sample sizes preclude support for a treatment guideline for this topic	Level II—The use of corticosteroids is not recommended to improve outcome or reduce ICP for children with severe TBI
Analgesics, Sedatives, and Neuromuscular Blockade	Level III—In the absence of outcome data, the choice of dosing and sedatives, analgesics, and neuromuscular-blocking agents used in the management of infants and children with severe TBI should be left to the treating physician; however, the effect of individual sedatives and analgesics on ICP in infants and children with severe TBI can be variable and unpredictable	Level III—Etomidate may be considered to control severe intracranial hypertension; however, the risks resulting from adrenal suppression must be considered Level III—Thiopental may be considered to control intracranial hypertension Footnotes below recommendations: In the absence of outcome data, the specific indications, choice and dosing of analgesics, sedatives, and neuromuscular-blocking agents used in the management of infants and children with TBI should be left to the treating physician As stated by the Food and Drug Administration, continuous infusion of propofol for either sedation or the management of refractory intracranial hypertension in infants and children with severe TBI is not recommended)
Glucose and Nutrition	Level III—Replace 130% to 160% of resting metabolism expenditure after TBI in pediatric patients	Level II—The evidence does not support the use of an immune-modulating diet for the treatment of severe TBI to improve outcome
Antiseizure Prophylaxis	Level II—Prophylactic use of antiseizure therapy is not recommended for children with severe TBI for preventing late posttraumatic seizures Level III—Prophylactic antiseizure therapy may be considered as a treatment option to prevent early posttraumatic seizure in young pediatric patients and infants at high risk for seizures after head injury	Level III—Prophylactic treatment with phenytoin may be considered to reduce the incidence of early posttraumatic seizures in pediatric patients with severe TBI

CPP, cerebral perfusion pressure; TBI, traumatic brain injury; ICP, intracranial pressure.

rather than diagnosis or prognosis; 3) chapters from the first edition which were eliminated from the second edition include Trauma Systems, Prehospital Airway Management,^b Resuscitation of Blood Pressure and Oxygenation,^c Intracranial Pressure Monitoring Technology,^d and the Critical Pathway for Treatment of Intracranial Hypertension^e; 4) broader representation on the committee of the relevant specialties in the field, including pediatric anesthesiology, child neurology, and neuroradiology; and 5) international representation on the

guidelines committee includes Drs. Kissoon and Tasker.

As indicated, some publications included in the first edition were eliminated, because the methods team found they did not meet criteria (Appendix A, publications from the first edition not included in the second edition).

Table 1 summarizes changes in the recommendations from the first edition to the second edition of these guidelines.

The field is moving forward and it is clear that with advances in neuromonitoring and imaging and the publication, subsequent to the first edition of the guidelines, of the results of the first major multicentered randomized controlled trials in pediatric TBI, we are on the right track. Given the importance of severe TBI to the overall burden of childhood morbidity and mortality, we hope that these new guidelines aid caregivers and stimulate the pediatric TBI community to generate additional answers.

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^bPrehospital treatment of pediatric patients with TBI is addressed in the *Guidelines for Prehospital Management of Severe Traumatic Brain Injury* (14).

^cThere were no publications that met the inclusion criteria for this topic.

^dThis topic is addressed in the *Guidelines for the Management of Severe Traumatic Brain Injury, Third Edition* (15).

^eThe critical pathway will be developed and published as a separate document.

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Chapter 2. Methods

I. TOPIC REFINEMENT

The Brain Trauma Foundation (BTF) and BTF Center for Guidelines Management (Center) convened a virtual meeting of previous guidelines authors and colleagues new to the project. The panel consisted of 15 clinicians and three methodologists. They specified which previous topics would be maintained and agreed on new topics to include. Topics were not included in the second edition if they were adequately addressed in other guidelines documents (e.g., prehospital management of pediatric patients with traumatic brain injury is addressed in the *Guidelines for Prehospital Management of Severe Traumatic Brain Injury* [1]) or if there was no literature meeting inclusion criteria to support any level of recommendation. Specification of new topics of interest was determined by panel consensus. Previous topics that were updated are Indications for Intracranial Pressure Monitoring, Intracranial Pressure Treatment Threshold, Cerebral Perfusion Pressure, Antiseizure Prophylaxis, Hyperventilation, Cerebrospinal Fluid Drainage, Hyperosmolar Therapy, Decompressive Craniectomy, Barbiturates, Analgesics–Sedatives–Neuromuscular Blockades, and Steroids. Topics from the first edition not included in this update are Trauma Systems and Pediatric Trauma Centers, Prehospital Airway Management, Resuscitation of Blood Pressure and Oxygenation, Intracranial Pressure Monitoring Technology, and the Critical Pathway. New topics are Advanced Neuromonitoring and Neuroimaging. The previous topic of Temperature Control was expanded to Hypothermia and Temperature Control, and the previous topic of Nutrition was expanded to Glucose and Nutrition.

^aOne randomized controlled trial had a sample of 24 patients (Kloti, 1987) and one a sample of 18 (Fisher, 1992).

^bOne retrospective review had a sample of 24 patients (Pfenninger, 1983).

^cOne study included 16% of patients with moderate traumatic brain injury (Downard, 2000).

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II. LITERATURE SEARCH AND RETRIEVAL

Center staff worked with a doctoral-level research librarian to construct electronic search strategies for each topic (Appendix B). For new topics, the literature was searched from 1950 to 2009 and for previous topics from 1996 to 2009. A second search was conducted for 2009–2010 to capture any new relevant literature. Strategies with the highest likelihood of capturing most of the targeted literature were used, which resulted in the acquisition of a large proportion of nonrelevant citations.

Two contributing authors (coauthors) were assigned to each topic, and a set of abstracts was sent to each coauthor. Blinded to each other's work, they read the abstracts and eliminated citations using the prespecified inclusion/exclusion criteria. Center staff compared the coauthors' selections and identified and resolved discrepancies either through consensus or through use of a third reviewer. A set of full-text publications was then sent to each coauthor. Again blinded to each other's work, they read the publications and selected those that met the inclusion criteria.

Results of the electronic searches were supplemented by recommendations of peers and by reading reference lists of included studies. Relevant publications were added to those from the original search, constituting the final library of studies that were used as evidence in this document. The yield of literature from each phase of the search is presented in Appendix C.

III. STUDY SELECTION

Inclusion Criteria

Inclusion criteria consisted of severe traumatic brain injury (Glasgow Coma Scale score <9); human subjects; English language publications; pediatric patients (age ≤18 yrs); randomized controlled trials (N ≥25)^a; cohort studies, prospective or retrospective (N ≥25)^b; case–control studies (N ≥25); and case series (N ≥5).

The intervention (independent variable) must be specific to the topic.

The outcome must be a relevant health outcome (morbidity or mortality) or a surrogate outcome that associates with a health outcome.

Minimum sample sizes were identified to circumscribe the body of literature and manage the scope of the project. There is no evidence that the selected cutoffs associate with levels of confidence in the reported results.

Exclusion Criteria

Exclusion criteria consisted of penetrating brain injury; animal studies; cadaver studies; non-English language publications; and adult patients (age >18 yrs).

Also excluded were studies in which the sample contained >15% of adult patients or >15% of patients with pathologies other than traumatic brain injury without separate analysis (Appendix D).^c

Case studies/editorials/comments/letters were excluded.

For each topic, relevant information from the *Guidelines for the Management of Severe Traumatic Brain Injury* (2) is reviewed. The panel agreed that data from the adult guidelines would not be used to contribute to recommendations for this document.

Inclusion of Direct and Indirect Evidence

Figures 1 and 2 illustrate different links in a “causal pathway” that represent either direct or indirect evidence. In Figure 1, arc A represents direct evidence, derived from a comparative study, of the influence of an intervention on an important health outcome (like functional status). Arc B represents direct evidence of the influence of an intervention on a surrogate outcome (like partial pressure of brain tissue oxygen), and arc C represents a correlation between measures on the surrogate outcome and the important health outcome. Taken together, arcs B and C represent indirect evidence of the influence of the intervention on an important health outcome. Studies were included if they contained direct evi-

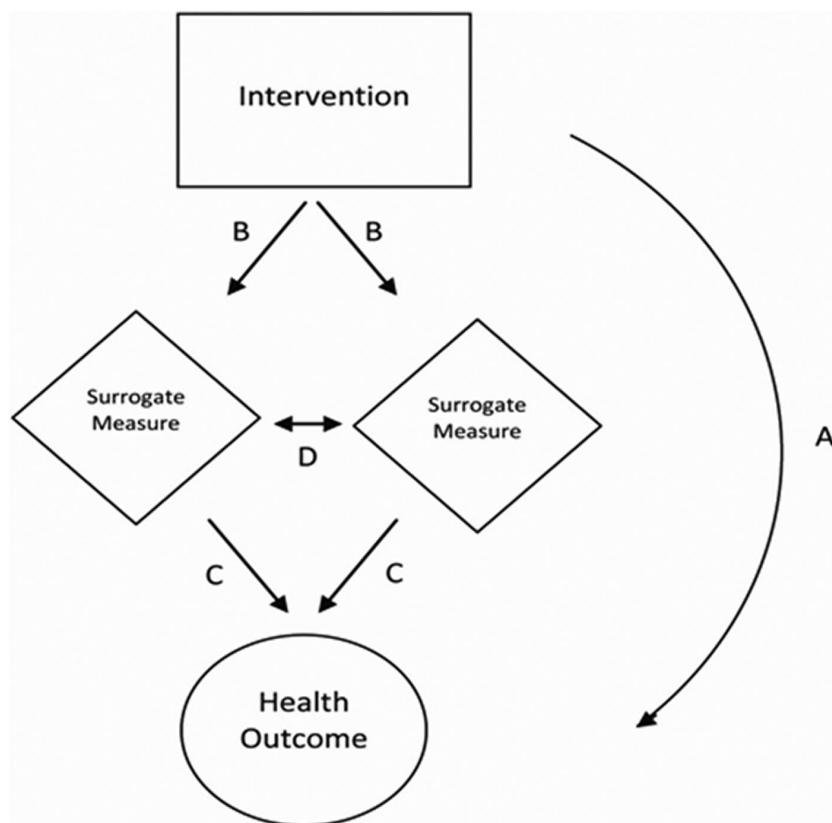


Figure 1. Direct and indirect evidence.

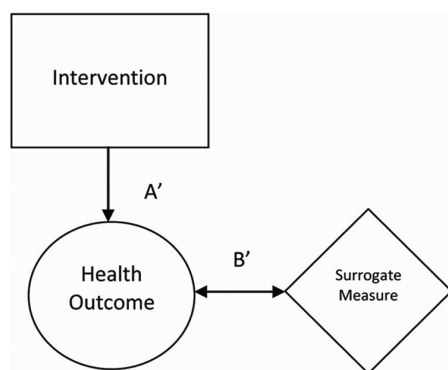


Figure 2. Indirect evidence.

dence or if they contained both components of the indirect evidence illustrated in Figure 1.

Figure 2 illustrates a second kind of indirect evidence that we included. In some studies, an intervention was introduced to the entire study sample (without a comparison group). Change in an important health outcome was measured, and then authors looked for associations between surrogate measures and the health outcome. For example, in the

chapter on Cerebral Perfusion Pressure, Downard et al (3) conducted a retrospective analysis of 118 patients who were all treated for severe traumatic brain injury and assessed for Glasgow Outcome Scale score at ≥ 3 months, dichotomized as “good” or “poor.” Then, using a logistic regression analysis, they looked for significant associations between cerebral perfusion pressure, a surrogate measure, and outcome. Lower cerebral perfusion pressure was associated with poorer out-

comes. This association was used as weak class III evidence for the chapter’s recommendations. In Figure 2, arc A’ represents an uncontrolled association between an intervention and an important health outcome, and arc B’ represents a correlation between measures on the surrogate outcome and the important health outcome. Studies were included if they contained both components of the indirect evidence illustrated in Figure 2.

IV. DATA ABSTRACTION AND SYNTHESIS

Remaining blinded, coauthors read each publication and abstracted data using an evidence table template (Appendix E). They compared results of their data abstraction and through consensus finalized the data tables that constitute the evidence on which the recommendations are based. As a result of heterogeneity of studies within topics, and the lack of literature of adequate quality, data were not combined quantitatively.

Coauthors drafted manuscripts for each topic. The entire team gathered for a 2-day work session to discuss the literature base and craft the recommendations. Manuscripts were revised. Virtual meetings were held with a subset of the coauthors to complete the editing process. The final draft manuscript was circulated to the peer review panel and was revised incorporating selected peer review input.

V. QUALITY ASSESSMENT OF INDIVIDUAL STUDIES AND CLASSIFICATION OF EVIDENCE

In April of 2004, the BTF established a formal collaboration with the Evidence-Based Practice Center from Oregon Health & Science University. Center staff worked with two Evidence-Based Practice Center epidemiologists to develop criteria and procedures for the quality assessment of individual studies and classification of level of evidence provided by each included study. These criteria are designed to assess risk of bias for individual studies based on study design and conduct. Criteria for classification of evidence are in Table 1 and are derived from criteria developed by the U.S. Preventive Services Task Force (4), the National Health Service Centre for Reviews and Dissemination (U.K.) (5), and the Cochrane Collaboration (6). These criteria were used to assess the literature.

Table 1. Criteria for assessment of risk of bias and classification of evidence

Class of Evidence	Study Design	Quality Criteria
I	Good-quality RCT	Adequate random assignment method Allocation concealment Groups similar at baseline Outcome assessors blinded Adequate sample size Intention-to-treat analysis Follow-up rate $\geq 85\%$ No differential loss to follow-up Maintenance of comparable groups
II	Moderate or poor-quality RCT	Violation of one or more of the criteria for a good quality RCT ^a
II	Good-quality cohort	Blind or independent assessment in a prospective study or use of reliable ^b data in a retrospective study Comparison of two or more groups must be clearly distinguished Nonbiased selection Follow-up rate $\geq 85\%$ Adequate sample size Statistical analysis of potential confounders ^c
II	Good-quality case-control	Accurate ascertainment of cases Nonbiased selection of cases/controls with exclusion criteria applied equally to both Adequate response rate Appropriate attention to potential confounding variables
III	Moderate or poor-quality RCT or cohort	Violation of one or more criteria for a good-quality RCT or cohort ^a
III	Moderate or poor-quality case-control	Violation of one or more criteria for a good-quality case-control ^a
III	Case series, databases, or registries	Prospective collected data that are purely observational and retrospectively collected data

RCT, randomized controlled trial.

^aAssessor needs to make a judgment about whether one or more violations are sufficient to downgrade the class of study based on the topic, the seriousness of the violation(s), their potential impact on the results, and other aspects of the study. Two or three violations do not necessarily constitute a major flaw. The assessor needs to make a coherent argument why the violation(s) either do, or do not, warrant a downgrade; ^breliable data are concrete data such as mortality or reoperation; ^cpublication authors must provide a description of robust baseline characteristics and control for those that are unequally distributed between treatment groups.

Three members of the Center staff, two of whom are Evidence-Based Practice Center epidemiologists, conducted all of the quality assessments. Two assessors, blinded to each other's work and to publication identification, read the selected studies and classified them as class I, II, or III based on the criteria in Table 2. Discrepancies were resolved through consensus or through a third person's review.

Class I evidence is derived from randomized controlled trials. However, some randomized controlled trials may be poorly designed, lack sufficient patient numbers, or suffer from other methodologic inadequacies.

Class II evidence is derived from clinical studies in which data were collected prospectively and retrospective analyses that were based on clearly reliable data. Comparison of two or more groups must be clearly distinguished. Types of studies include observational, cohort, prevalence, and case-control. Class II evidence may also be derived from flawed randomized controlled trials.

Class III evidence is derived from prospectively collected data that are purely observational and retrospectively collected data. Types of studies include case series, databases, or registries. Class III evidence may also be derived from flawed randomized controlled trials or flawed observational, cohort, prevalence, or case-control studies.

VI. QUALITY OF BODY OF EVIDENCE AND STRENGTH OF RECOMMENDATIONS

At the beginning of each recommendation section in this document, the recommendations are categorized in terms of strength and quality of evidence. The strength of the recommendation is derived from the overall quality of the body of evidence used to assess the topic.

Quality of Body of Evidence

The underlying methods for assessing risk of bias for individual studies are represented in Table 1. However, ultimately

the individual studies must be considered in aggregate, whether through meta-analyses or through qualitative assessment. Thus, the strength of recommendations must be derived from the quality of the overall body of evidence used to address the topic.

Consistent with recommendations for grading a body of evidence adopted by the Agency for Healthcare Research and Quality (7), we assessed the overall quality of the body of evidence considering the domains of 1) risk of bias from individual studies; 2) consistency of findings across studies; 3) directness of evidence; and 4) precision of estimates of effect. The quality of the overall body of evidence for each recommendation in this document is classified as high, moderate, or low. Factors that may decrease the quality include potential bias, differing findings across studies, the use of indirect evidence, or lack of precision. For example, if two or more class I studies demonstrate contradictory findings for a particular topic, the overall quality most probably will be low because there is un-

certainty about the effect. Similarly, class I or II studies that provide indirect evidence may only constitute low-quality evidence, overall.

Strength of Recommendations

Consistent with methods generated by the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) Working Group, recommendations in this document are categorized as either strong or weak. As stated in the American Thoracic Society's official statement (8), in which they endorsed the GRADE methods for their guidelines endeavors, "The strength of a recommendation reflects the degree of confidence that the desirable effects of adherence to a recommendation outweigh the undesirable effects."

Strong recommendations are derived from high-quality evidence that provides

precise estimates of the benefits or downsides of the topic being assessed. With weak recommendations, 1) there is lack of confidence that the benefits outweigh the downsides; 2) the benefits and downsides may be equal; and/or 3) there is uncertainty about the degree of benefits and downsides.

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Chapter 3. Indications for intracranial pressure monitoring

I. RECOMMENDATIONS

Strength of Recommendations: Weak.

Quality of Evidence: Low, from poor and moderate-quality class III studies.

A. Level I

There are insufficient data to support a level I recommendation for this topic.

B. Level II

There are insufficient data to support a level II recommendation for this topic.

C. Level III

Use of intracranial pressure (ICP) monitoring may be considered in infants and children with severe traumatic brain injury (TBI).

II. EVIDENCE TABLE (see Table 1)

III. OVERVIEW

Secondary injury to the brain after severe TBI occurs, in part, as a result of reduced perfusion of surviving neural tissue, resulting in reduced oxygen and metabolite delivery and reduced clearance of metabolic waste and toxins. Secondary injury also occurs as the result of cerebral herniation syndromes, resulting in focal ischemic injury and brain stem compression along with other mechanisms. Intracranial hypertension represents a key pathophysiological variable in each of these secondary injury mechanisms (1–3).

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 (4). A study by Tilford and colleagues (5) demonstrated that an intensive care unit with higher incidence of ICP monitoring in severely brain-injured

children, plus certain medical interventions, had a trend toward lower mortality than two other pediatric intensive care units. Similarly, a study by Tilford and colleagues (4) 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 simultaneously introduced 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 computed tomography (CT) imaging to detect mass lesions, 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 (6–8). It is less clear, however, whether intracranial hypertension or reduced cerebral perfusion secondary to intracranial hypertension is the primary mechanism of secondary injury. Cerebral perfusion pressure (equals mean arterial pressure minus ICP) is the simplest correlate of global cerebral perfusion (9–12). The relative value of ICP monitoring as a means of evaluating and manipulating cerebral perfusion pressure, vs. avoidance of cerebral herniation events, is also unclear (13).

The lack of controlled trials on ICP monitoring limited the strength of the recommendations contained in the first edition of the *Guidelines for the Management of Severe TBI in Children* (14). This dearth of strong evidence is associated with mixed adoption of guidelines-directed management in the United States and abroad (15–17). In a 2007 survey of U.S. neurosurgeons and nonneurosurgeons caring for such patients, Dean et al (15) found approximately 60% agreement and conformity with guidelines recommendations. In the United

Kingdom, only 59% of children presenting with severe TBI underwent ICP monitoring with only half of clinical units caring for such children using monitoring technology (16, 17). The use of monitoring in children <2 yrs of age with severe TBI may be even less likely. A study by Keenan et al (18) 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 incidence of using various interventions for the treatment of intracranial hypertension at different centers (5).

IV. PROCESS

For this update, MEDLINE was searched from 1996 through 2010 (Appendix B for search strategy), and results were supplemented with literature recommended by peers or identified from references lists. Of 36 potentially relevant studies, seven studies were added to the existing table and used as evidence for this topic.

V. SCIENTIFIC FOUNDATION

Two moderate and 14 poor-quality class III studies met the inclusion criteria for this topic and provide evidence to support the recommendation (9, 19–33).

Are Children With Severe TBI at Risk of Intracranial Hypertension?

A number of small studies demonstrate a high incidence of intracranial hypertension in children with severe TBI (20, 21, 23, 24, 26, 28, 31, 33). Some of these studies identify in preliminary fashion other clinical factors that, in combination with severe TBI in a child, are indicative of a high incidence of intracranial hypertension. In these patients, “diffuse cerebral swelling” on CT scan is 75% specific for the presence of intracranial hypertension (26). In a study of 56 severely brain-injured patients (39 of whom had severe TBI), 32% of children had an initial ICP measurement >20 mm Hg but 50% had ICP maximum >20 mm Hg at some point during their intensive care

Table 1. Evidence table

Reference	Study Description	Data Class, Quality, and Reasons	Results and Conclusion
Studies from previous guidelines			
Alberico et al, 1987 (19)	Design: single-center, prospective, observational study N = 100 Age: 0–19 yrs Glasgow Coma Scale score: ≤ 7 Purpose: Assessment of relationship between ICP and outcome Outcome: GOS score at 3 months and 1 yr	Class III Poor quality: no control for confounders	Reducible intracranial hypertension was significantly associated with better outcome than nonreducible intracranial hypertension
Barzilay et al, 1988 (20)	Design: retrospective case series with analysis of minimum ICP N = 56 Age: mean 6.2 yrs Purpose: assessment of relationship between ICP and outcome in patients treated for high ICP with hyperventilation and medical management Outcome: survival at hospital discharge	Class III Poor quality: no control for confounders	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); $p < 0.01$
Bruce et al, 1979 (21)	Design: single-center, observational study N = 85, 40 had ICP monitoring Age: 4 months to 18 yrs Purpose: assess relationship between ICP monitoring and medical management in a protocol emphasizing hyperventilation therapy to control intracranial hypertension, but also including barbiturates, mannitol, and/or surgery Outcome: dichotomized GOS at 6 months	Class III Poor quality: no control for confounders	Intracranial hypertension (ICP > 20 mm Hg) was more prevalent in children without (80%) than with (20%) spontaneous motor function Of the total group (N = 85): 87.5% of children achieved good recovery or moderate disability; 3.5% persistent vegetative state, 9% died. 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 ICP maximum predictive of poor outcome was > 35 mm Hg in adults and children
Chambers et al, 2001 (9)	Design: single-center, observational study N = 84 Age: 0–16 yrs Purpose: assessment of relationship between ICP and CPP and outcome Outcome: GOS at 6 months	Class III Poor quality: no control for confounders; unclear if patient selection was unbiased	
Downard et al, 2000 (22)	Design: retrospective review N = 118 Age: < 15 yrs Glasgow Coma Scale score: mean 6, 84% < 8 Purpose: assess relationship among ICP, CPP, and outcome in children with severe TBI in two trauma centers Outcome: the final available GOS in the medical record	Class III Poor quality: as an intervention study; moderate quality as a prognosis study; logistic regression performed to determine factors associated with GOS, but no comparison of groups based on any intervention	In a stepwise logistic regression analysis, ICP > 20 mm Hg was significantly associated with an increased risk of death

Table 1.—Continued

Reference	Study Description	Data Class, Quality, and Reasons	Results and Conclusion
Esparza et al, 1985 (23)	Design: single-center, observational study N = 56 Age: 3 months to 14 yrs Purpose: assessment of relationship between ICP monitoring and surgical and medical therapy and outcome after severe TBI in children Outcome: GOS dichotomized as good (mild disability) or poor (disability, persistent vegetative state, or death)	Class III Poor quality: no control for confounders; unclear if outcome assessment was unbiased	Outcomes were as follows: 93% good, 3% poor for patients with ICP maximum ≤ 20 mm Hg, 71% good, 29% poor for patients with ICP maximum 20–40 mm Hg; 0% good, 100% poor for patients with ICP maximum 40–60 mm Hg and 0% good, 100% poor for patients with ICP maximum > 60 mm Hg (no significance test reported)
Kasoff et al, 1988 (24)	Design: single-center, retrospective, observational study N = 25 Age: 3 months to 17 yrs Purpose: assess relationship between ICP and outcome in children treated with mannitol and if refractory, mannitol plus barbiturates Outcome: mortality	Class III Poor quality: no control for confounders; unclear if patients selection was unbiased	Mortality rate was 20% Children with elevated ICP had a lower survival rate than children with normal ICP, although no statistical analysis is presented Mean highest ICP of those who died was 81 mm Hg (range, 55–120); for ICP only group 18.7 (range, 10–30), for mannitol group 42.11 (range, 10–70), for pentobarbital and mannitol group 72 (range, 30–120) Four children had normal ICP and did not require medical therapy; nine required mannitol therapy and eleven mannitol and then barbiturate therapy for sustained intracranial hypertension
Michaud et al, 1992 (25)	Design: single-center, observational study N = 51 Age: 3 months to 14 yrs Purpose: assessment of relationship between ICP and outcome Outcome: GOS at discharge	Class III Moderate quality: no power calculation; otherwise met all criteria	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 to 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
Shapiro and Marmarou, 1982 (26)	Design: retrospective case series N = 22 Age: 3 months to 15 yrs Purpose: study the use of pressure volume index assessment using external ventricular drains Outcome: GOS—time of assessment not indicated	Class III Poor quality (diagnostic study): narrow spectrum of patients enrolled; small sample size; unclear if reliability of test assessed	86% of children with severe TBI had ICPs exceeding 20 mm Hg “Diffuse cerebral swelling” on computed tomography scan was 75% specific for the presence of intracranial hypertension Intracranial hypertension could be controlled in 14 of the 16 children whose pressure volume index was measured, and in those patients, there were no deaths

Table 1.—Continued

Reference	Study Description	Data Class, Quality, and Reasons	Results and Conclusion
New studies			
Adelson et al, 2005 (27)	Design: randomized controlled trial of hypothermia treatment N = 75 Age: <17 yrs Purpose: ICP monitoring and randomized, controlled trial of moderate hypothermia vs. normothermia plus medical management of intracranial hypertension Outcome: GOS at 3 and 6 months	Class III Poor quality: no control for confounders. (class II for hypothermia trial)	High (no. not specified) incidence of intracranial hypertension ICP >20 was most sensitive and specific for poor outcome Low mean ICP, percent time ICP <20 and mean CPP were all significantly associated with good outcome 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; $p = .036$) The percent time less than 20 mm Hg differed between outcome groups (good, $90.8\% \pm 10.8\%$; poor, $68.6\% \pm 35.0\%$; $p = .01$) 82% had favorable outcome, 17.8% unfavorable; 4.4% died; 13.3% had severe disability Higher ICP ($p \leq .02$) for days 1–5 was significantly associated with decreased cerebral oxygen extraction and worse clinical outcome
Cruz et al, 2002 (28)	Design: single-center retrospective study N = 45 Age: 1–12 yrs Purpose: assessment of the effect of ICP monitoring and medical therapy on outcome; also examined relationship to oxygen metabolism through jugular bulb catheter Outcome: GOS at 6 months	Class III Poor quality: no control for confounders	Survival rate was 97.9% (1 death); favorable outcome in 89.6% There was no difference in ICP maximum in groups with good (22.2 mm Hg) vs. poor (24.6 mm Hg) outcomes
Grinkeviciute et al, 2008 (29)	Design: single-center prospective observational study N = 48 Age: 2.4 months to 18 yrs Purpose: examination of relationship between ICP, CPP, and outcome in children including 13 treated with decompressive craniectomy for medically refractory intracranial hypertension Outcome: GOS at 6 months	Class III Poor quality: no control for confounders	Survival rate was 97.9% (1 death); favorable outcome in 89.6% 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, 2008 (30)	Design: single-center observational study N = 96 Age: 3–18 yrs Purpose: assessment of relationship between ICP, treatment and outcome in patients treated with variable combination of evacuation of mass lesions, ventricular drainage, medical management and decompressive craniectomy Outcome: GOS at 2 yrs	Class III Moderate quality: unclear if analysis of ICP monitoring controlled for confounders	Death was associated with refractory raised ICP ($p = .0001$), but not with ICP maximum, irrespective of the surgical or medical methods(s) used for successful reduction of intracranial hypertension Outcome: quality of life was related to medical management of elevated ICP ($p = .04$) Long-term outcomes were not correlated with peak ICP
Pfenninger and Santi, 2002 (31)	Design: retrospective single-center observational study N = 51 Age: 1 month to 16 yrs Purpose: assess relationship between ICP, medical or surgical management or jugular venous monitoring and outcome Outcome: GOS at 6–12 months	Class III Poor quality: no control for confounders	Moderate to severe intracranial hypertension (mean sustained ICP ≥ 20 mm Hg) was associated with poor outcome ($p < .05$) 69% of monitored patients had sustained ICP >20 mm Hg

Table 1.—Continued

Reference	Study Description	Data Class, Quality, and Reasons	Results and Conclusion
Wahlstrom et al, 2005 (32)	Design: single-center observational study N = 41 Age: 3 months to 14.2 yrs Purpose: assess affect of ICP management using the Lund protocol on outcome Outcome: GOS assessed between 2.5 and 26 months	Class III Poor quality: no control for confounders	Survival rate was 93%; favorable outcome (GOS 4 and 5) in 80% ICP in 3 nonsurvivors was significantly higher than in 38 survivors (mean 43 ± 26 mm Hg vs. 13 ± 4 mm Hg) The relationship between ICP and outcome in survivors was not statistically analyzed
White et al, 2001 (33)	Design: retrospective observational study N = 136 admitted to pediatric intensive care unit; 37 with ICP monitoring Age: 0–17 yrs Purpose: assess relationship between ICP and survival Outcome: survival	Class III Poor quality: no control for confounders for ICP analysis	14% of survivors and 41% of nonsurvivors had ICP >20 mm Hg in the first 72 hrs Those with lower mean ICP were more likely to be survivors ($p < .005$) ICP maximum and ICP measured 6, 12, and 24 hrs after admission were all significantly lower in survivors

ICP, intracranial pressure; GOS, Glasgow Outcome Scale score; CPP, cerebral perfusion pressure; TBI, traumatic brain injury.

course (20). 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%) (21).

These studies suggest that children presenting with severe TBI are at notable risk of intracranial hypertension. No specific markers have been identified that reliably determine the presence or absence of intracranial hypertension without monitoring in this population.

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 (9, 19–28, 30–33).

One small study of 48 patients failed to demonstrate a clear association between intracranial hypertension and poor outcome (29). Specifically, a study by Grinkeviciute et al reported similar mean ICP in children with good and poor outcome. In their study, however, 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 cerebral perfusion

pressure in directing the management of pediatric patients with severe TBI.

Does ICP Monitoring and Treatment Improve Outcome?

Two studies of combined treatment strategies also suggest that improved clinical outcomes are associated with successful control of intracranial hypertension (19, 30). A prospective observational study of 100 children with severe TBI treated with varying combinations of hyperventilation, diuretics, cerebrospinal fluid drainage, sedation, pharmacologic paralysis, and barbiturates reported that children whose intracranial hypertension was successfully lowered had better 1-yr outcomes than children whose intracranial hypertension was uncontrollable (but worse than those without intracranial hypertension) (19). A retrospective review of a prospectively acquired TBI database showed that reduced survival and worsened outcome in children with severe TBI were associated with intracranial hypertension refractory to treatment rather than peak ICP *per se* (30). In this study, successful control of intracranial hypertension, irrespective of treatment modality (osmolar therapy, cerebrospinal fluid drainage, decompression, etc.), was deemed to be important.

Although they represent only class III evidence for long-term outcome related to ICP monitoring and are only correlative, these studies support the association

of successful ICP monitor-based management of intracranial hypertension with improved survival and neurologic outcome.

VI. INFORMATION FROM OTHER SOURCES

A. Indications From the Adult Guidelines

The adult guidelines offer the following recommendation.

Level II: ICP should be monitored in all salvageable patients with a severe TBI (Glasgow Coma Scale score of 3–8 after resuscitation) and an abnormal CT scan. An abnormal CT scan of the head is one that reveals hematomas, contusions, swelling, herniation, or compressed basal cisterns.

Level III: ICP monitoring is indicated in patients with severe TBI with a normal CT scan if two or more of the following features are noted at admission: age >40 yrs, unilateral or bilateral motor posturing, or systolic blood pressure <90 mm Hg.

What Patients Are at High Risk of ICP Elevation? Patients with severe TBI (Glasgow Coma Scale ≤ 8) are at high risk for intracranial hypertension (8, 34). The combination of severe TBI and an abnormal head CT scan suggests a high likelihood (53% to 63%) of raised

ICP (34). However, even with a normal admission CT scan, intracranial hypertension may be present (35, 36). Data collected predominantly in adult patients suggest that detection and treatment of intracranial hypertension may protect cerebral perfusion pressure, avoid cerebral herniation, and improve neurologic outcome (8, 11, 34, 37–39).

In certain conscious patients with CT findings suggesting risk of neurologic deterioration (hematomas, contusions, swelling, herniation, or compressed basal cisterns), however, monitoring may be considered based on the opinion of the treating physician (35, 38). Inability to perform serial neurologic examinations, because of pharmacologic sedation or anesthesia, may also influence a clinician's decision to monitor ICP in an individual patient (40, 41).

How Does ICP Data Influence Patient Management? ICP data allow the management of severe TBI by objective criteria. This is particularly important because many, perhaps all, medical and surgical measures for the treatment of intracranial hypertension have significant potential adverse consequences (2, 7, 42). Thus, ICP monitoring allows the judicious use of interventions such as hyperosmolar therapy, sedatives, neuromuscular blockade, barbiturates, ventilator management, etc., with a defined end point that is correlated with clinical outcome. This may avoid potentially harmful, overly aggressive treatment.

Does ICP Monitoring Improve Outcome? In adults, intensive management protocols for severe TBI, including ICP monitoring, have been associated with lowered mortality rates as compared with historical controls or centers in other countries not using monitoring techniques (8, 43–45). A study by Eisenberg et al (46) reported that improved ICP control was associated with improved outcome in severely head-injured patients with medically intracranial hypertension. Finally, in a small, single-institution study of patients triaged according to the attending neurosurgery call schedule, mortality was over four times higher in nonmonitored than in monitored patients with severe TBI (47).

B. Information Not Included as Evidence

Various class III studies have demonstrated improved outcomes, vs. historical

controls, in the era of ICP monitor-directed intensive therapy of patients with severe TBI (11, 35, 43, 48, 49). Two specific ICP monitor-directed therapies effective in treating acute intracranial hypertension have been associated with improved survival and clinical outcomes after severe TBI in children. As indicated in the evidence table, a study by Bruce et al (1) reported that aggressive therapy with hyperventilation and/or barbiturates to treat intracranial hypertension in 85 children with severe TBI resulted in 87.5% good outcomes and only 9% mortality. Not included as evidence, Peterson et al (50) performed a retrospective study of severe TBI in 68 infants and children, which showed that effective treatment of refractory intracranial hypertension using continuous infusion of hypertonic (3%) saline resulted in a mortality rate (15%) lower than expected as a result of trauma severity score (40%). There were only three deaths in this study (4%) resulting from uncontrolled intracranial hypertension.

VII. SUMMARY

Four lines of evidence support the use of ICP monitoring in children with severe TBI: a frequently reported high incidence of intracranial hypertension in children with severe TBI, a widely reported association of intracranial hypertension and poor neurologic outcome, the concordance of protocol-based intracranial hypertension therapy and best-reported clinical outcomes, and improved outcomes associated with successful ICP-lowering therapies. Evidence reviewed in the adult guidelines mirrors that for pediatric patients, further suggesting that ICP monitoring is of clinical benefit in patients with severe TBI.

Intracranial hypertension is both difficult to diagnose and is associated with poor neurologic outcomes and death in infants and young children. Intracranial hypertension may be present in children with open fontanelles and sutures (18). ICP monitoring is of significant use in these patient populations.

The presence of intracranial hypertension can also be influenced by the type of pathology on CT such as diffuse injury or specific etiologies such as traumatic sinus thrombosis.

By contrast, ICP monitoring is not routinely indicated in children with mild or moderate TBI. Treating physicians may, however, in some circumstances,

choose to use ICP monitoring in conscious children who are at relative risk for neurologic deterioration as a result of the presence of traumatic mass lesions or in whom serial neurologic examination is precluded by sedation, neuromuscular blockade, or anesthesia.

VIII. KEY ISSUES FOR FUTURE INVESTIGATION

- Studies of specific subpopulations of pediatric patients with TBI in whom ICP monitoring is indicated; in particular, in the categories of infants and young children with abusive head trauma and/or infants with open fontanelles and sutures.
- Studies of the incidence of intracranial hypertension based on clinical and radiologic parameters in children of different ages and injury mechanisms.
- Focused multivariate analyses of children with intracranial hypertension to predict those who respond better to specific ICP-lowering therapies.
- Careful monitoring of the impact of adoption of ICP monitoring-directed protocols by hospitals and health systems should be undertaken to provide further evaluation of the impact of these measures on outcome as well as system performance variables.
- Studies are also needed to determine whether the type of ICP monitor (e.g., ventricular, parenchyma) or approach to monitoring (e.g., continuous or intermittent with cerebrospinal fluid drainage) influences outcome.

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Chapter 4. Threshold for treatment of intracranial hypertension

I. RECOMMENDATIONS

Strength of Recommendation: Weak.

Quality of Evidence: Low, from poor-quality class III studies.

A. Level I

There are insufficient data to support a level I recommendation for this topic.

B. Level II

There are insufficient data to support a level II recommendation for this topic.

C. Level III

Treatment of intracranial pressure (ICP) may be considered at a threshold of 20 mm Hg.

II. EVIDENCE TABLE (see Table 1)

III. OVERVIEW

In children with severe traumatic brain injury (TBI), mortality is often the result of a refractory increase in ICP. Furthermore, the need to prevent raised ICP is recognized as central to current neurocritical care of children after severe TBI. Management of severe TBI in the pediatric intensive care unit is largely focused on the management of raised ICP and preservation of cerebral perfusion pressure (CPP). Brief increases in ICP that return to normal in <5 mins may be insignificant; however, sustained increases of ≥ 20 mm Hg for ≥ 5 mins likely warrant treatment (1). Based in large part on studies in adults, an ICP treatment threshold of 20 mm Hg has been used in most centers for decades. However, the optimal ICP target or targets for pediatric TBI remain to be defined. Normal values for mean arterial blood pressure and hence CPP are lower in children, particularly in infants and young children. It has also been shown in anesthetized children without TBI that the lower CPP limit of autoregulation of cerebral blood flow is, surpris-

ingly, similar in young children vs. older children—and does not decrease below approximately 60 mm Hg (2). Thus, young children have less autoregulatory reserve than older children—i.e., 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 for infants and young children than older children or adults with TBI. As shown in the “Scientific Foundation” section, most of the evidence specific to pediatrics supports an ICP threshold of 20 mm Hg; however, individual reports do support lower ICP thresholds (as low as 15 mm Hg). However, some pediatric studies suggest higher thresholds (35 or even 40 mm Hg). Thus, although an ICP threshold of 20 mm Hg is generally used, and even lower threshold may physiologically make sense for infants and young children, the optimal threshold for ICP-directed therapy and whether or not it should be adjusted for children of different ages deserves additional investigation. It should also be recognized that some of the studies defining the ICP threshold used therapies that are not contemporary such as aggressive hyperventilation. Finally, in light of the heterogeneity of the pathology and pathophysiology in pediatric TBI, ICP management may need to be individualized in some cases.

IV. PROCESS

For this update, MEDLINE was searched from 1996 through 2010 (Appendix B for search strategy), and results were supplemented with literature recommended by peers or identified from reference lists. Of 60 potentially relevant studies, nine were added to the existing table and used as evidence for this topic.

V. SCIENTIFIC FOUNDATION

Eleven poor-quality class III studies met the inclusion criteria for this topic and provide evidence to support the recommendations (3–13).

No prospective or retrospective studies were identified that specifically compared the effect of ICP-directed therapy

on outcome (either short or long-term) using two (or more) predefined thresholds in pediatric TBI. One study examined this issue within the context of a randomized controlled trial (9).

We are thus left with various studies, both prospective and retrospective, that examined the association between outcome and different ICP thresholds in patients who, for the most part (5 of 13) (3–5, 8, 11), were managed with a therapeutic goal of <20 mm Hg for ICP-directed therapy. Of the 11 studies in the evidence table, one study used an ICP treatment threshold of 15 mm Hg (10) and another specifically used CPP rather than ICP treatment thresholds to guide treatment (13). One study described target “ranges” for the ICP threshold including 15–25 mm Hg and 20–25 mm Hg (12), and one used an age-dependent ICP treatment threshold ranging from 15 mm Hg in infants to 20 mm Hg in older children (9). Thus, it must be recognized that most of the studies in this evidence table have an inherent bias—ICP <20 mm Hg was the *a priori* therapeutic target for some or all of the patients. In addition to this limitation, statistical approaches to adjust for confounding variables in examining the association between ICP and outcome were variably used. Another important limitation of these studies is that there was no consistent approach to assess the relationship with outcome between either the time of assessment of ICP after TBI or the duration of time ICP was above a given threshold value. Generally mean or peak values or ICP values within a given epoch were used.

Although defining a safe ICP threshold has proved elusive, all but one of the 11 studies report that sustained intracranial hypertension is associated with mortality or poor outcome in children after severe TBI.

A study by Pfenninger et al (4) retrospectively reviewed 24 patients with severe TBI. The stated goal of the treatment was “to maintain ICP <20 mm Hg and abolish ICP elevations that were >25–30 mm Hg that lasted for >3 min.” The treatment regimen that was used included severe hyperventilation (Paco₂ 25–30 mm Hg), fluid restriction, mild hypothermia (rectal temperature 35.5–

Table 1. Evidence table

Reference	Study Description	Data Class, Quality, and Reasons ^a	Results and Conclusion
Studies from previous guidelines			
Esparza et al, 1985 (3)	Design: single-center retrospective review N = 56 Age: 3 months to 14 yrs Treatment threshold set at ICP >20 mm Hg Protocol: Treatment regimen not contemporary and included severe hyperventilation and dexamethasone	Class III Poor quality: no control for confounders; unclear if outcome assessment was unbiased No statistical comparison made between groups	13 of 13 (100%) patients with ICP >40 mm Hg had poor outcome (severe disability, vegetative, or dead) and all the patients with poor outcome died 4 of 14 (approximately 28%) patients with ICP 20–40 mm Hg had poor outcome 2 of 29 (approximately 7%) patients with ICP 0–20 mm Hg had poor outcome ICP >40 mm Hg was associated with higher mortality ($p < .001$)
Pfenninger et al, 1983 (4)	Design: single-center retrospective review N = 24 Age: 3 month to 14 yrs GCS: ≤7 Protocol: Treatment threshold was defined to maintain ICP ≤ 20 mm Hg, abolish ICP >25–30 mm Hg (sustained for >3 mins) and maintain CPP >50 mm Hg	Class III Poor quality: no control for confounders	13 of 16 patients with ICP 20–40 mm Hg had good outcome or moderate disability; three of 3 patients with ICP <20 mm Hg had good outcome or moderate disability
Studies from other chapters of previous guidelines			
Alberico et al, 1987 (5)	Design: single-center, prospective, observational study N = 100 Age: 0–19 yrs GCS: ≤7 Protocol: treatment threshold set at 20 mm Hg Treatment regimen included severe hyperventilation Outcome: GOS	Class III Poor quality: no control for confounders	70% good outcome GOS in children with ICP <20 mm Hg with treatment vs. 8% good outcome in children with ICP refractory to treatment (>20 mm Hg), $p < .05$
Chambers et al, 2001 (6)	Design: single-center retrospective study N = 84 Age: 3 months to 16 yrs Protocol: the ICP threshold for treatment and the specific treatments used were not provided Data recordings were made for a median of 41 hrs; ROC curves calculated to determine threshold value for ICP and CPP; for ICP, the ROC curves were created over 1-mm Hg intervals over the range of 0–90 mm Hg Outcome: dichotomized 6-month GOS	Class III Poor quality: no control for confounders; unclear if patient selection was unbiased	Overall, thresholds of 35 mm Hg for ICP and 45 mm Hg for CPP were the best predictors of outcome The ROC-defined cutoffs varied depending on the Marshall computed tomography classification and ranged from 21 mm Hg to 59 mm Hg
Downard et al, 2000 (7)	Design: two-center retrospective study N = 118 Age: <15 yrs GCS: ≤8 in 99 patients (84%) Protocol: no standard treatment protocol; sedation, mannitol, hyperventilation, vasopressors, ventriculostomy, or decompressive craniectomy used at the discretion of the treating physician	Class III Poor quality as an intervention study Moderate quality as a prognosis study; logistic regression performed to determine factors associated with GOS; but no comparison of groups based on any intervention	In a stepwise logistic regression analysis, mean ICP >20 mm Hg in the initial 48 hrs was significantly associated with an increased risk of death It was not indicated whether or not other ICP thresholds were investigate
Kassof et al, 1988 (8)	Design: single-center, retrospective, observational study N = 25 Age: 3 months to 17 yrs Protocol: treatment threshold set at 20 mm Hg Treatment regimen not contemporary and included severe hyperventilation and dexamethasone	Class III Poor quality: no control for confounders; unclear if patients selection was unbiased	Mean of peak ICP in patients who died (N = 5) was 81 mm Hg (range, 55–120 mm Hg); in contrast, 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

Table 1.—Continued

Reference	Study Description	Data Class, Quality, and Reasons ^d	Results and Conclusion
New studies			
Adelson et al, 2005 (9)	Design: prospective multicenter randomized controlled trial of moderate hypothermia vs. normothermia plus medical management N = 47 Age: <13 yrs Protocol: ICP treatment threshold varied with age and included 15 mm Hg, 18 mm Hg, or 20 mm Hg, for children 0–24 months, 25–96 months, and 97–156 months, respectively Contemporary guidelines-based treatment regimen including randomized use of moderate hypothermia Outcome: <i>post hoc</i> analysis of relationship between ICP and outcome (3- and 6-month GOS)	Class III Poor quality: no control for confounders in ICP analysis	Mean ICP was lower in children with good (11.9 ± 4.7 mm Hg) vs. poor (24.9 ± 26.3 mm Hg, $p < .05$) outcome; the percent time with ICP <20 mm Hg differed significantly in the good ($90.8\% \pm 10.8\%$) vs. poor ($68.6\% \pm 35.0\%$, $p < .05$) outcome groups ICP >20 mm Hg was the most sensitive and specific for poor outcome
Cruz et al, 2002 (10)	Design: single-center prospective study N = 45; children with ICP <15 mm Hg were excluded Age: 1–12 yrs Protocol: the ICP threshold for treatment was ≥ 15 mm Hg Treatment protocol to maintain normalized ICP, CPP, and cerebral oxygen extraction, included sedation, mannitol, severe hyperventilation ($\text{PaCO}_2 < 30$ mm Hg), barbiturates, and decompression for ICP >25 mm Hg Outcome: 6-month GOS	Class III Poor quality: no control for confounders	ICP peaked on day 4 in both groups ICP was significantly higher ($p = .02$) on days 2–5 in children with unfavorable vs. favorable outcomes 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 82% of the patients had a favorable outcome
Grinkeviciute et al, 2008 (11)	Design: single-center prospective study N = 48 Age: 2.4 months to 18 yrs Protocol: treatment threshold defined as ICP >20 mm Hg Patients were treated according to ICP-targeted protocol of the management of severe pediatric traumatic brain injury 27.1% of patients with decompressive craniectomy Outcome: 6-month dichotomized GOS	Class III Poor quality: no control for confounders. Insufficient power to detect outcome	The survival rate was remarkably high at 97.9% for children admitted to the pediatric intensive care unit Differences in peak ICP (22.2 mm Hg 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 minimal CPP Only 5 patients were described as having poor outcome
Pfenninger and Santi, 2002 (12)	Design: single-center retrospective observational study N = 51 of whom 26 underwent ICP monitoring and critical care management Age: 1 month to 16 yrs Protocol: an ICP target of 20–25 mm Hg was used ICP-directed therapy included diuretics, hypertonic saline, hyperventilation, pressors, and barbiturate coma Outcome: dichotomized 6- to 12-month GOS	Class III Poor quality: no control for confounders, potential selection bias in children who received ICP monitoring	Mean sustained ICP ≥ 20 mm Hg was associated with poor outcome ($p < .05$)
White et al, 2001 (13)	Design: single-center retrospective observational study N = 136; 37 of these patients underwent ICP monitoring Age: 0–17 yrs Protocol: an ICP target was not identified, but a CPP target of ≥ 50 mm Hg in infants and ≥ 70 mm Hg for children was used A contemporary treatment regimen was used	Class III Poor quality: no control for confounders for ICP analysis, potential selection bias in patients who received ICP monitoring	14% of survivors and 41% of nonsurvivors had ICP >20 mm Hg in the first 72 hrs; no other threshold was specifically examined. ICP maximum and ICP measured 6, 12, and 24 hrs after admission were all significantly lower in survivors

ICP, intracranial pressure; GCS, Glasgow Coma Scale; CPP, cerebral perfusion pressure; GOS, Glasgow Outcome Scale; ROC, receiver operating characteristic.

^dNo study provided data for a comparison between specific ICP thresholds for initiation of therapy on outcome.

36.5°C), dexamethasone, and barbiturate infusion for refractory ICP >20 mm Hg. Sustained ICP >40 mm Hg was associated with death ($p < .001$). Thirteen of 16 patients with sustained ICP 20–40 mm Hg had a good outcome or moderate disability. The three patients with ICP <20 mm Hg had a good outcome or moderate disability.

A study by Esparza et al (3) was a retrospective review of 56 pediatric children with severe TBI. The study included two victims of abusive head trauma. Treatment threshold was also ICP >20 mm Hg. The treatment regimen used again was not contemporary in that it included severe hyperventilation and dexamethasone. The group of patients with an ICP >40 mm Hg had a mortality rate of 100%, those with ICP >20–40 mm Hg had a mortality rate of 28%, whereas those with ICP 0–20 mm Hg had an incidence of poor outcome (severe disability, vegetative, or dead) of only approximately 7%, supporting use of an ICP treatment threshold ≤ 20 mm Hg.

A study by Alberico et al (5) was carried out as a prospective, observational study of 100 children (age range, 0–19 yrs) with severe TBI using an ICP treatment threshold again of 20 mm Hg. The treatment regimen once again included severe hyperventilation, limiting somewhat the ability to generalize the findings to current treatment. Patients with ICP maintained <20 mm Hg had a 70% good outcome (Glasgow Outcome Scale) in contrast to those with refractory intracranial hypertension who had only an approximately 8% good outcome. This study also supports an ICP treatment threshold of 20 mm Hg.

A retrospective, observational study by Kasoff et al (8) reported on data from 25 children (ages 3 months to 17 yrs). The patients included one victim of abusive head trauma. An ICP treatment threshold was again set at 20 mm Hg along with a CPP threshold of 40 mm Hg. The treatment regimen again was not contemporary and included both severe hyperventilation and dexamethasone. Only a limited amount of data on the relationship between ICP and outcome was presented, although it was clear from the study that severe refractory ICP was associated with poor outcome. The mean of peak ICP in patients who died ($n = 5$) was 81 mm Hg (range, 55–120 mm Hg), whereas the mean of peak ICP was 18.7 mm Hg (range, 10–30 mm Hg) and there were no deaths in patients who did not require ICP-directed therapies. However,

no statistical analysis was performed. Given the practicalities associated with clinical use of a threshold, for the purpose of making guideline recommendations, we have categorized this study as supporting a threshold of 20 mm Hg.

A study by Downard et al (7) was a retrospective observational study that included two level I trauma centers in the state of Oregon, the Oregon Health Sciences University trauma registry and the Legacy Emanuel Hospital and Health Center. A total of 118 children <15 yrs of age were included. Glasgow Coma Scale score was ≤ 8 in 99 patients (84%). No standard treatment protocol was described; therapies including sedation, mannitol, hyperventilation, vasopressors, ventriculostomy, or decompressive craniectomy were used at the discretion of the treating physician. It was not indicated that an ICP of 20 mm Hg was the treatment threshold; however, it was the only ICP threshold that was included in the logistic regression. A stepwise logistic regression analysis showed that a mean ICP >20 mm Hg in the initial 48 hrs was significantly associated with an increased risk of death with an odds ratio of 2.39. It was not indicated whether or not other ICP thresholds were investigated. A CPP <40 mm Hg was also associated with poor outcome.

A study by Chambers et al (6) retrospectively reviewed data on 84 children with severe TBI and receiver operating characteristic curves were calculated to determine threshold values for CPP and ICP. ICP treatment thresholds and specific therapies used were not specified. Data recordings were made for a median of 41.2 hrs. Using receiver operating characteristic curves, an ICP threshold of 35 mm Hg was determined to correlate best with Glasgow Outcome Scale at 6 months. The receiver operating characteristic-defined cutoffs varied greatly depending on the Marshall computed tomography classification. Specifically, for types I, II, and III diffuse injury, the ICP cutoffs were 21 mm Hg, 24 mm Hg, and 33 mm Hg, respectively. For evacuated and unevacuated mass lesion categories, the cutoffs were 40 mm Hg and 59 mm Hg, respectively. Thus, this report supports an ICP treatment threshold of 35 mm Hg and also suggests that optimal ICP thresholds may differ for different computed tomography classifications. However, caution is advised given that the sample size in the various subgroups is limited, the study was retrospective,

and biological plausibility for some of the thresholds is questionable. Nevertheless, this study raises the question as to whether or not ICP thresholds should be different in children with diffuse injury vs. focal contusion.

A retrospective study by White et al (13) reported on 136 children with severe TBI (Glasgow Coma Scale score ≤ 8) of whom 37 were managed with ICP monitoring. A CPP-directed protocol with targets of >50 mm Hg in infants and >70 mm Hg in children, rather than a specific ICP target, was used to direct therapy. A contemporary approach to treatment was used with only mild or no hyperventilation along with sedation, osmolar therapy, barbiturates, and vasopressors. Hypothermia was not used. They reported that 41% of nonsurvivors vs. 14% of the survivors had ICP >20 mm Hg in the first 72 hrs. No other ICP threshold was specifically examined. The highest recorded ICP value was 26 ± 18 mm Hg vs. 59 ± 33 mm Hg in survivors vs. nonsurvivors ($p = .03$). ICP values measured 6, 12, and 24 hrs after admission were all significantly lower in survivors (19 ± 29 , 18 ± 18 , 16 ± 24 mm Hg) vs. nonsurvivors (43 ± 27 , 45 ± 27 , 43 ± 34 mm Hg), respectively. It is not clear why only 27% of children with severe TBI received ICP monitoring in this study. Nevertheless, they revealed an association between ICP >20 mm Hg and mortality in a cohort of patients that were not specifically treated using an ICP target of 20 mm Hg.

A study by Cruz et al (10) reported data from 45 children with severe TBI prospectively studied using a unique protocol that targeted an ICP threshold of ≥ 15 mm Hg along with prevention of increased cerebral oxygen extraction as a surrogate marker of cerebral ischemia assessed with a jugular venous bulb catheter. The treatment protocol included sedation, fast high-dose mannitol (0.7–1.2 g/kg), barbiturates, and surgical decompression for refractory ICP >25 mm Hg. Outcome was defined using dichotomized 6-month Glasgow Outcome Scale score. ICP peaked on day 4 in both groups and was significantly ($p < .05$) higher on days 2–5 in children with unfavorable vs. favorable outcomes (6-month Glasgow Outcome Scale). 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 on days 2–5 in the unfavorable outcome group. Uncontrolled ICP >40 mm Hg occurred in the two children who died. This article is

unique in using an ICP treatment threshold of 15 mm Hg across the age spectrum in pediatric TBI, although they did not necessarily achieve that target. Nevertheless, using that threshold for treatment, favorable outcome was seen in tier analysis at a value of <19 mm Hg. Given the practicalities associated with clinical use of a numerical threshold, for the purpose of making guideline recommendations, we have categorized this study as supporting a threshold of 20 mm Hg rather than 19 mm Hg.

A study by Pfenninger and Santi (12) retrospectively reviewed data from 51 children with severe TBI and compared it with data from two historical cohorts (1994–1998 vs. 1978–83 and 1988–92). Within the more contemporary cohort, 51% of the children underwent ICP monitoring. Nonmonitored patients were not salvageable ($n = 5$), underwent immediate decompressive craniectomy for early deterioration ($n = 2$), or underwent jugular bulb venous saturation monitoring instead ($n = 17$). ICP-directed therapy included diuretics, hypertonic saline, hyperventilation, and barbiturate coma targeting an ICP of 20–25 mm Hg. Neither decompressive craniectomy nor hypothermia was used to control ICP. Mean sustained ICP ≥ 20 mm Hg was associated with poor outcome ($p < .05$) defined as a dichotomized 6- to 12-month Glasgow Outcome Scale score. Favorable outcome was observed in all eight children with maximum mean sustained ICP <20 mm Hg, eight of 15 with ICP 20–40 mm Hg, and one of three children with ICP >40 mm Hg. This study is complex in that the treatment threshold appeared to be a range of 20–25 mm Hg and suggests and ICP threshold of <20 mm Hg associated with a favorable outcome.

A study by Adelson et al (9) was a prospective multicentered randomized controlled trial of moderate hypothermia vs. normothermia plus medical management in 47 children <13 yrs of age with severe TBI. The study was unique in that the ICP treatment threshold varied with age using 15 mm Hg, 18 mm Hg, or 20 mm Hg for children 0–24 months, 25–96 months, and 97–156 months, respectively. Although this study was rated level II for assessment of effect of hypothermia, it was rated level III as evidence pertaining to ICP threshold. A contemporary guidelines-based treatment regimen was used that also included randomized treatment with or without moderate hypothermia. *Post hoc* analysis of the relationship between ICP and outcome (3-

and 6-month Glasgow Outcome Scale) was carried out with the expressed purpose (stated in the text) of addressing a gap in the pediatric TBI guidelines. That analysis examined the association between outcome and ICP from 0 to 90 mm Hg in children treated with this specific regimen. Mean ICP was lower in children with good (11.9 ± 4.7 mm Hg) vs. poor (24.9 ± 26.3 mm Hg, $p < .05$) outcome. The percent time with ICP <20 mm Hg differed significantly in the good ($90.8\% \pm 10.8\%$) vs. poor ($68.6\% \pm 35.0\%$, $p < .05$) outcome groups. ICP >20 mm Hg was the most sensitive and specific for poor outcome. Based on these findings, this study supports an ICP treatment threshold of 20 mm Hg. However, it should be recognized that hypothermia could represent an important confounder in the report. This study also represents the only study in the evidence table to guide ICP-directed treatment with age, although the impact of these age-dependent thresholds on outcome within the three age categories was not assessed.

A prospective study by Grinkeviciute et al (11) of 48 children with severe TBI who underwent ICP monitoring and ICP-directed therapy at a target of 20 mm Hg using a contemporary therapeutic regimen included decompressive craniectomy in >27% of cases. The survival rate was remarkably high at 97.9% for children admitted to the pediatric intensive care unit, although the total denominator for all severe TBI victims presenting to the emergency department was not provided. Surprisingly, differences in peak ICP (22.2 mm Hg vs. 24.6 mm Hg, respectively) in groups with favorable and unfavorable outcomes (6-month dichotomized Glasgow Outcome Scale score) were not statistically significant. Similarly, no difference between outcome groups was seen for minimal CPP. However, despite the fact that many patients had ICP >25 mm Hg, >90% of the patients had a favorable outcome and this study included only five patients with a poor outcome; thus, the statistical power to examine the relationship of raised ICP across outcomes was limited. In addition, the use of peak ICP could also limit data interpretation.

Only class III studies are available and although the studies support several different thresholds for ICP treatment, given that eight of the 11 class III studies supported a threshold of approximately 20 mm Hg, that level represents the most strongly supported value for ICP and thus

is the threshold supported as a level III recommendation. We recognize that additional studies in pediatric patients with TBI are needed to determine the optimal ICP threshold or thresholds for infants and children and also define whether or not the threshold is dependent on age, injury mechanism, computed tomography injury pattern, location of the monitor, and/or other factors.

VI. INFORMATION FROM OTHER SOURCES

A. Indications From the Adult Guidelines

There is level II evidence that treatment should be initiated at an ICP threshold of 20 mm Hg as stated in the recommendations section of the adult guidelines document (14). In addition, in the summary section of the adult guidelines, it is stated that current data support 20–25 mm Hg as an upper threshold to initiate treatment. There are no large randomized trials in adults that directly compare different ICP treatment thresholds.

In a study by Marmarou et al (15), 428 patients with severe TBI were prospectively analyzed for monitoring parameters that determined outcome and their ICP threshold values. Using logistic regression, the threshold value of 20 mm Hg best correlated with 6-month Glasgow Outcome Scale score. The proportion of hourly ICP reading >20 mm Hg was a significant independent determinant of outcome. There are small, noncontrolled studies that suggest a range of 15–25 mm Hg. In one of these studies, Saul and Ducker (16) changed the ICP threshold from 25 to 15 mm Hg in two sequentially treated groups of patients and found a decrease in mortality from 46% to 28%. In the same study by Chambers et al (4) (see evidence table; Table 1) for which we used data from pediatric patients as evidence for this document, 207 adult patients were also assessed. They had ICP and CPP monitoring, and receiver operating characteristic curves were used to determine whether there were significant thresholds for the determination of outcome. The sensitivity for ICP rose for values >10 mm Hg, but it was only 61% at 30 mm Hg. In a smaller prospective study by Ratanalert et al (17) of 27 patients grouped into ICP treatment thresholds of 20 or 25 mm Hg, there was no difference in outcome between this

narrow range of treatment threshold. Finally, in a report by Schreiber et al (18) of 233 patients with ICP monitoring analyzed prospectively, an opening ICP >15 mm Hg was identified as one of five risk factors associated with a higher mortality rate.

Any chosen ICP threshold must be closely and repeatedly corroborated with the clinical examination and computed tomography imaging in an individual patient because pupillary abnormalities occurred in patients with ICP values as low as 18 mm Hg (19).

In addition, the critical value of ICP and its interaction with CPP and with other measures (jugular venous oxygen saturation, partial pressure of brain tissue oxygen, cerebral blood flow) remains unknown. The adult guidelines conclude that because the importance of these other parameters is recognized, the absolute value of ICP may be less important (14). The relationship between partial pressure of brain tissue oxygen and ICP in children has only recently begun to be explored (20).

VII. SUMMARY

There is evidence (eight of 11 class III studies) that sustained elevations in ICP (>20 mm Hg) are associated with poor outcome in children after severe TBI, and thus the level III recommendation. What is not well established is the absolute target for ICP-directed therapy that is needed to maximize outcome since this was not specifically addressed prospectively in any of the studies reviewed. Although one of these studies was carried out in the setting of a randomized controlled trial, no randomized controlled trial has directly compared the effect of two or more thresholds for ICP-directed therapy on outcome in pediatric TBI. There are also individual poor-quality level III studies that support either lower (a range of 15–25 mm Hg) or higher (35 or 40 mm Hg) threshold values than 20 mm Hg, although thresholds <20 mm Hg do, as discussed previously, have theoretical support for infants and young children. Finally, based on the fact that normal values of blood pressure and ICP are age-dependent, it is anticipated that the optimal ICP treatment threshold may be age-dependent. However, data on this point are extremely limited; only a

single study on this topic in children that met the inclusion criteria varied the ICP treatment threshold with age using 15 mm Hg, 18 mm Hg, or 20 mm Hg for children 0–24 months, 25–96 months, and 97–156 months, respectively (9).

VIII. KEY ISSUES FOR FUTURE INVESTIGATION

- A direct comparison of two specific ICP treatment thresholds on outcome in children, particularly values <20 mm Hg.
- Investigation to determine whether threshold values for ICP-directed therapy are age-dependent.
- Determination whether or not injury mechanism (e.g., abusive head trauma) or computed tomography pattern changes the optimal ICP treatment threshold.
- Examination of physiological and biochemical surrogates (e.g., microdialysis, partial pressure of brain tissue oxygen, pressure volume index) of outcome are needed either to complement or supplant ICP-directed therapy in children.
- Assessment as to whether the treatment threshold for ICP-directed therapy changes with either time after injury or duration of intracranial hypertension.
- Investigations that better define the relative value of ICP- vs. CPP-directed therapy in pediatric TBI.

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Chapter 5. Cerebral perfusion pressure thresholds

I. RECOMMENDATIONS

Strength of Recommendations: Weak.

Quality of Evidence: Low, from poor- and moderate-quality class III studies.

A. Level I

There are insufficient data to support a level I recommendation for this topic.

B. Level II

There are insufficient data to support a level II recommendation for this topic.

C. Level III

A minimum cerebral perfusion pressure (CPP) of 40 mm Hg may be considered in children with traumatic brain injury (TBI).

A CPP threshold 40–50 mm Hg may be considered. There may be age-specific thresholds with infants at the lower end and adolescents at the upper end of this range.

II. EVIDENCE TABLE (see Table 1)

III. OVERVIEW

Global or regional cerebral ischemia is an important secondary insult to the acutely injured brain. CPP, as defined by mean arterial pressure (MAP) minus the mean intracranial pressure (ICP), is the pressure gradient driving cerebral blood flow, which, in turn, in the normal state is autoregulated and coupled with cerebral metabolic rate for oxygen. Autoregulation and coupling between cerebral blood flow and cerebral metabolic rate for oxygen may be disrupted in the brain after TBI, and a decrease in CPP may therefore induce cerebral ischemia. With the use of continuous monitoring capabilities including invasive blood pressure and ICP equipment, the CPP could be manipulated by treatment in an attempt to avoid both regional and global ischemia. The

optimal CPP threshold and therapeutic approach to achieve it both remain to be defined.

There are age-related differences in MAP, cerebral blood flow, and cerebral metabolic rate for oxygen from infancy through to adulthood. Because pediatric values are, in the main, lower than adult values, we need to know whether there are age-specific thresholds or targets for CPP that should be used during the critical care management of pediatric severe TBI.

Cerebral perfusion pressure is relatively easy to measure. The main reason for undertaking the invasive monitoring required for calculating this number is to titrate treatment using the level of each of the constituent parameters as a guide (i.e., CPP, ICP, and MAP) (1, 2). 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, particularly when it is not standardized. Theoretically, to calculate actual CPP both MAP and ICP need to be zero-calibrated to the same level. Intraparenchymal fiber-tip sensors measure ICP at the tip of the device in relation to atmospheric pressure and no adjustment is possible. When using other types of devices, it is common practice to calibrate blood pressure to the right atrium and ICP to the level of the foramen of Monro. The calculation of CPP will underestimate actual CPP by an error proportional to the distance between the two zeroing points multiplied by the sine of the angle of bed elevation. For a given bed elevation, this error increases with increasing size of the patient, and for a given size of child, this error increases with increasing bed elevation. From first principles, across the pediatric age range, at bed elevation of 30°, adolescents will have almost double the error of infants (11 vs. 6 mm Hg). At a given size, increasing the bed elevation by 30° will double the error when adolescents are compared with infants (10

vs. 5 mm Hg). The studies included as evidence for this chapter describe practice in children covering the full pediatric age range. Bed elevation is only described in two studies: at 0–30° elevation (3) and 15–30° elevation (4). The ICP monitoring devices that were used are not described in two studies (5, 6) and three studies used cerebral intraparenchymal monitoring (4, 7, 8). The reference levels for zero calibration of ICP or blood pressure are not described in any of the reports.

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. Four studies do not describe any ICP- or CPP-directed strategy in their management (5, 9–11). One study used an ICP threshold of 20 mm Hg to direct therapy (7). The other four studies used an age-related scale in threshold for CPP-directed intervention. In two studies, the lower limit of the scale that was used was 40 mm Hg (6, 8), and in the other two studies, it was 45 mm Hg (3, 4). The upper threshold in the scale was 50–70 mm Hg. It is evident from these data that low level of CPP will, therefore, also indicate failure to achieve the CPP target as well as a failure to respond to treatment. Table 2 provides a summary of the targets and treatments used in each of the studies included in the evidence table.

Third, the CPP summary statistic that is used in the analysis is different in many of the studies (Table 2). Minimum or lowest CPP during monitoring is used in four studies (5, 6, 9, 11). The other five studies report mean CPP: as an initial value (4), average in the first 24 hrs and daily for 5 days (3), or as an average for the whole period of monitoring (7, 8, 10). Another important consideration in regard to the summary statistic is whether or not preterminal data in nonsurvivors were included. Only one report describes excluding preterminal data (10); 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

Table 1. Evidence table

Reference	Study Description	Data Class, Quality, and Reasons	Results and Conclusion
Studies from previous guidelines Barzilay et al, 1988 (9)	Design: retrospective case series with analysis of minimum CPP N = 56 Age: mean age 6.2 yrs; 41 with severe TBI, 5 with central nervous system infection, and 10 miscellaneous conditions GCS: 54 cases with GCS $\leq$ 8 Purpose: patients were treated for increased or decreased CPP Protocol: CPP management protocol was not specified Outcome: survival at hospital discharge	Class III Poor quality: no control for confounders	Among 41 patients with severe TBI: CPP was 65.5 ± 8.5 mm Hg for survivors vs. 6.0 ± 3.9 mm Hg for nonsurvivors ($p < .01$)
Downard et al, 2000 (12)	Design: retrospective case series with analysis of mean hourly CPP calculation in the first 48 hrs of care N = 118 Age: mean 7.4 ± 4.6 yrs GCS: mean GCS 6 ± 3 (99 severe cases), 50% with space-occupying lesions Protocol: intracranial pressure monitors established within 24 hrs of admission Outcome: last recorded GOS in records at ≥ 3 months, and dichotomized to "good" and "poor" outcomes	Class III Moderate quality: outcome assessment methods not clearly described, otherwise met all criteria	All children with mean CPP < 40 mm Hg died 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 there was no analysis of this in the publication
Kaiser and Pfenninger, 1984 (10)	Design: retrospective case series with analysis of minimum CPP N = 24 Age: mean 6.3 yrs GCS: all with GCS < 8 , 21.5% with intracranial hemorrhage Protocol: CPP management included intubation, hyperventilation, control of body temperature, dexamethasone, barbiturates, and osmotic agents Outcome: GOS follow-up at mean 2.5 yrs (range, 1.5–4.4 yrs) after injury	Class III Poor quality: unclear if selection methods unbiased; no control for confounders	All survivors (N = 19) had minimum CPP > 50 mm Hg; 3 of the 5 children who died also had CPP > 50 mg Hg
New studies Adelson et al, 2005 (3)	Design: randomized controlled trial of hypothermia therapy with analysis of average CPP over the first 5 days of care N = 102 Age: < 17 yrs (mean age in two-part study 6.89 and 6.95 yrs) CPP management goal was targeted by age using 45–50 mm Hg, 50–55 mm Hg, and 55–60 mm Hg for children aged 0–24 months, 25–96 months, and 97–156 months (first cohort) or 97–214 (second cohort), respectively Protocol: not specified Outcome: GOS was dichotomized at 6 months after injury	Class III Poor quality: no control for confounders in CPP analysis (for hypothermia, this is a class II study)	Mean CPP on day 1 was higher in the hypothermia group (70.75 mm Hg) than the normothermia group (64.84 mm Hg), $p = .037$ There were no statistically significant differences between groups on days 2 to 5, and GOS was not assessed in relation to differences in CPP on day 1 Average CPP was 69.19 ± 11.96 mm Hg for favorable vs. 56.37 ± 20.82 mm Hg for unfavorable ($p = .0004$) outcome groups; the percent time with CPP > 50 mm Hg was $94.2\% \pm 16.9\%$ for favorable vs. $87.3\% \pm 29.5\%$ for unfavorable ($p = .0001$)
Barlow et al, 1999 (11)	Design: retrospective case series with analysis of lowest CPP N = 17 Age: 1–20 months (mean, 5.1 months) with inflicted TBI Protocol: not specified; increased intracranial pressure and decreased CPP were treated in all cases Outcome: a 6-point outcome scale assessed 3–122 months (mean, 33 months) postinjury	Class III Poor quality: no control for confounders; unclear if selection and outcome assessment measures were unbiased	Lowest CPP correlated with poor outcome ($p < .005$)

Table 1. —Continued

Reference	Study Description	Data Class, Quality, and Reasons	Results and Conclusion
Chaiwat et al, 2009 (5)	Design: retrospective case series analysis of lowest CPP in the first 72 hrs after severe TBI; a Doppler-derived cerebral blood flow autoregulatory index was also studied and calculated as percent change in estimated cerebrovascular resistance per percent change in CPP N = 36 patients (2 inflicted TBI) Age: 9.1 ± 5.3 yrs (range, 0.8–16 yrs) Protocol: when ICP was not monitored, CPP or mean arterial blood pressure was increased according to whichever following variable was greater: 1) 20% above baseline; or 2) a set value of 80 mm Hg for the group <9 yrs and 90 mm Hg for the group aged 9–16 yrs, respectively Outcome: GOS dichotomized at 6 months after discharge	Class III Moderate quality: the methods for outcome were adequate and nonbiased but the adequacy of the sample size is unclear	On univariate analysis CPP <40 mm Hg during the first 72 hrs 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
Chambers et al, 2001 (13)	Design: retrospective case series with analysis of CPP N = 84 Age: 3 months to 16 yrs (median, 10 yrs) Outcome: GOS dichotomized at 6 months	Class III Poor quality: no control for confounders; unclear if patient selection was unbiased	Poor outcome in all 8 cases with CPP <40 mm Hg; more patients had good outcome than poor outcome when mean CPP was >40 mm Hg
Figaji et al, 2009 (4)	Design: prospective case series with analysis of CPP data N = 52 Age: <15 yrs (median, <7 yrs) Protocol: patient management based on treatment recommendations in previous edition of the Pediatric Guidelines; target values for CPP were >50 mm Hg in children >2 yrs old and >45 mm Hg in children <2 yrs old Outcome: GOS was dichotomized into “favorable” and “unfavorable” outcome ≥ 6 months after injury	Class III Moderate quality: outcome assessment methods not clearly described, otherwise met all criteria	Median (interquartile range) for lowest CPP was significantly lower in unfavorable outcome patients: 29 (20–45) mm Hg vs. 44 (35–51) mm Hg, $p = .023$ Unfavorable outcome patients also had more episodes of CPP <40 mm Hg: 3 (0–10 vs. 0–1), $p = .03$ There was no difference in the number of episodes of CPP <50 mm Hg
Kapapa et al, 2010 (6)	Design: retrospective case series with analysis of CPP in relation to age-specific lower limit (up to 1 month, >40 mm Hg; 2 months up to 1 yr, >45 mm Hg; 1 yr up to 7 yrs, >50 mm Hg; >7 yrs, 55–60 mm Hg) N = 16 Age: 0–16 yrs GCS: <9 Protocol: treatment algorithm including CPP management was used Outcome: GOS was dichotomized at varied times after injury	Class III Poor quality: small sample size with inadequate case selection and outcome measures; unclear details of the regression analysis reporting the relationship between CPP and outcome	Patients with CPP value below the age-specific lower limit for just a single occurrence had a significantly worse outcome ($p = .013$)
Narotam et al, 2006 (7)	Design: prospective case series with analysis of mean CPP N = 16 Age: 1.5–18 yrs (mean, 14 yrs) GCS: 3–12 (mean, 5; 15 cases were severe) Protocol: patients were managed for prevention of cerebral ischemia with ventilation, vasopressors, respiratory treatments, etc. Outcome: GOS at 3 months after injury	Class III Poor quality: no control for confounders for GOS analysis; unclear if selection and outcome assessment methods unbiased	All survivors had good outcome; mean CPP was 81.52 ± 16.1 mm Hg for survivors vs. 50.33 ± 31.7 mm Hg for nonsurvivors ($p < .033$)

Table 1. —Continued

Reference	Study Description	Data Class, Quality, and Reasons	Results and Conclusion
Stiefel et al, 2006 (8)	Design: retrospective case series with analysis of mean daily CPP N = 6 Age: 6–16 yrs Protocol: treatment targeted age-appropriate CPP (≤ 40 mm Hg) Outcome: GOS was dichotomized at discharge	Class III Poor quality: no control for confounders, very small sample, unclear if selection methods unbiased	Mean daily CPP in survivors was 75.63 ± 11.73 mm Hg

CPP, cerebral perfusion pressure; TBI, traumatic brain injury; GCS, Glasgow Coma Scale; GOS, Glasgow Outcome Scale.

Table 2. Summary of treatments, cerebral perfusion pressure target, and cerebral perfusion pressure statistics used in studies

Reference	Treatments Used				CPP Target Strategy	CPP Statistic
	Hyperventilation	Induced Hypothermia	Barbs	Decompressive Craniectomy		
Adelson et al, 2005 (3)	No	Yes	Yes	Yes	Age-related 45 mm Hg	Mean CPP
Barlow et al, 1999 (11)	TH	TH	TH	TH	TH	Lowest CPP
Barzilay et al, 1988 (9)	Yes	Yes	Yes	No	—	Lowest CPP
Chaiwat et al, 2009 (5)	—	—	—	—	—	Lowest CPP
Chambers et al, 2001 (13)	TH	TH	TH	TH	TH	Minimum CPP
Downard et al, 2000 (12)	Yes	No	No	Yes	—	Mean CPP 48 hrs
Figaji et al, 2009 (4)	Yes	Yes	Yes	Yes	Age-related 45 mm Hg	Initial and lowest CPP
Kaiser and Pfenninger, 1984 (10)	Yes	Yes	Yes	No	—	Mean CPP
Kapapa et al, 2010 (6)	Yes	Yes	Yes	Yes	Age-related 40 mm Hg	Lowest CPP
Narotam et al, 2006 (7)	Yes	No	No	No	Intracranial pressure-related	Mean CPP
Stiefel et al, 2006 (8)	—	—	—	—	Age-related 40 mm Hg	Mean CPP

CPP, cerebral perfusion pressure.

In the studies that describe therapy: “Yes” denotes use of therapy and “No” denotes where treatment is not used. “TH” denotes where the study is aimed at defining a threshold about burden from CPP insult and outcome rather than it being an intervention study. Dashes (—) indicate where no information is given in the report.

the pediatric TBI CPP studies and applying the information to treatment strategies for TBI.

IV. PROCESS

For this update, MEDLINE was searched from 1996 through 2010 (Appendix B for search strategy), and results were supplemented with literature recommended by peers or identified from reference lists. Of 77 potentially relevant studies, eight were added to the existing table and used as evidence for this topic.

V. SCIENTIFIC FOUNDATION

Three moderate-quality class III studies and eight poor-quality class III studies about CPP met the inclusion criteria for this topic and provide evidence to support the recommendations (3–13).

A randomized controlled trial of hypothermia (32–33°C) therapy, a class II study for the evidence about hypothermia, but class III 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 (3). The study was performed in two parts: part 1, 48 cases of pediatric

TBI with Glasgow Coma Scale score ≤ 8 , aged 6.89 ± 3.46 yrs; and part 2, 27 cases of pediatric TBI with Glasgow Coma Scale score ≤ 8 , aged 6.95 ± 5.68 yrs. The authors used dichotomized Glasgow Outcome Scale 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 69.19 ± 11.96 mm Hg vs. poor outcome 56.37 ± 20.82 mm Hg ($p = .0004$). In

addition, the percent time with CPP >50 mm Hg was higher in the good outcome group: good outcome 94.2% $\pm$ 16.9% vs. poor outcome 87.3% $\pm$ 29.5% ($p = .0001$).

Five studies found higher CPP associated with better outcomes and their findings were as follows. A study by Barzilay et al (9) studied 41 consecutive TBI admissions to their pediatric intensive care unit with coma for at least 6 hrs before admission. Survivors had higher minimum CPP than nonsurvivors: 65.5 $\pm$ 8.5 vs. 6.0 $\pm$ 3.9 mm Hg, respectively ($p < .01$). A study by Figaji et al (4) 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 Glasgow Outcome Scale outcome assessed at least 6 months after injury, those with favorable outcome had lowest CPP median (interquartile range) of 44 (35–51) mm Hg vs. 29 (20–45) mm Hg in those with an unfavorable outcome ($p = .023$). A study by Narotam et al (7) analyzed data from 16 children aged 1.5–18 yrs (mean, 14 yrs), 15 of whom had Glasgow Coma Scale score ≤ 8 . All ten survivors had an excellent recovery at 3 months (Glasgow Outcome Scale score 5). Mean CPP was higher in survivors (81.52 $\pm$ 16.1 mm Hg) than nonsurvivors (50.33 $\pm$ 31.7 mm Hg, $p = .033$). A study by Stiefel et al (8) studied brain tissue oxygen monitoring in six patients (aged, 6–14 yrs, Glasgow Coma Scale score 3–7) and found mean daily CPP in the five survivors was 75.63 $\pm$ 11.73 mm Hg. Last, in a sample of TBI cases restricted to 17 young children with inflicted injury (aged 1–20 months; mean, 5.1 months), Barlow et al (11) reported that higher lowest CPP during intensive care was associated with better outcomes in a 6-point scale 3–122 months (mean, 33 months) after injury ($p = .0047$).

Four studies reported findings in relation to a threshold in CPP of 40 mm Hg. In the study reported by Figaji et al (4) (see previously), the authors found that more episodes of CPP <40 mm Hg were observed in those with an unfavorable (3 [0–10]) vs. favorable (0 [0–1]) outcome ($p = .03$). In the other study, a more complex relationship between CPP and outcome involved data from autoregulation of cerebral blood flow. A study by Chambers et al (13) analyzed 84 children aged 3 months to 16 yrs (median, 10 yrs) and examined minimum CPP in relation

to dichotomized Glasgow Outcome Scale at 6 months. Sixty-three of 76 cases with CPP >40 mm Hg had good outcome and all eight cases with CPP <40 mm Hg had a poor outcome ($p < .0001$, Fisher's exact test). A study by Downard et al (12) analyzed 118 pediatric TBI cases aged up to 15 yrs (mean age, 7.4 yrs; 99 cases with Glasgow Coma Scale score 3–8) and reported dichotomized Glasgow Outcome Scale score at 3 months or later in relation to CPP thresholds. Seventy-two of 96 patients with CPP >40 mm Hg had a good outcome, whereas all 22 cases with CPP <40 mm Hg died. The difference in mortality was statistically significant ($p < .0001$, Fisher's exact test). A study by Chaiwat et al (5) analyzed 36 cases of TBI for predictors of poor outcome. ICP of >20 mm Hg and CPP <40 mm Hg during the first 72 hrs were not associated with outcome. However, on logistic regression, an estimate of impaired cerebral blood flow autoregulation using Doppler ultrasonography—the autoregulatory index—was an independent predictor of poor outcome (adjusted odds ratio, 23.1; 95% confidence interval, 1.9–279.0). Impaired autoregulatory index was an independent risk factor when the authors entered CPP <40 mm Hg, systolic blood pressure lower than the fifth percentile for age and gender during the first 72 hrs after TBI, low middle cerebral artery velocity, and impaired autoregulatory index into the model (adjusted odds ratio, 29.8; 95% confidence interval, 1.7–521.4). Because autoregulatory index is calculated as the percent change in cerebrovascular resistance per percent change in CPP, and cerebrovascular resistance is defined as the ratio of CPP to middle cerebral artery velocity, it is impossible to disentangle the relationship between outcome and CPP. Autoregulatory index represents a research tool.

Five class III studies contain data concerning CPP threshold >40 mm Hg. Two retrospective case series support the idea that there may be an age-related CPP threshold >40 mm Hg. A study by Kapapa et al (6) analyzed 16 children aged <16 yrs and reported dichotomized Glasgow Outcome Scale in relation to age-specific lower limits in CPP (i.e., >40 mm Hg, infants up to 1 month; >45 mm Hg, infants aged 2 months to 1 yr; >50 mm Hg, children aged between 1 and 7 yrs; 55–60 mm Hg, children aged >7 yrs). The authors found that patients with CPP values below the age-specific lower limit for just a single occurrence had a

significantly worse outcome ($p = .013$). A study by Kaiser and Pfenninger (10) reported findings in 24 consecutive admissions to their pediatric intensive care unit of patients with a Glasgow Coma Scale score <8, average age = 6.3 yrs (ten patients between 1 and 5 yrs) and showed that all survivors had CPP >50 mm Hg ($p < .005$, Fisher's exact test). The two remaining studies in this group of four did not observe a threshold >40 mm Hg. In the study reported by Figaji et al (4) (see previously), the authors also reported outcome in relation to the number of episodes during monitoring that CPP was <50 mm Hg; there was no difference in the number episodes in those with an unfavorable (8 [2–18.5]) vs. favorable (3 [0–8.8]) outcome ($p = .137$). Of note, two-thirds of the children in this series were <8 yrs. As discussed, in the study reported by Downard et al (12), 100% of children with mean CPP <40 mm Hg died as compared with only 25% of children who had a CPP >40 mm Hg. The difference in mortality was statistically significant ($p < .0001$, Fisher's exact test). Last, in the study of young children with inflicted TBI reported by Barlow et al (11) (see previously), only one infant in the series of 17 had the lowest CPP of >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.

VI. INFORMATION FROM OTHER SOURCES

A. Indications From the Adult Guidelines

In adults, with respect to CPP, it appears that the critical threshold for cerebral ischemia generally lies in the region of 50–60 mm Hg and can be further delineated in individual patients by ancillary monitoring (14). It is becoming increasingly apparent that elevating the CPP through pressors and volume expansion is associated with serious systemic toxicity, may be incongruent with frequently encountered intracranial conditions, and is not clearly associated with any benefit in terms of general outcome.

A study by Clifton et al (15) was a *post hoc* analysis of the data on CPP within the data set from 392 patients in the randomized controlled trial of therapeutic hypothermia for severe TBI. When they analyzed individual predictive variables separately, they found CPP of <60 mm Hg to be associated with an increased proportion of patients with poor outcome. They found similar associations for ICP >25 mm Hg, MAP <70 mm Hg, and fluid balance <−594 mL. When these variables were combined into a stepwise logistic regression model, however, low CPP had no effect on outcome, although the other three variables remained within the group of most powerful variables in determining outcome. Based on a purely pragmatic assessment of these data, the authors noted that a CPP target threshold should be set approximately 10 mm Hg above what is determined to be a critical threshold to avoid dips below the critical level (15). The overall assessment of the adult CPP guidelines therefore suggests “a general threshold in the realm of 60 mm Hg, with further fine-tuning in individual patients based on monitoring of cerebral oxygenation and metabolism and assessment of the status of pressure autoregulation” (14).

The adult guidelines state that there are insufficient data to support a level I recommendation for this topic. Under “Options,” it states the following: aggressive attempts to maintain CPP >70 mm Hg with fluids and pressors should be avoided because of the risk of adult respiratory distress syndrome; CPP of <50 mm Hg should be avoided; and CPP values to target lie within the range of 50–70 mm Hg. Patients with intact pressure autoregulation tolerate higher CPP values and ancillary monitoring of cerebral parameters including blood flow, oxygenation, or metabolism may facilitate CPP management.

VII. SUMMARY

Survivors of severe pediatric TBI undergoing ICP monitoring consistently have higher CPP values vs. nonsurvivors, but no study demonstrates that active maintenance of CPP above any target threshold in pediatric TBI reduces mortality or morbidity. In comparing the

findings from pediatric and adult TBI studies, there does appear to be an age-related difference in CPP threshold. Whether these differences are the result of differences in measurements, goal in CPP management, or the makeup in age range of the small numbers in the pediatric studies remains unclear. CPP should be determined in a standard fashion with ICP zeroed to the tragus (as an indicator of the foramen of Monro and midventricular level) and MAP zeroed to the right atrium with the head of the bed elevated 30°.

VIII. KEY ISSUES FOR FUTURE INVESTIGATION

- A standard method for measuring CPP level and duration and reporting data would be useful across pediatric TBI studies that focus on targeting CPP.
- Multimodal neuromonitoring studies to help determine the relationships between CPP and autoregulation and between CPP and ischemia in individual patients.
- Controlled, prospective, randomized studies in children to determine optimal level of CPP based on ischemia monitoring in various pediatric age groups and mechanisms of injury.
- Long-term (>1 yr), age-appropriate functional outcome studies to assess the relative importance of ICP- and CPP-targeted therapies as well as analyses evaluating outcomes in relation to treatment responders and nonresponders.
- Studies to determine whether a CPP target threshold set above (e.g., 10 mm Hg) what is determined to be a critical threshold could avoid dips below the critical CPP level.

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Chapter 6. Advanced neuromonitoring

I. RECOMMENDATIONS

Strength of Recommendation: Weak.

Quality: Low, from one moderate- and one poor-quality class III study.

A. Level I

There are insufficient data to support a level I recommendation for this topic.

B. Level II

There are insufficient data to support a level II recommendation for this topic.

C. Level III

If brain oxygenation monitoring is used, maintenance of partial pressure of brain tissue oxygen (P_{btO_2}) ≥ 10 mm Hg may be considered.

II. EVIDENCE TABLE (see Table 1)

III. OVERVIEW

Children with severe traumatic brain injury (TBI) frequently have abnormal cerebral hemodynamics, including intracranial hypertension, cerebral hypoxia, delayed and/or altered processing of electrophysiological signals, and impaired cerebral autoregulation. In addition to intracranial pressure (ICP) monitoring, advanced neuromonitoring techniques such as microdialysis, electrophysiological assessments, and examination of cerebral autoregulation may help identify and treat patients with these derangements after TBI. The development of advanced monitoring systems to provide information regarding both cerebrovascular and metabolic function after TBI is critical to providing optimal neurocritical care. If treatment preventing unwanted cerebral pathophysiological processes is shown to improve outcome in children with severe TBI, the use of monitoring systems, beyond ICP monitoring, will mark an important advance in the care of patients with TBI. Advanced neuromoni-

tors may provide useful information about derangements in cerebral oxygenation, blood flow and metabolism, autoregulation, and function after severe pediatric TBI.

IV. PROCESS

For this new topic, MEDLINE was searched from 1950 through 2010 (Appendix B for search strategy), and results were supplemented with literature recommended by peers or identified from reference lists. Of 44 potentially relevant studies, two were included as evidence for this topic.

V. SCIENTIFIC FOUNDATION

Two class III publications met the inclusion criteria for this topic and provide evidence to support the recommendations on the use of advanced neuromonitoring in this chapter are for patients with no contraindications for neuromonitoring such as coagulopathy (brain oxygenation) and for patients who do not have a diagnosis of brain death.

In 2009, a study by Figaji et al (1) reported the relationship between P_{btO_2} and long-term outcome in 52 children with severe TBI. Patients with compromised P_{btO_2} were treated to a threshold ≥ 20 mm Hg. Overall mortality was nearly 10%. After considering other conventional predictors, authors reported that $P_{btO_2} < 5$ mm Hg for > 1 hr or < 10 mm Hg for > 2 hrs were associated with a significantly increased risk of unfavorable outcome (Glasgow Outcome Scale and Pediatric Cerebral Performance Category scores) and mortality, independent of other factors that were also significant (e.g., ICP, cerebral perfusion pressure, Glasgow Coma Scale, computed tomography classification, and systemic hypoxia). This study provided no comparison group. All patients with compromised P_{btO_2} were treated to maintain the targeted threshold, and at the same time they may have received various treatments depending on other physiological variables such as ICP, cerebral perfusion pressure, systemic oxygen, and hemoglo-

bin. What can be inferred is that in this sample of patients, those with higher P_{btO_2} and fewer episodes of $P_{btO_2} < 10$ mm Hg had better outcomes. We cannot say that this relationship is a direct response to treatment.

In 2006, a study by Narotam et al (2) described changes in P_{btO_2} in relation to changes in cerebral perfusion pressure, F_{iO_2} , and P_{aO_2} in 15 children ranging from 1.5 to 18 yrs and Glasgow Coma Scale score ≤ 8 . Like with the previous study, patients were managed to maintain a P_{btO_2} level ≥ 20 mm Hg. In addition, the authors aimed to assess a treatment protocol (Critical Care Guide) for manipulation of physiological factors that influence oxygen delivery to the brain. Survival was associated with normal initial P_{btO_2} (≥ 10 mm Hg). There was no difference in the mean initial P_{btO_2} among the ten survivors and six deaths at 3 months. Final P_{btO_2} in survivors was higher than that in nonsurvivors (mean P_{btO_2} , 22.7 ± 9.05 vs. 7.2 ± 7.85 mm Hg; $p = .0045$). However, only six patients had elevated ICP, making the relationship between ICP and P_{btO_2} difficult to interpret. Like with the previous study, we cannot infer from this study that response to treatment influenced outcome.

In these two studies, a treatment threshold for P_{btO_2} of 20 mm Hg was used; however, they both reported an association between unfavorable outcome and $P_{btO_2} < 10$ mm Hg. Although the study by Figaji et al (1) reported an even stronger association between $P_{btO_2} < 5$ mm Hg and unfavorable outcome, until proven otherwise, if this advanced monitoring modality is used, it would be prudent to target the more conservative threshold of > 10 mm Hg.

VI. INFORMATION FROM OTHER SOURCES

Several articles on advanced neuromonitoring in the pediatric TBI literature were identified in the search but excluded from the evidentiary table because they simply described use of a given advanced neuromonitoring device rather than targeting a treatment value for that monitor (i.e., a threshold parameter on

Table 1. Evidence table

Reference	Study Description	Data Class, Quality, and Reasons	Results and Conclusion
New studies			
Figaji et al, 2009 (1)	Design: prospective cohort N = 52 Age: 6.5 ± 3.4 yrs (9 months to 14 yrs) Protocol: treatment protocol was used in patients with compromised PbtO ₂ to manage to a threshold ≥20 mm Hg Purpose: to examine the relationship between factors, including PbtO ₂ , and outcome Outcome: mortality; 6 months Glasgow Outcome Scale score and Pediatric Cerebral Performance Category	Class III Moderate quality: unclear if outcome assessment was unbiased	PbtO ₂ <5 mm Hg for >1 hr or PbtO ₂ <10 mm Hg for >2 hrs were independently associated with higher risk of unfavorable outcome defined as severe disability or death (adjusted odds ratio, 27.4; 95% confidence interval, 1.9–391), independent of other significant factors such as intracranial pressure, computed tomography, low PaO ₂ , and cerebral perfusion pressure PbtO ₂ <5 mm Hg for >1 hr or PbtO ₂ <10 mm Hg for >2 hrs were independently associated with mortality (adjusted odds ratio 26.8; 95% confidence interval, 2.7–265)
Narotam et al, 2006 (2)	Design: prospective case series N = 16 Age: 14 yrs (range, 1.5–18 yrs) Glasgow Coma Scale: 3–12; 15 children had Glasgow Coma Scale ≤ 8 Protocol: patients with low PbtO ₂ were managed to a threshold ≥20 mm Hg Purpose: to direct treatment based on initial PbtO ₂ and to examine the effect of a critical care guide to treat low oxygen delivery Outcome: 3-month mortality	Class III Poor quality: unclear if sample selection was unbiased; unclear if outcome assessment was unbiased; no control for confounders for mortality outcome	None of the patients with normal initial PbtO ₂ (≥10 mm Hg) died There was no difference in the mean initial PbtO ₂ among the 10 survivors and 6 deaths (measured at 3 months) (16.07 ± 18.7 vs. 6.76 ± 6.69 mm Hg, <i>p</i> = .247) Final PbtO ₂ in survivors was higher than that in nonsurvivors (mean PbtO ₂ , 25.0 ± 11.57 vs. 8.53 ± 11.0 mm Hg; <i>p</i> = .01)

PbtO₂, partial pressure of brain tissue oxygen.

the advanced monitoring device was not specifically manipulated). Given that this guidelines document is focused on treatment, for these reports, a treatment recommendation regarding the monitoring device could not be given. The devices in those studies included brain microdialysis (3), cerebral blood flow and autoregulation monitors (4–7), signal processing of hemodynamic and hydrostatic signals (8), and jugular venous oxygen saturation monitoring (9).

A. Indications From the Adult Guidelines

Evidence from the adult guidelines (10) supported a level III recommendation for use of jugular venous saturation and PbtO₂ monitoring, in addition to standard ICP monitors, in the management of adults with severe TBI. Evidence suggests that episodes of jugular venous desaturation (saturation <50%) are associated with poor outcome and that this value represents a treatment threshold when using this monitoring technique. Similarly, low values of PbtO₂ (<15 mm

Hg) and the extent of their duration (>30 mins) are associated with high rates of mortality and that 15 mm Hg represents a treatment threshold value for PbtO₂. However, the accuracy of jugular venous saturation and PbtO₂ monitoring was not evaluated. Although many technologies including cerebral microdialysis, thermal diffusion probes, transcranial Doppler, and near-infrared spectroscopy were recognized to hold promise in advancing the care of adults with severe TBI, there was insufficient evidence to comment on the use of these advanced neuromonitors in this population.

VII. SUMMARY

Overall, advanced neuromonitors have been subjected to very limited clinical investigation in pediatric TBI, particularly study of their use specifically to guide therapy. Most of the medical literature on these agents is composed of observational studies on relatively small numbers and case series receiving some form of local standard TBI care. The lack of sufficient high-quality pediatric stud-

ies limits the conclusions that can be made and differences between study centers in the treatment of TBI and inpatient populations limit the generalizability of findings.

VIII. KEY ISSUES FOR FUTURE INVESTIGATION

- Examine critical thresholds for each neuromonitoring modality and determine the risk-benefit ratio, cost-effectiveness, comparative effectiveness, and impact of neuromonitors on patient long-term functional outcomes.
- Address issues of single vs. multimodal neuromonitoring, reliability of technology, optimal combination of monitors, location of neuromonitor vs. site of injury (hemispheric, pericontusional), relationship between neuromonitor data and imaging data, neuromonitor use for optimization of treatment and patient

prognosis as well as optimal duration of advanced monitoring.

- Evaluate the role of advanced neuromonitoring on clinical decision-making and patient outcomes.
- Develop additional bedside and non-invasive advanced neuromonitors.

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Chapter 7. Neuroimaging

I. RECOMMENDATIONS

Strength of Recommendation: Weak.

Quality of Evidence: Low from one poor-quality class III study.

A. Level I

There are insufficient data to support a level I recommendation for this topic.

B. Level II

There are insufficient data to support a level II recommendation for this topic.

C. Level III

In the absence of neurologic deterioration or increasing intracranial pressure (ICP), obtaining a routine repeat computed tomography (CT) scan >24 hrs after the admission and initial follow-up study may not be indicated for decisions about neurosurgical intervention.

II. EVIDENCE TABLE (see Table 1)

III. OVERVIEW

Early neuroimaging has assumed an increasingly important role in evaluating the extent and severity of traumatic brain injury (TBI) in children (1). CT is important for the rapid detection of different types of intracranial injury including extra-axial hemorrhage (e.g., subdural or epidural hematomas), acute hydrocephalus, fractures, or other intracranial lesions that may require acute neurosurgical intervention. The early use of CT is also useful for triage of patients to detect those who are likely to need neurosurgery, require management in an intensive care unit vs. general hospital setting as well as those who can be safely discharged from the emergency department and managed at home. Although magnetic resonance imaging (MRI) sensitivity is understood to be superior to CT for intracranial evaluation, it is not as easily

obtained acutely after injury and has not been as widely validated in large studies, particularly regarding influence on management decisions. At the current time, there is little evidence to support the use of MRI in influencing management of patients with severe TBI.

It is understood that acute CT imaging is universally performed in the developed world for patients with severe TBI. Two studies (2, 3) show that children with severe TBI have a high incidence of intracranial injury on CT scan (75% and 62%, respectively). In these studies, intracranial injury included brain contusion, extracerebral hematoma, intracerebral hematoma, diffuse axonal injury, acute brain swelling, penetrating cranio-cerebral injury, pneumocephalus, subarachnoid hemorrhage, alterations to cisterns, midline shift, or fractures. Neither study included treatment-related outcome data related to the findings on CT scan and thus could not be used as specific evidence for this guideline.

Although CT is always obtained acutely in patients with severe TBI, the use of two or more CT studies is not agreed on. 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) (4). Studies have reported delayed or progressive lesions in 1% to 50% of adult/pediatric patients with TBI (5). Because epidural hematoma/subdural hematoma requiring surgical intervention can develop hours to days after the acute injury, some investigators have suggested that a follow-up CT scan be routinely acquired at 1–3 days postinjury even when clinical deterioration is not evident under the assumption that early diagnosis prompts early intervention leading to a better long-term outcome (4). However, because children with severe TBI are medically unstable and (if portable CT is not available) may further deteriorate during transport to the CT scanner (hemodynamic instability, increased ICP, oxygen desaturation), the decision to order a repeat scan is a treatment decision,

weighing the knowledge gained against the risk of additional secondary brain injury. Likewise, because of the long-term effects of CT radiation exposure (lifetime risk of fatal cancer resulting from one head CT in a 1-yr-old child is as high as one in 1500), the neurosurgical decision to order a CT scan also should be considered a treatment decision, weighing the knowledge gained against the risk of long-term radiation exposure (6). This guideline addressed the issue of the value of routinely acquiring repeat CT scans in children with severe TBI.

IV. PROCESS

For this new topic, MEDLINE was searched from 1950 through 2010 (Appendix B for search strategy), and results were supplemented with literature recommended by peers or identified from reference lists. Of 120 potentially relevant studies, one was included as evidence for this topic.

V. SCIENTIFIC FOUNDATION

One class III study met the inclusion criteria for this topic and provides evidence to support the recommendation (7).

A retrospective study of 40 children with severe TBI (Glasgow Coma Scale score <8, age 2 months to 17 yrs; US, January 1990 to December 2003) examined whether serial CT scans led to urgent neurosurgical operative intervention (7). Entry criteria also included ICP monitoring during hospitalization, no craniotomy at admission to study, and at least a second CT scan within the first 48 hrs. 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 (4.3%) patients had a surgical intervention based on the results of the serial CT scan (one epidural hematoma, craniotomy; one subdural hemorrhage, burr hole; three for additional ventriculostomy placements). All five scans were ordered based on a clinical indicator (ICP or neurologic status), not as routine follow-up. The au-

Table 1. Evidence table

Reference	Study Description	Data Class, Quality, and Reasons	Results and Conclusion
New study Figg et al, 2006 (7)	Design: case series N = 40 942 screened Age: mean 9.6 yrs (SD 4.4) Glasgow Coma Scale score: Mean 5.1 (SD 1.5) Purpose: Examined whether serial computed tomography scans lead to urgent neurosurgical operative intervention	Class III Poor quality: no control for potential confounders	Serial scans after the admission and initial follow-up study (N = 115 scans) showed: no change (53%), improvement (34%), or worsening (13%) Five (4.3%) patients had a surgical intervention based on findings from the serial computed tomography scans; however, all five scans were ordered as a result of clinical indicators (intracranial pressure or neurologic status), not as routine follow-up

thors recommended that a highly selective approach to ordering serial CT scans should be practiced with the understanding that only scans ordered for increased ICP or neurologic change are likely to lead to surgical interventions.

VI. INFORMATION FROM OTHER SOURCES

Several additional studies had data regarding the value of acquiring a second CT scan in children with severe TBI but none had information regarding treatment-related outcomes and therefore could not be included as evidence for this guideline. One retrospective cohort study of 521 pediatric patients with TBI who met inclusion criteria from a total of 8505 blunt trauma admissions (1994–2003) described the prevalence of worsening brain injury on repeat CT, predictors of worsening CT findings, and the frequency of neurosurgical intervention after the repeat CT (4). Potential predictors of worsening CT findings and neurosurgical intervention were recorded by chart review. Logistic regression and recursive partitioning were used to identify predictors. Patients were grouped into three categories (moderate/severe, mild, all TBI). In the moderate/severe group (n = 252), 202 (80%, mean Glasgow Coma Scale score 3.7) had severe and 50 (20%, Glasgow Coma Scale score 10.5) had moderate injury. For children with severe TBI, the multivariate adjusted odds ratio for worsening or new second CT findings was 2.4 (95% confidence interval, 1.6–3.8). Children with moderate/severe head injuries, especially if they had intracranial injury, were more likely to have deteriorating CT findings (107 of 248 [43%]) and of these children, 4% (n = 11) required surgery. In contrast,

141 (57%) had stable CT scans and only 2% (n = 4) required surgery. In most surgical patients, repeat CT was preceded by rapid decline in neurologic status or elevated ICP. Four clinical factors were identified for stratifying risk of worsening brain injuries on repeat CT (normal initial CT scan, abnormal initial CT scan, moderate or severe head injury by Glasgow Coma Scale, and coagulopathy). This method identified 100% of patients who underwent surgery and 89% of patients who had worsening brain injuries on repeat CT.

Another retrospective study of 173 consecutive children (ages 8 months to 16 yrs; mean 7.1 yrs) with severe (83%) or moderate (17%) TBI (mean Glasgow Coma Scale score of 6.8 ± 2.1) assessed the yield of a routine predetermined repeat CT scan within 24–36 hrs (5). Forty-seven (27%) of the second CT scans showed new lesions including six with intracranial hypertension, 17 cases of worsening brain edema, and 18 newly diagnosed brain contusions. None of these findings necessitated surgical intervention or any change in therapy. Of the 67 patients who underwent a third CT scan, two cases required surgical intervention because of new findings on the third CT. The authors stated that a second routine prescheduled head CT scan within 24–36 hrs after admission in pediatric patients with moderate to severe head trauma is unlikely to yield any change in therapy. Clinically oriented and ICP-directed CT scans may better select and diagnose patients who require changes in therapy, including surgery.

Another retrospective study of 351 children with severe TBI who had two or more CT scans within 72 hrs of admission found that 41% had delayed and progres-

sive lesions (3). The decision to repeat the scan was based on clinical judgment and although the morbidity and mortality of these patients were worse, the rate of surgical intervention or change in therapy after the second CT was not reported; hence, the yield of the imaging is unknown. Injury progression correlated with the severity of the initial head trauma, presence of extracranial injury, and the presence of coagulopathy on admission.

VII. SUMMARY

One study met the criteria for inclusion as evidence for this topic given that we required that publications about imaging link the assessment to a treatment decision and the decision to an outcome. Our level III recommendation, based on one class III study, questions the use of repeat CT scans in the absence of neurologic deterioration or increasing ICP.

VIII. KEY ISSUES FOR FUTURE INVESTIGATION

There is a dearth of information regarding the use of neuroimaging in directing targeted therapies and stratification. Although MRI is being used more frequently in the acute evaluation of children with TBI, particularly for suspected abusive head trauma, most of the literature is directed at evaluating diagnostic sensitivity or outcome prediction. It is also known that advanced MRI techniques provide unique information about brain function that is not available by CT, but it remains uncertain how this information can alter management or improve treatment-related outcomes. Adult TBI literature also suggests that patterns of injury on neuroimaging may be helpful

for improving stratification of injury severity and therefore aid in selecting patients for targeted treatment. Important questions to address are:

- Do patterns of injury (from findings provided by multimodality neuroimaging) improve accuracy of injury stratification?
- Does MRI provide added value to CT in influencing management of children with severe TBI?
- What is the use of neuroimaging (CT, MRI, etc.) in directing targeted therapies and improving treatment-related outcomes?
- What is the use of repeat neuroimaging in special settings, such as in patients

who cannot be examined or in the presence of coagulopathy?

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Chapter 8. Hyperosmolar therapy

I. RECOMMENDATIONS

Strength of Recommendations: Weak.
Quality of Evidence: Moderate, based on two moderate-quality class II studies and one poor-quality class III study.

A. Level I

There are insufficient data to support a level I recommendation for this topic.

B. Level II

Hypertonic saline should be considered for the treatment of severe pediatric traumatic brain injury (TBI) associated with intracranial hypertension. Effective doses for acute use range between 6.5 and 10 mL/kg.

C. Level III*

Hypertonic saline should be considered for the treatment of severe pediatric TBI associated with intracranial hypertension. 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 intracranial pressure (ICP) <20 mm Hg should be used. Serum osmolality should be maintained <360 mOsm/L.

*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.

II. EVIDENCE TABLE (see Table 1)

III. OVERVIEW

Hyperosmolar Therapy for Intracranial Hypertension

Intravenous administration of hyperosmolar agents was shown to reduce ICP early in the 20th century (1). A study by Wise and Chater (2) introduced mannitol into clinical use in 1961. Despite widespread use of a number of osmolar agents

(mannitol, urea, glycerol) up until the late 1970s (2), mannitol gradually replaced other hyperosmolar agents in the management of intracranial hypertension. Subsequently, hypertonic saline was introduced and now both are used in contemporary management of intracranial hypertension. In recent studies of hyperosmolar therapy use in pediatric TBI, euvolemia rather than dehydration has been the general therapeutic target based on fluid balance and/or central venous pressure monitoring, and a Foley catheter is routinely used in these patients to quantify urine output and avoid bladder rupture.

The use of hyperosmolar therapy in the management of pediatric severe TBI is a topic in which there was investigation shortly before the 2003 pediatric guidelines, notably studies focused on the use of hypertonic saline for raised ICP (3–5). However, since those guidelines, no new study on hyperosmolar therapy met the inclusion criteria for this guideline.

Mannitol

Mannitol is commonly used in the management of raised ICP in pediatric and adult TBI (6). In a practice survey in the United Kingdom in 2001, it was reported to be used in 70% of pediatric intensive care units, and recently, even in infants with severe TBI, mannitol was reported to be the second most common therapeutic intervention, surpassed only by intubation (7). Despite this fact, mannitol has not been subjected to controlled clinical trials vs. placebo, other osmolar agents, or other therapies in children. Most of the investigations on the use of mannitol have focused on the treatment of adults (8–21). Either children were excluded or the composition or outcome of the pediatric trial was not defined (8–24).

Mannitol can reduce ICP by two distinct mechanisms. Mannitol at 1 g/kg has been shown to reduce ICP by reducing blood viscosity. This effect is immediate and results from a viscosity-mediated reflex vasoconstriction (intact autoregulation), which allows cerebral blood flow to be maintained despite a reduced level of cerebral blood volume (17, 25–27). Thus, cerebral blood volume and ICP both decrease. The effect of

mannitol administration on blood viscosity is rapid but transient (<75 mins) (17). Mannitol administration also reduces ICP by an osmotic effect, which develops more slowly (over 15–30 mins), as a result of the gradual movement of water from the brain parenchyma into the systemic circulation. The effect persists up to 6 hrs and requires an intact blood–brain barrier (28, 29). Mannitol may accumulate in injured brain regions (30), where a reverse osmotic shift may occur with fluid moving from the intravascular compartment into the brain parenchyma, possibly increasing ICP. This phenomenon has been suggested to occur when mannitol is used for extended periods of time (31). The gap between serum and cerebrospinal fluid (CSF) osmolality decreased below baseline in some adult patients treated with mannitol for >48–60 hrs (18). Mannitol possesses antioxidant effects (32), but the contribution of this mechanism to its overall efficacy is unclear.

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 osmolality levels >320 mOsm in adults (33–35). However, the literature supporting this finding is limited in scope and was generated at a time when dehydration therapy was common. A euvolemic hyperosmolar state generally is targeted with contemporary care.

Hypertonic Saline

In the initial description in 1919 of the reduction in ICP by intravenous administration of hyperosmolar agents, hypertonic saline was the agent used (1). Its use in the treatment of increased ICP, however, failed to gain clinical acceptance. Resurgence in interest in this treatment resulted from the report of Worthley et al (36), who described two cases in which hypertonic saline (small volumes of an extremely hypertonic solution, approximately 29% saline) reduced refractory ICP elevations. In the last decade, many have studied the use of small volume hypertonic saline in resuscitation

Table 1. Evidence table

Reference	Study Description	Data Class, Quality, and Reasons	Results and Conclusion
Studies from previous guidelines			
Fisher et al, 1992 (3)	Design: randomized controlled crossover trial N = 18 Age: mean 8.3 yrs (range, 0.6–14.5 yrs) Protocol: comparison of 3% saline (sodium 513 mEq/L, 1027 mOsm/L) and 0.9% saline (308 mOsm/L); doses of each agent were equal and ranged between 6.5 and 10 mL/kg in each patient Purpose: comparison of effect on ICP over 2 hrs exposure Outcome: ICP	Class II Moderate quality: randomization and allocation concealment methods not reported; crossover study lacking reporting on first-period comparison of baseline characteristics; small sample size	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 approximately 7 mEq/L after 3% saline
Peterson et al, 2000 (4)	Design: retrospective chart review N = 68 Age: mean 7.8 ± 3.6 yrs Protocol: use of a continuous infusion of 3% hypertonic saline (513 mEq/L, 1027 mOsm/L) titrated to reduce ICP ≤ 20 mm Hg; doses of $0.1\text{--}1.0\text{ mL}\cdot\text{kg}^{-1}\cdot\text{hr}^{-1}$ resulting in mean daily dosages between approximately 11 and $27\text{ mL}\cdot\text{kg}^{-1}\cdot\text{day}^{-1}$ were used Purpose: assess effect of continuous infusion of hypertonic saline on acute and long-term outcome Outcome: ICP, 6-month Glasgow Outcome Scale score	Class III Poor quality: no control for confounders	Survival rate was higher than expected based on Trauma and Injury Severity Score (41 predicted, 58 actual) 53% had good outcome, 20% moderate, 10% severe, 0.1% vegetative, and 15% died; 3 died of uncontrolled ICP No patients developed renal failure Central pontine myelinolysis, subarachnoid hemorrhage, or rebound increases in ICP were not observed
Simma et al, 1998 (5)	Design: randomized controlled trial N = 35 Age: mean 87 months (± 42 ; range, 12–173 months) Protocol: comparison of hypertonic saline vs. lactated Ringer's solution Purpose: comparison of 1.7% hypertonic saline (sodium 268 mmol/L, 598 mOsm/L) vs. lactated Ringer's solution (sodium 131 mmol/L, 277 mOsm/L) as a continuous infusion for maintenance fluid administration over a 3-day exposure Outcome: ICP, cerebral perfusion pressure, need for other interventions, fluid requirements, intensive care unit stay, survival rate	Class II Moderate quality: not blinded, insufficient power	There was 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 solution to maintain ICP control ($p < .01$) The hypertonic saline treatment group had shorter length of intensive care unit stay ($p = .04$), shorter duration of mechanical ventilation ($p = .10$), and fewer complications than the lactated Ringer's-treated group ($p = .09$ for two or more complications, not significant, without p value reported for one complication)

ICP, intracranial pressure.

of hemorrhagic shock and polytrauma with or without TBI in experimental models and in adult humans (37–42). However, the recent National Institutes of Health-funded resuscitation outcomes consortium trial of hypertonic saline in TBI resuscitation in adults was stopped for futility after enrollment of 1073 patients (43).

Like mannitol, the penetration of sodium across the blood–brain barrier is low (39). Sodium thus shares both the favorable rheologic and osmolar gradient effects involved in the reduction in ICP by several theoretical beneficial effects including restoration of normal cellular resting membrane potential and cell volume (44, 45), stimulation of arterial na-

triuretic peptide release (46), inhibition of inflammation (39), and enhancement of cardiac output (47). Possible side effects of hypertonic saline 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 (39).

Much higher levels of serum osmolarity (approximately 360 mOsm) may be tolerated in children when induced with hypertonic saline (4, 48) vs. mannitol, although one recent report suggested increases in serum creatinine in children treated with hypertonic saline when serum sodium concentration was allowed

to increase to >160 mmol/L (49). However, the recommendation of an upper safety threshold of 360 mOsm/L for hypertonic saline (in the 2003 pediatric TBI guidelines) (50) was viewed as the item that generated the greatest disagreement among 194 physicians treating pediatric patients with TBI in a recent survey (51).

In 14 adults with severe TBI, a study by Lescot et al (11) suggested important differences in the response of contused vs. noncontused brain tissue to hypertonic saline with reductions in the volume of noncontused brain but increases in the volume of contusions after treatment. Studies of regional effects of hyperosmolar therapy have not been carried out in pediatric TBI.

A second use of hypertonic saline is to treat hyponatremia resulting from cerebral salt wasting (CSW) if it develops in pediatric patients after TBI. Hyponatremia can result in cell swelling and seizures, both of which can compromise the injured brain (52). Hyponatremia in pediatric TBI can result from several mechanisms including CSW, the syndrome of inappropriate antidiuretic hormone secretion, sodium losses (from renal, CSF drainage, or other sources), or iatrogenic causes. It can manifest between 48 hrs and 11 days after injury, and the mechanistic underpinnings appear to involve increases in atrial natriuretic peptide (53, 54). Confirmation of the diagnosis is essential because management of CSW can differ greatly from the syndrome of inappropriate antidiuretic hormone or other causes of hyponatremia (55). The diagnosis is made by demonstrating hyponatremia and increased urine sodium concentration in the face of polyuria and hypovolemia (56). Dramatic examples of CSW in pediatric TBI show profound hyponatremia (serum sodium as low as 98 mmol/L) and marked polyuria (≥ 15 mL/kg/hr) requiring large volumes of combinations of 0.9% and 3.0% saline to match urinary losses and address the hyponatremia (53, 54). Some have suggested to limit the rate of correction of serum sodium concentration to <12 mmol/L per day (50) related to concerns about myelinolysis. The optimal rate of correction of hyponatremia in a child with severe TBI is unclear.

IV. PROCESS

For this update, MEDLINE was searched from 1996 through 2010 (Appendix B for search strategy), and results were supplemented with literature recommended by peers or identified from reference lists. Of 35 potentially relevant studies, no new studies were added to the existing table and used as evidence for this topic.

V. SCIENTIFIC FOUNDATION

Two class II studies (3, 5) and one class III study (4) met the inclusion criteria for this topic and provide evidence to support the recommendations.

Hypertonic Saline

A study by Fisher et al (3) was carried out as a double-blind crossover study

comparing 3% saline (513 mEq/L, 1027 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-hr trial, hypertonic saline use was associated with an approximate 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. As a result of design flaws (see evidence table; Table 1), the evidence from this study is class II.

A study by Simma et al (5) was carried out as a randomized controlled trial of 1.7% hypertonic saline (sodium 268 mmol/L, 598 mOsm/L) vs. lactated Ringer's solution (sodium 131 mmol/L, 277 mOsm/L) administered over the initial 3 days in 35 children with severe TBI. Patients treated with hypertonic saline required fewer interventions (including mannitol use) to control ICP than those treated with lactated Ringer's solution. Patients in the hypertonic saline treatment group also had a shorter length of pediatric intensive care unit stay ($p = .04$), shorter duration of mechanical ventilation ($p = .10$), and fewer complications than the lactated Ringer's-treated group ($p = .09$ for two or more complications, nonsignificant for one complication). As a result of design flaws and insufficient power (see evidence table), the evidence from this study is class II.

A study by Peterson et al (4) was a retrospective study on the use of a continuous infusion of 3% saline (sodium 513 mEq/L, 1027 mOsm/L) titrated to reduce ICP to ≤ 20 mm Hg in 68 infants and children with TBI. The mean daily doses of hypertonic saline over a 7-day period ranged between 11 and 27 mEq $\cdot$ kg $^{-1}\cdot$ day $^{-1}$. 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 categorization. No patient with a serum sodium concentration >180 mEq/L had a good outcome. No patients developed renal failure. Concomitant therapies included sedation, neuromuscular blockade, mannitol, hyperventilation, and barbiturates. CSF drainage was used in three children. The mean daily dose of mannitol was 1–2 g $\cdot$ kg $^{-1}\cdot$ day $^{-1}$. Rebound in ICP, central pontine myelinolysis, and subarachnoid hemorrhage was not seen.

In the three papers cited as evidence for hypertonic saline, several limitations should be recognized. These studies originated from only two centers and there was limited use of ventriculostomy catheters and CSF drainage; instead, hyperventilation and barbiturates were used. Also, the children were enrolled between 16 and 26 yrs ago. Finally, the report by Simma et al (5) compared 1.7% hypertonic saline with lactated Ringer's solution, which is hypotonic. It should be recognized that the therapeutic window, safety profile, and optimal doses or osmolar levels of hypertonic saline remain to be determined.

VI. INFORMATION FROM OTHER SOURCES

A. Indications From Adult Guidelines

Based on an evidence table in the adult guidelines (57) (one class II and seven class III studies), mannitol was deemed to be effective for controlling increased ICP after severe TBI at doses ranging from 0.25 g/kg to 1 g/kg of body weight. Serum osmolality <320 mOsm/L was recommended with mannitol use. Several key studies were cited. In the one class II study, Eisenberg et al (58) reported that a therapeutic regimen with mannitol was effective for ICP control in 78% of patients ($n = 73$). In addition, a study by Schwartz et al (21) was carried out as a randomized comparison of mannitol vs. barbiturates in 59 adults with severe TBI. Cerebral perfusion pressure was better maintained in the mannitol-treated group. Use of mannitol for TBI was subjected to Cochrane review, and no conclusion could be reached regarding efficacy vs. placebo or any other therapy (59). Two class III level studies of hypertonic saline were cited in the adult guidelines (57). The body of work on hypertonic saline in pediatric TBI showing beneficial effects on ICP was discussed as was the pediatric guidelines level III recommendation of continuous infusion of 3% saline. However, it was stated that limited data on hypertonic saline in adults with severe TBI did not allow for conclusions.

B. Information Not Included as Evidence

Mannitol. When constructing an evidence-based document on the use of hyperosmolar therapy to control ICP in pe-

diatric TBI, one must recognize that evidence supporting the use of mannitol in adults relies on studies that often included but did not explicitly define the proportion of children. Mannitol was used concomitantly to control ICP in the aforementioned studies of hypertonic saline in the evidence table. One must thus weigh the value of long-standing clinical acceptance and safety of a therapy (mannitol) that has no evidentiary support for its efficacy against a newer therapy (hypertonic saline) with less clinical experience but reasonably good performance in contemporary clinical trials (two class II studies for ICP and one class III study) (3–5, 48).

There is no study that met the inclusion criteria for this guideline, for either ICP or neurologic outcome, that documents efficacy of mannitol in infants and children with severe TBI. In several reports (29, 60–62), the specific effect of mannitol on ICP or outcome was not reported, the sample size was very small, or mannitol was shown to reduce ICP reliably, but the sample represented a mixture of adults and children (29).

Hypertonic Saline. One additional study was not included as evidence because it represented a prospective observational study with an inadequate sample size ($n = 10$). A study by Khanna et al (48) administered 3% saline (sodium 513 mEq/L, 1027 mOsm/L) on a sliding scale to maintain ICP <20 mm Hg in ten children with increased ICP resistant to conventional therapy. The maximal rate of increase in serum sodium was $15 \text{ mEq}\cdot\text{L}^{-1}\cdot\text{day}^{-1}$, and the maximal rate of decrease in serum sodium was $10 \text{ mEq}\cdot\text{L}^{-1}\cdot\text{day}^{-1}$. A reduction in ICP spikes and an increase in cerebral perfusion pressure were seen during treatment with 3% saline. The mean duration of treatment was 7.6 days, and the mean highest serum sodium concentration and osmolality were 170.7 mEq/L and 364.8 mOsm/L, respectively. The maximum serum osmolality in an individual patient was 431 mOsm/L. Sustained hyponatremia and hyperosmolality were generally well tolerated in the children. Two patients, both with sepsis and/or multiple organ failure, developed acute renal failure. Both received continuous venovenous hemofiltration and recovered renal function. One patient died of uncontrolled intracranial hypertension. Despite its exclusion from the evidence table, the findings of this report are con-

sistent with our recommendations supporting the use of 3% saline.

Hypertonic saline in pediatric patients with severe TBI is also used in the management of hyponatremia from CSW. No publications meeting the inclusion criteria for this guideline and addressing treatment of CSW were identified. Most reports suggest aggressive replacement of urine salt and water losses, but only case reports in pediatric TBI or case series with various diagnoses (including severe TBI) have been reported (53, 54, 63). The sodium replacement used ranged in dose between 0.1 and 2.4 mmol/kg/hr.

VII. SUMMARY

There is class II evidence supporting the use of hypertonic saline (3%) for the acute treatment of severe pediatric TBI associated with intracranial hypertension and class III evidence to support its use as a continuous infusion during the intensive care unit course. There is insufficient evidence to support or refute the use of mannitol, concentrations of hypertonic saline $>3\%$, or other hyperosmolar agents for the treatment of severe pediatric TBI. One must thus weigh the value of longstanding clinical acceptance and safety of mannitol, which has no evidence to support its efficacy that met the inclusion criteria for this guideline, against hypertonic saline, for which there is less clinical experience but reasonably good performance in contemporary clinical trials.

VIII. KEY ISSUES FOR FUTURE INVESTIGATION

- Documentation of the effect of hyperosmolar therapy on ICP, cerebral perfusion pressure, and outcome in studies of infants and children.
- Studies comparing mannitol administration with hypertonic saline, particularly studies evaluating long-term outcome. This should include assessment of the combination of mannitol and hypertonic saline.
- Study of the use of hyperosmolar therapy vs. other therapies such as CSF drainage or barbiturates, including investigation of both control of ICP and long-term outcome.
- Studies as to whether or not hyperosmolar therapy can be effective in the setting of herniation.
- Study of the prevention of intracranial hypertension by continuous infusion of hypertonic saline vs. treatment in re-

sponse to spikes and its impact on long-term outcome.

- Additional mechanistic studies in children with severe TBI examining issues such as the serum–CSF osmolar gap, regional effects of hyperosmolar therapies on contused vs. noncontused brain tissue using computed tomography or advanced magnetic resonance imaging, and their effects on other surrogate markers of brain injury such as blood flow, metabolism, and biomarkers.
- Studies of the use of hyperosmolar therapy across various etiologies (abusive vs. nonabusive) and head computed tomography injury patterns (contusion vs. diffuse injury) in children.
- Optimal dosing and better definitions of treatment threshold for the development of nephrotoxicity, rebound intracranial hypertension or hyponatremia, central pontine myelinolysis, and other complications with mannitol and hypertonic saline.
- Studies on the use of hypertonic saline in the management of CSW and other causes of hyponatremia in pediatric patients with TBI.

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Chapter 9. Temperature control

I. RECOMMENDATIONS

Strength of Recommendations: Weak.

Quality of Evidence: Moderate, from class II and III studies with some contradictory findings.

A. Level I

There are insufficient data to support a level I recommendation for this topic.

B. Level II

Moderate hypothermia (32–33°C) beginning early after severe traumatic brain injury (TBI) for only 24 hrs' duration should be avoided.

Moderate hypothermia (32–33°C) beginning within 8 hrs after severe TBI for up to 48 hrs' duration should be considered to reduce intracranial hypertension.

If hypothermia is induced for any indication, rewarming at a rate of $>0.5^{\circ}\text{C/hr}$ should be avoided.

C. Level III*

Moderate hypothermia (32–33°C) beginning early after severe TBI for 48 hrs, duration may be considered.

*After completion of these guidelines, the committee became aware that the *Cool Kids* trial of hypothermia in pediatric TBI was stopped because of futility. The implications of this development on the recommendations in this section may need to be considered by the treating physician when details of the study are published.

II. EVIDENCE TABLE (see Table 1)

III. OVERVIEW

The definitions of hypothermia and hyperthermia are controversial. Posttraumatic hypothermia is often classified as a core body temperature $<35^{\circ}\text{C}$, whereas a temperature >38.0 – 38.5°C represents fever/pyrexia if it results from an altered thermoregulatory set point and represents hyperthermia if it is imposed on a normal set point. For simplicity, the term

hyperthermia is used to reflect an elevated core body temperature throughout this chapter. At present, the data in the basic science literature on adult animal models indicate that hyperthermia contributes to greater posttraumatic damage by increasing the acute pathophysiological response after injury through a multitude of mechanisms.

The rationale for use of therapeutic hypothermia is a reduction in mechanisms of secondary injury resulting from decreased cerebral metabolic demands, inflammation, lipid peroxidation, excitotoxicity, cell death, and acute seizures. Clinical studies reviewed on temperature regulation have focused, by definition for these guidelines, on global functional outcome but also the effect on intracranial hypertension. The impact of reduction of intracranial pressure (ICP) after severe TBI in children on outcome remains to be determined. As discussed in previous chapters, the lowering of severely elevated ICP with respect to the treatment threshold may be a desirable outcome.

Lastly, based on experimental studies in animal models and clinical studies in adults, in which hyperthermia was correlated with poor outcome, it has been recommended that hyperthermia after TBI in children should be prevented. However, no study of the impact of hyperthermia on outcome after TBI met the inclusion criteria for this guideline. There also may be a role for therapeutic hypothermia in reducing intracranial hypertension in severe pediatric TBI.

IV. PROCESS

For this update, MEDLINE was searched from 1996 through 2010 (Appendix B for search strategy), and results were supplemented with literature recommended by peers or identified from reference lists. Of 17 potentially relevant studies, two were added to the existing table for this topic.

V. SCIENTIFIC FOUNDATION

Two moderate-quality class II studies and one poor-quality class III study met

the inclusion criteria for this topic and provide evidence to support the recommendations (1–3).

Level II Recommendations

Outcome. This review provides a level II recommendation for the avoidance of moderate hypothermia (32–33°C) initiated early after severe TBI and applied for only 24 hrs' duration followed by rapid rewarming at a rate of $>0.5^{\circ}\text{C/hr}$. This was based on the Hutchison et al (3) study that reported a phase III multicentered randomized trial (225 children with severe TBI; Glasgow Coma Scale Score 3–8) of moderate hypothermia (32–33°C) for 24 hrs followed by rewarming at a rate of 0.5 – 1.0°C every hour. In this study, hypothermia was used in a prophylactic manner as a neuroprotective strategy whether or not raised ICP was present. The findings from this study trended toward worse outcomes at 6 months after injury in children treated with hypothermia vs. normothermia using the Pediatric Cerebral Performance Category score (30% vs. 22%; $p = .08$) and increased mortality (21% vs. 14%; $p = .06$). In this study, the investigators screened the patients within 8 hrs, and the mean time to initiation of cooling was 6.3 hrs with a range of 1.6–19.7 hrs. As well, the protocol included a rapid rewarming rate as described previously so that the patients were normothermic by a mean of 19 hrs or within 48 hrs of injury. They found that hypothermia reduced intracranial hypertension with ICP significantly lower in the hypothermia vs. normothermia group during the cooling period, but this was followed by a significantly higher ICP in the hypothermia vs. normothermic groups during rewarming. A potentially confounding factor in this study was that marked hyperventilation ($\text{Paco}_2 < 30$ mm Hg) was used as part of standard management in $>40\%$ of the patients in the study and hypertonic (3%) saline use was significantly reduced in the hypothermia vs. normothermia group.

Intracranial Hypertension. In contrast, a level II recommendation was made supporting the use of moderate hypothermia (32–33°C) in severe pediatric

Table 1. Evidence table

Reference	Description of Study	Data Class, Quality, and Reasons	Results and Conclusion
Studies from previous guidelines Hendrick et al, 1959 (1)	Design: uncontrolled case series N = 18 Protocol: patients who presented with decerebrate posturing were cooled to 32–33°C; adjunctive therapies included promethazine and chlorpromazine	Class III Poor quality: no control for confounders	8 deaths Among 10 survivors, 4 no disability, 1 minimal hearing loss, 2 minimal hemiparesis and aphasia, 1 hemiparesis, 1 diplopia and mild personality changes, 1 gross intellectual impairment
New studies Adelson et al, 2005 (2)	Design: randomized controlled trial N = 75 Protocol: cooled to 32–33°C within 8 hrs of injury for 48 hrs as compared with normothermia Outcome: mortality, 3- and 6-month Glasgow Outcome Scale	Class II Moderate quality: unclear reporting of randomization methods, allocation concealment methods, and attrition	No difference between groups in mortality or 3- and 6-month Glasgow Outcome Scale ICP: overall, there was no statistical difference in mean ICP between the groups during the 5-day period ($p = .37$) except within the first 24 hrs, when the ICP was reduced in the hypothermia group ($p = .024$) No difference between groups in complication rates
Hutchison et al, 2008 (3)	Design: randomized controlled trial N = 225 Protocol: Randomized to cooling to 32–33°C within 8 hrs of injury for 24 hrs vs. normothermia; patients rewarmed at 0.5°C per hour	Class II Moderate quality: some differences between groups on baseline prognostic factors	No difference between groups on functional outcomes at 6 months Trend toward increased mortality and morbidity in the hypothermia group ICP was lower during cooling in the hypothermia group at 16 hrs and 24 hrs ($p < .02$ and $p < .01$, respectively) Significant increase in hypotension and pressor requirements in the hypothermia group

ICP, intracranial pressure.

TBI in the setting of refractory intracranial hypertension for 48 hrs' duration followed by slow rewarming at a rate of 0.5–1.0°C per 12–24 hrs if the injury occurred within 8 hrs. The recommendation was based on two class II studies with benefit of hypothermia on ICP (2, 3).

As mentioned, Hutchison et al (3) showed that hypothermia reduced intracranial hypertension with ICP significantly lower in the hypothermia vs. normothermia groups during the cooling period, although this rebounded to higher ICP during rewarming. However, hypothermia in that study was used only for up to 24 hrs. A study by Adelson et al (2) was a phase II multicentered randomized trial in 75 children with severe TBI (Glasgow Coma Scale score 3–8) of moderate hypothermia (32–33°C) for 48 hrs followed by rewarming at a rate of 0.5–1.0°C every 3–4 hrs. Additional details of this study as it relates to outcome are provided subsequently. Although there was no overall effect of hypothermia vs. normothermia on ICP, ICP was significantly decreased in the initial 24 hrs after

TBI in the hypothermia vs. normothermia groups.

Level III Recommendation

Outcome. Supporting the level III recommendation for early administration of therapeutic hypothermia for 48 hrs' duration with slow rewarming, Adelson et al (2) carried out a phase II multicentered randomized trial in 75 children with severe TBI (Glasgow Coma Scale score 3–8) of moderate hypothermia (32–33°C) for 48 hrs followed by rewarming at a rate of 0.5–1.0°C every 3–4 hrs. They reported that hypothermia was safe, associated with a decreased mortality rate (8% vs. 16%), and did not increase complications. Once again, in this study, hypothermia was used in a prophylactic manner as a neuroprotective strategy whether or not raised ICP was present. Similar to the report of Hutchison et al (3), they also noted rebound intracranial hypertension in the previously cooled patients during rewarming.

In support of this recommendation is Hendrick (1), a case series of 19 children

with severe TBI who presented with decerebrate posturing that, although before actual classification of severity of injury, would translate to a present-day Glasgow Coma Scale score of 4. These children were treated with moderate hypothermia (32–33°C). There were ten long-term survivors with only one severely impaired. It was concluded that systemic cooling after injury was effective as a “useful adjunct” that could improve outcome in children after TBI.

VI. INFORMATION FROM OTHER SOURCES

A. Indications From the Adult Guidelines

In the third edition of the adult guidelines (4), there was a chapter entitled “Prophylactic Hypothermia” based on a sufficient number of studies assessing the efficacy of therapeutic hypothermia after severe TBI in adults. Much of the previous edition of the pediatric guidelines was based on a scarcity of pediatric spe-

cific information with the use of hypothermia to treat patients with severe TBI originally reported >50 yrs ago (1). However, its use did not become established because early studies lacked modern scientific methods and adequate outcome measures to definitively prove or refute efficacy, and there were concerns over side effects. Renewed interest in moderate hypothermia after severe TBI did not occur until the past 15–20 yrs, when preliminary data from single-center clinical trials were published in adults. Studies by Shiozaki et al (5), Marion et al (6), Clifton et al (7), and Marion et al (8) all demonstrated that moderate hypothermia reduced ICP and tended to improve overall outcomes. In the first randomized controlled trial that followed these single-center studies, Clifton et al (9) reported lack of effectiveness in adults in a multicentered clinical trial of moderate hypothermia after severe TBI. Despite failure to replicate the earlier single-center findings in the larger multicentered trial, there was a suggestion of improved outcome in those patients who presented as hypothermic and were then kept cool and in the younger age groups within the study (<40 yrs of age). Children (≤ 16 yrs) were not included in the Clifton study or in subsequent studies. In the recent adult guidelines (4), it was noted that although hypothermia is often induced prophylactically on admission and used for ICP elevation in the intensive care unit in many trauma centers, the scientific literature has failed to consistently support its positive influence on mortality and morbidity. Four meta-analyses of hypothermia in adult patients with TBI have been published (10–13). All analyses concluded that the evidence was insufficient to support routine use of hypothermia and recommended further study to determine factors that might explain variation in results. As a result, the authors of the adult guidelines undertook another meta-analysis of the six trials that were assessed to be of moderate quality (7–9, 14–16). The overall risk reduction for mortality from this large data set was not significantly different between hypothermia and normothermia treatment groups, but hypothermia was associated with a 46% increased chance of good neurologic outcome (relative risk, 1.46; 95% confidence interval, 1.12–1.92). This led to a level III recommendation based on this pooled data. Additionally, preliminary findings suggested that a greater decrease in mortality risk is

observed when target temperatures are maintained for >48 hrs (4). The results of these clinical trials of hypothermia in adult patients with TBI and even the resultant meta-analyses cannot be extrapolated directly to the management of severe TBI in children because children were not included in the samples analyzed.

B. Information Not Included as Evidence

A study by Li et al (17) reported on the use of local hypothermia (head cooling) rather than systemic cooling to an intracranial temperature of $34.5 \pm 0.5^\circ\text{C}$ within 8 hrs of injury vs. normothermia (37.5 – 38.5°C) for a period of 72 hrs. Although the study showed a positive effect of cooling on intracranial hypertension and biomarkers, neuron-specific enolase, S-100B, and CK-BB at 8, 24, and 48 hrs after injury, suggesting neuronal protection, neurologic outcomes could only be determined for eight patients (three of whom had died), because almost two-thirds were lost to clinical follow-up. A study by Biswas et al (18) reported on 21 children with severe TBI (Glasgow Coma Scale score 3–8), ten of whom were cooled to moderate hypothermia (32 – 34°C) within 6 hrs of injury for 48 hrs followed by rewarming to normothermia within 12 hrs. Although the study showed a positive effect of cooling on intracranial hypertension, there was no significant difference between hypothermic and normothermic groups in other outcome measures including Glasgow Outcome Scale, Pediatric Cerebral Performance Category, or Pediatric Overall Performance Category. Despite the small sample size overall, of the 21 children treated, 11 of 11 and six of six in the normothermia group had a good outcome at 3 and 12 months postinjury, respectively, whereas six of ten and five of eight in the hypothermia group had a good outcome at 3 and 12 months postinjury. Both of these studies supported the level II recommendation despite being poor-quality studies for the end points defined.

A study by Aibiki et al (14) evaluated ventilated adults and children with severe TBI (Glasgow Coma Scale score 3–8) treated with moderate hypothermia (32 – 33°C) for 3–4 days as compared with normothermia for prostanoid production. Although not the focus on the article, data as to age and outcome (Glasgow Outcome Scale at 6 months) could be abstracted.

There were 11 children treated and two of four in the normothermia vs. six of seven in the hypothermia groups had a good outcome. Similar to the study by Gruszkiewicz et al (19), confounding this study was the cotreatment with dexamethasone. The study by Grinkeviciute and Kevalas (20) reported on a prospective cohort to determine the safety of mild hypothermia after TBI. There were eight patients included in the study, with a mean age of 10.7 yrs, who had severe TBI (Glasgow Coma Scale score 4–8), and who were treated with mild hypothermia (33 – 34°C) with a rapid induction of 2–3 hrs and maintained for 48 hrs with passive rewarming at 1°C per 4 hrs. Using the Glasgow Outcome Scale, all patients had a good outcome. Average Glasgow Outcome Scale score was 4.13 at 6 months after injury.

Finally, a study by Gruszkiewicz et al (19) reported on a prospective, randomized study of 20 children <16 yrs of age who had severe TBI presenting with a clinical examination of decerebrate rigidity (Glasgow Coma Scale score = 4). The children were randomized to hypothermia vs. hypothermia combined with dexamethasone (2 mg twice a day). There was no normothermic group. Sixteen of these 20 patients were hyperthermic at presentation and sustained various mechanisms of injury. Outcome was determined by duration of coma and time until “recovery,” although the length of follow-up was <7 months in all instances. Although no statistical analysis was performed, the authors described a similar duration of coma and neurologic recovery for the two groups, although the depth and duration of the hypothermia differed. Some patients were cooled to 30 – 32°C , whereas others to 35 – 36°C . There was also variability of application from 18 hrs to 17 days. There were 19 survivors. Adjunctive therapies included promethazine, chlorpromazine, mannitol, and lumbar puncture to reduce ICP.

Although no study on the effect of hyperthermia after TBI in children met the inclusion criteria for these guidelines, a study by Heindl and Laub (21) reported that posttraumatic hyperthermia (defined as a temperature $>38.2^\circ\text{C}$, lasting for at least 1 wk) was associated with a poor outcome vs. normothermia in an extremely severe cohort of 82 patients who remained in a persistent vegetative state at least 30 days postinjury. In this purely observational study, patients with hyperthermia had a poorer outcome

vs. those that did not (81% vs. 19%; $p < .01$). The time window that hyperthermia may contribute to secondary injury after severe TBI and the best approach to preventing or treating it were not addressed, although this study suggests that it may be important to prevent or treat hyperthermia after pediatric TBI.

VII. SUMMARY

Considerable uncertainty exists regarding the specifics of the use of targeted temperature management in pediatric TBI. A number of studies, including two new studies with class II evidence, show that mild or moderate hypothermia, vs. normothermia, can attenuate intracranial hypertension. However, the efficacy of this therapy vs. others as either a first-line agent or to treat refractory intracranial hypertension remains unclear. Similarly, conflicting results have been obtained regarding the effect of hypothermia on mortality and/or neurologic outcomes. It appears that details of the protocols used both to induce and maintain hypothermia and rewarm may be extremely important with short (24-hr) periods of cooling and rapid rewarming exhibiting the most complications. Finally, no study of the effect of hyperthermia on outcome after TBI in children met the inclusion criteria to allow a recommendation on this aspect of management.

VIII. KEY ISSUES FOR FUTURE INVESTIGATION

- The effect of temperature control, including prevention of hyperthermia, on outcome after pediatric TBI needs to be further studied.
- Issues such as the duration of vulnerability to hyperthermia and the optimal way to prevent or treat it should be addressed.
- The role of therapeutic hypothermia, both as a neuroprotective measure and for refractory intracranial hypertension, deserves investigation in pediatric TBI. Direct comparisons to other therapies should be conducted.
- Evaluations of therapeutic hypothermia should be age-stratified. Additional documentation of the effect of hypothermia and temperature regulation in studies restricted to infants and children are needed.
- Studies of the effect of hypothermia on specific TBI pathologies such as contusion, diffuse injury, and abusive head trauma are needed.
- Studies addressing both the therapeutic window and optimal duration are needed.
- Studies of the optimal timing and rate of rewarming are also needed.
- Studies are needed to better understand the effect of temperature regulation on key physiological and pharmacologic parameters (e.g., ICP, cerebral perfusion pressure, cardiac output, immune status, drug metabolism and drug dosing, etc.) and how these effects might influence long-term outcome.

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Chapter 10. Cerebrospinal fluid drainage

I. RECOMMENDATIONS

Strength of Recommendations: Weak.

Quality of Evidence: Low from poor- and moderate-quality class III studies with some contradictory findings.

A. Level I

There are insufficient data to support a level I recommendation for this topic.

B. Level II

There are insufficient data to support a level II recommendation for this topic.

C. Level III

Cerebrospinal fluid (CSF) drainage through an external ventricular drain may be considered in the management of increased intracranial pressure (ICP) in children with severe traumatic brain injury (TBI).

The addition of a lumbar drain may be considered in the case of refractory intracranial hypertension with a functioning external ventricular drain, open basal cisterns, and no evidence of a mass lesion or shift on imaging studies.

II. EVIDENCE TABLE (see Table 1)

III. OVERVIEW

With the use of the external ventricular drain as a common means of measuring ICP of patients with TBI, the potential added therapeutic benefits of CSF drainage is of interest. Before the use of the external ventricular drain in TBI, the principal use of CSF drainage was in patients with hydrocephalus, but the ability of this procedure to potentially affect ICP led to its increased use as a therapeutic device for TBI. The role of CSF drainage is to reduce intracranial fluid volume and thereby lower ICP. Both intermittent and continuous drainage approaches have been reported in the pediatric literature

(1). Therapy may be associated with an increased risk of complications from hemorrhage and malpositioning.

IV. PROCESS

For this update, MEDLINE was searched from 1996 through 2010 (Appendix B for search strategy), and results were supplemented with literature recommended by peers or identified from reference lists. Of six potentially relevant studies, one was added to the existing table and used as evidence for this topic.

V. SCIENTIFIC FOUNDATION

Four class III studies met the inclusion criteria and are used as evidence for this topic (2–5). Ventricular drainage alone was used in two studies, and lumbar drainage in combination with an external ventricular drain was used in the other two.

A study by Shapiro and Marmarou (4) retrospectively studied 22 children with severe TBI defined as a Glasgow Coma Scale score of ≤ 8 , all of whom were treated with ventricular drainage. Parameters measured included ICP, pressure-volume index, and mortality. Draining CSF increased pressure-volume index and decreased intracranial hypertension. Two neurologic deaths occurred in patients with refractory intracranial hypertension; however, the ICP of the other three patients who died, and the four survivors with severe disability, is not reported. Consequently, the absolute influence of CSF drainage in this sample cannot be determined.

A study by Jagannathan et al (5) retrospectively studied 96 children with severe TBI comparing management of ICP alone vs. ICP along with surgery using either external ventricular drainage or operative treatment (evacuation of hematoma or decompressive craniectomy). ICP control was achieved in 82 patients (85%). Methods used to achieve ICP control included maximal medical therapy (sedation, hyperosmolar therapy, and neuromuscular blockade) in 34 patients (35%), external ventricular drain in 23 patients (24%), and surgery in 39 pa-

tients (41%). Refractory ICP resulted in 100% mortality. Authors concluded that controlling elevated ICP is an important factor in patient survival after severe pediatric TBI. The modality used for ICP control appears to be less important. No long-term follow-up to determine neurocognitive sequelae was performed.

Drainage of CSF is not limited to the ventricular route. The other level III recommendation is that although CSF drainage can be accomplished through an external ventricular drain catheter alone or in combination with a lumbar drain, the addition of lumbar drainage should only be considered in the case of refractory intracranial hypertension with a functioning external ventricular drain, open basal cisterns, and no evidence of a major mass lesion or shift on imaging studies. A study by Baldwin and Rekeate (2) reported a series of five children with severe TBI, in whom lumbar drains were placed after failure to control ICP with both ventricular drainage and barbiturate coma. Three children had quick and lasting resolution of raised ICP, two of them with good outcome and one with moderate remaining disability. In the other two cases, there was no effect on ICP and both children died.

In a later paper from the same institution, Levy et al (3) reported the effect on outcome of controlled lumbar drainage with simultaneous external ventricular drainage in 16 pediatric patients with severe TBI. In two patients, ICP was unaffected and both died. The remaining 14 survived, eight having a good outcome, three with moderate disability, and three having severe disability. Although there was no direct outcome study or analysis on the use of barbiturates in this series, the authors proposed that barbiturate coma and its associated morbidity could be avoided by the use of lumbar drainage, based on their findings in this series that not all patients were given barbiturates (five of 16 patients received no barbiturates and six of 16 received only intermittent dosing). The use of lumbar drainage, however, was contraindicated in the setting of a focal mass lesion or shift and the authors recommended the use of lumbar

Table 1. Evidence table

Reference	Study Description	Data Class, Quality, and Reasons	Results and Conclusion
Studies from previous guidelines			
Baldwin and Reke, 1991 (2)	Design: case series N = 5 Age: 8–14 yrs Protocol: external ventricular drain, then lumbar drain; lumbar drain should only be considered in the case of refractory intracranial hypertension with a functioning external ventricular drain, open basal cisterns, and no mass lesion or shift on imaging studies	Class III Poor quality: no control for confounders, small sample size	3 of 5 survived; (1 moderate disability, 2 good recovery) all had decrease in ICP after lumbar drainage
Levy et al, 1995 (3)	Design: case series N = 16 Age: 1–15 yrs Protocol: external ventricular drain, then lumbar drain; lumbar drain should only be considered in the case of refractory intracranial hypertension with a functioning external ventricular drain, open basal cisterns, and no mass lesion or shift on imaging studies	Class III Poor quality: no control for confounders, small sample size	ICP lowered in 14 of 16; 2 of 16 died, both of whom had uncontrolled ICP Of 14 survivors, 8 had good recovery; 3 moderate disability, 3 severe disability
Shapiro and Marmarou, 1982 (4)	Design: case series N = 22 Age: 2–15 yrs Protocol: external ventricular drainage, ICP/ PVI measured	Class III Poor quality: small sample size with narrow spectrum of patients	5 of 22 died 4 of 17 survivors were severely disabled; 13 of 17 had a good outcome or were moderately disabled 16 of 22 patients had PVI measured before and after therapy. Drainage increased PVI and decreased ICP in 14 of 16. 2 of the 5 deaths were due to uncontrolled intracranial hypertension
New study Jagannathan et al, 2008 (5)	Design: case series N = 96 Age: 3–18 yrs, mean 15.1 yrs Protocol: compared management of ICP alone (N = 34) vs. ICP along with surgery using an external ventricular drain (N = 23) or operative treatment (N = 39; 14 mass lesion evacuation, 25 decompressive craniectomy)	Class III Moderate quality: control for confounders unclear for ICP	ICP control achieved in 82 of 96 (85%) overall 20 of 23 (87%) achieved ICP control with external ventricular drain; of 3 not achieving ICP control, 2 died, 1 had craniectomy Refractory ICP was associated with 100% mortality; the method used to control ICP had no correlation with mortality

ICP, intracranial pressure; PVI, pressure–volume index.

drainage only in conjunction with a functioning external ventricular drain in the setting of open basal cisterns based on imaging.

VI. INFORMATION FROM OTHER SOURCES

A. Indications From the Adult Guidelines

The adult guidelines do not address CSF drainage as a treatment for TBI.

B. Information Not Included as Evidence

In one study that was not included as evidence because it did not report functional outcomes, Anderson et al (6) retrospectively studied 80 children with se-

vere TBI, all of whom were treated with an ICP monitor or an external ventricular drain (EVD) or both. The authors observed a fourfold increase in the risk of complications for EVD as compared with a fiberoptic monitor ($p = .004$). These included: greater hemorrhagic complications with the EVD in 12 of 62 (17.6%); fiberoptic in four of 62 (6.5%) ($p = .025$); malposition of the EVD requiring replacement in six of 68 (8.8%); and infection in one of 62 (1.5%). They concluded that the use of an EVD may be associated with increased risk of complications from hemorrhage and malposition.

Following earlier reports of an effect on ICP by drainage of CSF, Ghajar et al (7) performed a prospective study, without randomization, of the effect of CSF drainage in adults with TBI. Treatment

was selected by the admitting neurosurgeon and, after evacuation of mass lesions, patients either received ventriculostomies with drainage if ICP exceeded 15 mm Hg along with medical management (group 1) or medical management only (group 2). The medical management consisted of mild hyperventilation to P_{CO_2} 35 mm Hg, head-of-bed elevation, normovolemia, and mannitol (although only on admission). Patients in group 2 had no ICP monitor of any kind. The outcome measures were mortality and degree of disability. Mortality was 12% in group 1 vs. 53% in group 2. Of the patients in group 1, 59% were living independently at follow-up vs. 20% of group 2.

A study by Fortune et al (8) studied the effect of hyperventilation, mannitol, and CSF drainage on cerebral blood flow

in TBI. Twenty-two patients were studied with a mean age of 24 yrs (range, 14–48 yrs). Children were not reported separately. Although patient outcome was not reported, this study established that CSF drainage, hyperventilation, and intermittent mannitol were all effective in reducing ICP. They also found that mannitol use increased cerebral blood flow, CSF drainage had a negligible impact on cerebral blood flow, and hyperventilation decreased cerebral blood flow.

VII. SUMMARY

Four class III studies provide the evidence base for this topic resulting in a level III recommendation for the therapeutic use of CSF drainage for the management of intracranial hypertension. Two of these studies supported the use of ventricular CSF drainage. Although most commonly achieved with an EVD, a randomized controlled trial comparing the efficacy of treatment of intracranial hypertension in pediatric TBI with or without CSF drainage has not been carried out. In the setting of refractory intracranial hypertension, a lumbar drain may be considered but only in conjunction with a functional ventricular drain in patients with open cisterns on imaging and without major mass lesions or shift. This was also supported only as a level III recommendation. A randomized controlled trial

comparing the different available approaches to the treatment of refractory intracranial hypertension has also not been carried out. Overall, it is possible that control of refractory ICP may be the most important aspect of treatment in children with severe TBI and may not depend on a single modality of treatment, i.e., in this case, CSF drainage.

VIII. KEY ISSUES FOR FUTURE INVESTIGATION

- Prospective studies as to the risks and benefits of placement of an ICP monitor alone vs. placement of an EVD catheter.
- Prospective studies on the outcome benefits of CSF drainage vs. other therapies.
- Role of surrogate markers of outcome using CSF drainage.
- Studies to compare CSF drainage with other therapeutic modalities used in TBI management such as osmolar therapy, barbiturates, or surgery.
- Studies about the technical aspects of drain use such as continuous vs. intermittent drainage, age-specific use, and use related to mechanism of injury.
- Comparison of lumbar drainage with other second-tier therapies such as decompressive craniotomy/craniectomy.
- Study of the potential role of subgaleal drainage in infants.

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Chapter 11. Barbiturates

I. RECOMMENDATIONS

Strength of Recommendation: Weak.

Quality of Evidence: Low from poor-quality class III studies.

A. Level I

There are insufficient data to support a level I recommendation for this topic.

B. Level II

There are insufficient data to support a level II recommendation for this topic.

C. Level III

High-dose barbiturate therapy may be considered in hemodynamically stable patients with refractory intracranial hypertension despite maximal medical and surgical management.

When high-dose barbiturate therapy is used to treat refractory intracranial hypertension, continuous arterial blood pressure monitoring and cardiovascular support to maintain adequate cerebral perfusion pressure are required.

II. EVIDENCE TABLE (see Table 1)

III. OVERVIEW

Children with severe traumatic brain injury (TBI) may develop intracranial hypertension resistant to medical and surgical management. Reported rates of refractory intracranial hypertension vary (21% to 42%) (1–6). A recent study of 132 children from South America found that 43% experienced refractory intracranial hypertension that was treated with either high-dose barbiturates or decompressive craniectomy (7). Children have more diffuse swelling and higher rates of generalized hyperemia after severe TBI and compared with adults (8, 9) and young children have greater risk of intractable intracranial hypertension compared with older children (7).

Barbiturates lower intracranial pressure (ICP) when first-tier medical and surgical management have not resulted in adequate control. However, cardiorespiratory side effects are very common and potentially toxic, including decreased cardiac output, hypotension, and increased intrapulmonary shunt resulting in lower cerebral perfusion pressure and hypoxia. Thus, high-dose barbiturate therapy has been reserved for extreme cases of intracranial hypertension resistant to first-tier medical and surgical care.

The use of high-dose barbiturates is based on the logic that uncontrolled intracranial hypertension leads to ongoing secondary brain injury and a high risk of death or poor cognitive outcomes. Thus, control of ICP may improve patient survival and outcome. A recent randomized controlled study of 225 traumatic brain-injured children that used a tiered therapy protocol for management of ICP and cerebral perfusion pressure treated 16% of patients with barbiturates as a late therapy (10). So, although high-dose barbiturates are reserved for a high-risk group, use in North American pediatric severe TBI care is common.

High-dose barbiturates lower ICP through two distinct mechanisms: suppression of metabolism and alteration of vascular tone (11–13). Barbiturate therapy improves coupling of regional blood flow to metabolic demands resulting in higher brain oxygenation (14) with lower cerebral blood flow and decreased ICP from decreased cerebral blood volume. Other brain protective mechanisms include inhibition of oxygen radical mediated lipid peroxidation as well as inhibition of excitotoxicity (15).

Few studies have evaluated high-barbiturate pharmacokinetics and pharmacodynamics in head-injured children (16–19). Clearance appears to vary widely and may be increased with duration of barbiturate administration (17). Barbiturate levels are poorly correlated with electrical activity (18, 19). Monitoring electrographic patterns to achieve burst suppression is thought to be more reflective of therapeutic effect than drug levels.

Near maximum reduction in cerebral metabolism and cerebral blood flow occurs when burst suppression is induced.

High-dose barbiturates suppress metabolism and, although both use of pentobarbital and thiopental have been reported, there is insufficient information about comparative efficacy to recommend one over another, except in relation to their particular pharmacologic properties.

IV. PROCESS

For this update, MEDLINE was searched from 1996 through 2010 (Appendix B for search strategy), and results were supplemented with literature recommended by peers or identified from reference lists. Of 47 potentially relevant studies, none were added to the existing table and used as evidence for this question.

V. SCIENTIFIC FOUNDATION

Two class III studies met the inclusion criteria for this topic and provide evidence to support the recommendations (1, 20).

A study by Kasoff et al (1) reported a case series of 25 children with severe TBI. ICP was monitored in all patients and surgical lesions treated. Standard care for elevated ICP (in 1988) included targeted hyperventilation to partial pressure of arterial carbon dioxide 25–30 mm Hg, administration of dexamethasone, and mannitol for osmolar therapy. If ICP remained >20 mm Hg, patients received pentobarbital as an initial bolus of 4–7 mg/kg followed by a continuous infusion of 1–4 mg/kg/hr to a goal of clinical coma. All patients treated with high-dose barbiturates (n = 11) were monitored with a pulmonary artery catheter. Goals were to maintain ICP <20 mm Hg, cerebral perfusion pressure >40 mm Hg, and hemodynamic stability. Ninety-one percent (ten of 11) required dopamine to maintain blood pressure goals compared with 11% of children who did not receive barbiturate therapy. Eighty-two percent (nine of 11) developed hypotension (mean arterial pressure <80 mm Hg).

Table 1. Evidence table

Reference	Study Description	Data Class, Quality, and Reasons	Results and Conclusion
Studies from previous guidelines Kasoff et al, 1988 (1)	Design: case series N = 11 Age: 3 months to 17 yrs Protocol: patients were treated with high-dose pentobarbital for intracranial hypertension despite first-line therapy Outcome: hemodynamic monitoring, use of inotropic agents, and hospital mortality were assessed	Class III Poor quality: observational study with no control for confounding	4 of 11 (36%) died Hypotension (mean arterial pressure <80 mm Hg) occurred in 9/11 (82%) Systemic vascular resistance was depressed, left ventricular stroke work decreased, cardiac index depressed, pulmonary shunt fraction increased with pentobarbital therapy
Pittman et al, 1989 (20)	Design: case series N = 27 Age: 2 months to 15 yrs Protocol: patients were treated with high-dose pentobarbital for intracranial hypertension despite first-line therapy Outcome: cerebral perfusion pressure, intracranial pressure, and 1-yr outcome were reported	Class III Poor quality: observational study with no control for confounding	14 of 27 (52%) achieved intracranial pressure <20 mm Hg Of 13 with persistently elevated intracranial pressure, 6 died (22%), 2 were vegetative, 2 had moderate recovery, and 3 good recovery

The authors noted that children treated with high-dose barbiturates had diminished cardiac output, lower systemic vascular resistance, decreased left ventricular stroke volume, and increased intrapulmonary shunt. Thirty-seven percent of children treated with high-dose barbiturates died. The effects of barbiturate therapy on ICP and cerebral perfusion pressure were not reported.

A study by Pittman et al (20) reported a case series of 27 children with severe TBI treated with addition of pentobarbital if ICP remained >30 mm Hg after treatment with hyperventilation to a goal arterial carbon dioxide 25–30 mm Hg, serum osmolality >300 mOsm, cerebrospinal fluid drainage, and evacuation of surgical mass lesions. A pentobarbital dose of 5 mg/kg followed by an infusion of 1–2 mg/kg/hr with a goal barbiturate level of 30–40 mg% was used. Fourteen children (52%) responded to pentobarbital and ICP was controlled (<20 mm Hg). Mortality in this subgroup was not reported. Thirteen children had persistent intracranial hypertension despite addition of high-dose barbiturates. Six died within 48 hrs of starting barbiturates. Seven children had prolonged (>2 days) duration of elevated ICP with pressure >35 mm Hg for “extended” periods of time. Glasgow Outcome Scale score was assessed at 6 months and 1 yr after injury in the seven children who survived. Three improved to make a good recovery, two were left

with severe disability, and two were vegetative. Among children with elevated ICP despite the addition of high-dose barbiturates, poor outcome (severe disability–death) was reported in ten of 13 (77%). Glasgow Outcome Scale score was not reported for the 14 children with controlled ICP. In this series of children with intractable intracranial hypertension, addition of high-dose barbiturates controlled ICP in just over half the patients; however, the authors did not report rates of cardiovascular complications, mortality, or survival with neurologic morbidity, preventing conclusions regarding barbiturate-related control of ICP and its effect on outcome. Among children with uncontrolled ICP despite addition of high-dose barbiturates, good survival was possible (33%); however, this estimate is based on a small number (n = 13).

VI. INFORMATION FROM OTHER SOURCES

A. Indications From the Adult Guidelines

There are no published studies of prophylactic barbiturate use in children with severe TBI. The studies in adults are summarized in the *Guidelines for the Management of [Adult] Severe Traumatic Brain Injury* (21). There are two randomized clinical trials that examined early prophylactic administration of barbitu-

rates. Neither reported clinical benefit (22, 23). A study by Schwartz et al (22) did not define the lower age limit in their study and although the study by Ward et al (23) included adolescents aged >12 yrs, they did not separately report the effects of early barbiturate therapy among children. The study by Ward et al (23) reported that 54% of barbiturate-treated patients developed hypotension compared with 7% of control patients. Hypotension is a well-described risk factor for mortality and neurologic morbidity in head-injured pediatric patients (24).

A study by Eisenberg et al (25) reported a multicentered randomized clinical trial of high-dose barbiturates in severely head-injured patients with intractable intracranial hypertension. Patient age ranged from 15 to 50 yrs but results for the pediatric patients were not separately reported. ICP was the primary outcome and patients in the control group could be crossed over to barbiturate therapy at prespecified ICP failure points in the study. Among 68 study patients, 32 were randomized to high-dose barbiturate therapy and 32 of the 36 control patients ultimately crossed over to barbiturate therapy. Therapy before initiating barbiturates included hyperventilation, neuromuscular blockade, sedation, osmolar therapy with mannitol, steroids, and cerebrospinal fluid drainage when possible. The odds of ICP control were twofold greater in the barbiturate group

and survival 1 month after injury was 92% for responders compared with 17% for nonresponders. At 6 months, 36% of responders were vegetative compared with 90% of nonresponders. The cross-over design of this study precludes firm conclusions about the efficacy of high-dose barbiturates to control intractable ICP and improve outcome.

A number of barbiturate dosing regimens have been reported. The study by Eisenberg et al (25) used the following regimen for pentobarbital: a loading dose 10 mg/kg over 30 mins, then 5 mg/kg every hour for three doses, and a maintenance dose of 1 mg/kg/hr.

B. Information Not Included as Evidence

The Cochrane Review (26) has a pooled analysis from three trials of barbiturates and calculated the pooled risk estimated for barbiturate therapy on mortality was 1.09 (95% confidence interval, 0.81–1.47). They found that one in four barbiturate-treated patients developed hypotension and concluded that there is no evidence that barbiturate therapy in patients with acute severe head injury improves outcome.

A study by Nordby et al (27) used thiopental in a study that included children and adults with loading doses of 20–30 mg/kg and a maintenance of 3–5 mg/kg/hr. Doses of thiopental were reduced if blood pressure fell or ICP was <25 mm Hg.

The duration and optimal method to discontinue high-dose barbiturates have not been studied. Clinicians typically wait for at least a 24-hr period of ICP control without sustained elevations with stimulation before beginning to taper the barbiturate infusion (28).

Refractory Intracranial Hypertension

Use of high-dose barbiturates to treat elevated ICP in children with severe TBI has been reported since the 1970s. Marshall et al (29) were the first to report that both control of ICP and outcomes were improved with use of barbiturates; however, patient age was not specified in the report, which was a case series of 25 patients with ICP >40 mm Hg treated with high-dose pentobarbital. When ICP was controlled, mortality was significantly reduced compared with patients with persistently elevated ICP despite

addition of barbiturate therapy (21% vs. 83%).

VII. SUMMARY

Studies regarding high-dose barbiturate administration to treat severe TBI in pediatric patients are limited to two case series (class III evidence), which limits firm conclusions. The evidence suggests that barbiturates effectively lower ICP among a subset of children with intractable intracranial hypertension; however, a beneficial effect on survival or improved neurologic outcome has not been established. Administration of high-dose barbiturates is commonly associated with hypotension and the need for blood pressure support in both children and adults. Studies have not evaluated whether the risk of cardiovascular side effects differ by patient age. Administration of high-dose barbiturates to infants and children requires appropriate monitoring to avoid and rapidly treat hemodynamic instability and should be supervised by experienced critical care providers.

There is no evidence to support use of prophylactic barbiturates to prevent intracranial hypertension or for neuroprotective effects in children.

VIII. KEY ISSUES FOR FUTURE INVESTIGATION

- High-dose barbiturates are used to treat intractable intracranial hypertension in children. Studies are needed to better quantify their effect on ICP, long-term outcome, the risk of concurrent hemodynamic instability, and their association with morbidity and mortality. In addition, direct comparison to other therapies for refractory intracranial hypertension is needed.
- Age-dependent toxicity of high-dose barbiturates has not been evaluated.
- The effectiveness of high-dose barbiturate therapy for children with different anatomical lesions, including diffuse swelling, has not been evaluated for either control of ICP or outcome.
- High-dose barbiturate therapy to control intractable intracranial hypertension among infants with abusive head injury has not been described. These infants have poor cognitive outcomes (30).

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Chapter 12. Decompressive craniectomy for the treatment of intracranial hypertension

I. RECOMMENDATIONS

Strength of Recommendations: Weak.
Quality of Evidence: Low, from poor and moderate-quality class III studies.

A. Level I

There are insufficient data to support a level I recommendation for this topic.

B. Level II

There are insufficient data to support a level II recommendation for this topic.

C. Level III

Decompressive craniectomy (DC) with duraplasty, leaving the bone flap out, may be considered for pediatric patients with traumatic brain injury (TBI) who are showing early signs of neurologic deterioration or herniation or are developing intracranial hypertension refractory to medical management during the early stages of their treatment.

II. EVIDENCE TABLE (see Table 1)

III. OVERVIEW

DC in the setting of TBI is a controversial procedure that has recently become widely considered as a treatment option. It may be performed concomitantly with the removal of a mass lesion to either treat observed brain swelling or act as prophylaxis of anticipated swelling (secondary DC). Alternatively, it may be performed as a standalone procedure for the purpose of treating cerebral herniation or established intracranial hypertension, wherein the timing of the decompression may be predicated on the clinical examination, course of neurologic deterioration, initial degree of intracranial pressure (ICP) elevation, or the resistance of that elevation to various

thresholds of medical treatment (primary DC). These two conditions of employment are actually quite different and it is the second (DC as a primary treatment for cerebral swelling) that is the focus on this section.

The nature of the procedure varies widely. It may consist of uni- or bilateral subtemporal decompressions, hemispheric craniectomies of varying sizes (from relatively small to quite expansive), circumferential craniectomy, or bifrontal craniectomy. The choice of procedure may depend on the underlying pathology, as demonstrated on computed tomography imaging, or may simply be focused on developing the maximum possible compliance compartment. The management of the underlying dura also may vary, ranging from leaving it intact through simple scoring to opening it widely (with or without expansive duraplasty). Furthermore, the treatment of the dura may vary independently with the choice of bony decompressive procedure.

With respect to the use of DC for ICP control in adults, two randomized controlled trials were underway, the DECRA Trial (1) (international multicenter randomized controlled trial (on Early Decompressive Craniectomy in Traumatic Brain Injury), which recently reported their findings (2) of reduced ICP but significantly worsened outcomes, and the RescueICP Trial (3) (randomized evaluation of surgery with craniectomy for uncontrollable elevation ICP). No similar studies are ongoing for the pediatric population.

IV. PROCESS

For this update, MEDLINE was searched from 1996 through 2010 (Appendix B for search strategy), and results were supplemented with literature recommended by peers or identified from reference lists. Of 20 potentially relevant studies, seven new studies were included as evidence for this topic.

V. SCIENTIFIC FOUNDATION

Eight class III studies met the inclusion criteria for this topic and provide evidence to support the recommendations (4–11). These studies vary in critical areas such as their selection criteria for DC, the DC techniques used, and their outcome parameters. In addition, none of them 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.

Is Decompressive Craniectomy Effective in Lowering ICP?

The issue with respect to the efficacy of DC in lowering ICP is not the statistical significance of the change in ICP from before surgery to the postoperative state but rather it is in lowering severely or medically intractable ICP elevation with respect to the treatment threshold such that intracranial hypertension is no longer encountered (optimal outcome) or is easily controlled after surgery.

A study by Hejazi et al (6) was performed investigating early unilateral or bilateral DC with duraplasty for Glasgow Coma Scale score of 3–5 in seven pediatric patients with TBI within 70 mins from trauma resulting from “massive” bilateral or unilateral swelling, compressed supratentorial ventricular spaces, and perimesencephalic cisterns. The DC was frontotemporal and did not include the parietal and occipital regions. A low craniectomy was performed in all patients to decompress the brainstem. The initial ICP exceeded 45 mm Hg in all patients. In six of the seven, ICP remained <20 mm Hg after surgery. Persistent intracranial hypertension (although not to the level of preoperative) in the one patient was controlled with medical therapy. This suggests that DC might be effective in controlling ICP.

A study by Ruf et al (9) was also performed on unilateral or bilateral DC with duraplasty when the ICP exceeded 20 mm Hg for >30 mins in six pediatric patients

Table 1. Evidence table

Reference	Study Description	Data Class, Quality, and Reasons	Results and Conclusion
Study from previous guidelines Cho et al, 1995 (4)	Design: case series N = 13 Age: 2–14 months Protocol: medical treatment in first 4 and DC in 9 ICP and scores on COS measured between 6 months and 6 yrs postinjury (mean, 3.2 yrs) DC: bifrontal DC for diffuse swelling, or large unilateral frontotemporoparietal DCs for unilateral hemispheric swelling	Class III Poor quality: no control for confounders, very small sample and no power calculation	In the surgical group, DC lowered the mean ICP measurements from 54.9 mm Hg to 11.9 mm Hg; effect of medical treatment on ICP was not reported For the medically treated group, scores on the COS, measured at a mean of 3.2 years (range, 6 months to 6 yrs), were 2 dead (COS 5) and 2 vegetative (COS 4); for the surgical group, 2 patients had an “excellent” recovery (COS 1), 2 had a moderate recovery (COS 2), 4 had severe disability (COS 3), and 1 was vegetative; notably, although DC was performed based on ICP elevation alone, a mean of 32 mL of subdural blood was removed during the surgery
New studies Figaji et al, 2003 (5)	Design: case series N = 5 Age: 5–12 yrs Protocol: DC for clinical deterioration in patients presenting with or deteriorating rapidly to GCS $\leq$ 8 in intensive care unit; ICP not monitored before surgery Outcome: GOS DC: unilateral craniotomy with duraplasty either leaving the bone out or loosely suturing it in place (floating flap)	Class III Poor quality: no control for confounders, very small sample, and no power calculation	All patients had early clinical improvement after surgery and were GOS 4 or 5 at long term follow-up (14–40 months) In the 4 patients with postoperative ICP monitoring, 2 had no ICP elevations and 2 had mild, easily controlled elevations
Hejazi et al, 2002 (6)	Design: retrospective case series N = 7 Age: 5–14 yrs GCS: 3–5 on admission and bilateral swelling with compression of the perimesencephalic cisterns on CT; initial ICP >45 mm Hg in all patients Protocol: patients with traumatic brain injury treated with early DC Outcome: survival, ICP DC: unilateral craniectomy, frontal temporal only with duraplasty leaving the bone out or bilateral craniectomy with stellate dural opening	Class III Poor quality: no control for confounders, very small sample and no power calculation	All patients survived despite severe baseline intracranial hypertension; decompression decreased ICP from >45 mm Hg to < 20 mm Hg immediately and it remained controlled in 6 of 7 patients; one patient later developed intracranial hypertension but not to the level present before decompression All patients achieved a “complete recovery” on follow-up of >8 months although this is not defined
Jagannathan et al, 2007 (7)	Design: retrospective case series N = 23 Age: mean 1.9 yrs (2 patients: 19 yrs old and 21 of 23 patients <19 yrs old) GCS: mean 4.6 (3–9) Protocol: patients with traumatic brain injury treated with DC done for either 1) ICP >20 mm Hg refractory to maximal medical therapy; or 2) mass lesion Outcome: long-term functional outcome and independence levels were evaluated using the GOS and a Likert patient quality-of-life rating scale DC: large, wide with duraplasty; unilateral for hemispheric swelling or bifrontal for diffuse swelling; in bifrontal, the sagittal suture was suture ligated and falx sectioned	Class III Poor quality: no control for confounders, very small sample, and no power calculation	Survival rate of 70%; mortality was seen primarily in patients with multisystem trauma ICP control in 19 of 23 patients; high ICP associated with increased mortality; mean follow-up using GOS over 5 years was 4.2 (range, 1–5); majority had “good” outcomes (17 of 23) at 2 yrs 13 of 17 survivors returned to school

Table 1. —Continued

Reference	Study Description	Data Class, Quality, and Reasons	Results and Conclusion
Kan et al, 2006 (8)	Design: case series N = 6 Age: 0.3–14 yrs GCS: mean 4.6 Protocol: DC performed in the absence of mass lesion; all 6 with very severe injuries; DC done in 5 for refractory ICP >25 mm Hg and 1 for herniation Outcome: mortality and ICP DC: large unilateral craniectomy with duraplasty	Class III Poor quality: no control for confounders	5 of 6 patients died 3 of the 4 patients with postoperative ICP monitoring had ICP <20 mm Hg
Ruf et al, 2003 (9)	Design: retrospective case series N = 6 GCS: 3–7 Age: 5–11 yrs Protocol: DC for refractory ICP >20 mm Hg for >30 mins Outcome: 6-month survival and neurological assessment DC: unilateral or bilateral craniectomy (depending on CT) with duraplasty	Class III Poor quality: no control for confounders, very small sample, and no power calculation	3 patients were without disability; 2 had mild to moderate deficits at 6-month follow-up Postoperative ICP <20 mm Hg in 5 of 6 patients; sixth patient required contralateral subsequent DC, then ICP was maintained at ≤ 20 mm Hg
Rutigliano et al, 2006 (10)	Design: retrospective case series N = 6 Age: <20 yrs with 5 <18 yrs (range, 12–15 yrs) and having distinct data Protocol: DC done for refractory “elevated ICP” Outcome: Functional Independence Measure score and ICP DC = bifrontal craniectomies with duraplasty	Class III Poor quality: no control for confounders, very small sample, and no power calculation	All 5 had Functional Independence Measurement scores of independent or minimal assistance at discharge 5 of the 6 patients had no postoperative ICP elevations; 1 had ICP elevations requiring a second surgery for débridement, with no subsequent ICP elevations
Skoglund et al, 2006 (11)	Design: retrospective case series N = 19 Age: 8 <18 yrs (range, 7–16 yrs) and having distinct data GCS: mean 7 (3–15), with deterioration, evidence of herniation, or refractory ICP Protocol: DC done for either 1) ICP >20 mm Hg refractory to Lund therapy; or 2) acute neurologic deterioration immediately after trauma with CT showing diffuse edema Outcome: GOS at 1 yr DC: large with duraplasty; unilateral for hemispheric swelling or bifrontal for diffuse swelling	Class III Moderate quality: unclear if outcome assessment methods were unbiased	At ≥ 1 yr follow-up, 3 patients with GOS = 5, 1 GOS = 4, 3 GOS = 3, and 1 dead; 5 of these patients with neurologic deterioration or pupillary changes at the time of surgery

DC, decompressive craniectomy; ICP, intracranial pressure; COS, Children’s Outcome Scale; GCS, Glasgow Coma Scale; GOS, Glasgow Outcome Scale; CT, computed tomography.

with severe TBI. In five of the six, ICP remained <20 mm Hg after surgery. Persistent intracranial hypertension in the sixth patient prompted a return to surgery for a contralateral DC, which resulted in sustained ICP control. This suggests that DC might be effective in controlling ICP. Unfortunately, further information on how the choice of operation was made in these patients is lacking.

A study by Kan et al (8) was performed to investigate a large unilateral DC with duraplasty in pediatric patients with TBI, either in conjunction with the removal of a mass lesion (45 patients) or primarily for brain swelling (six patients, five for refractory ICP >25 mm Hg, and one for herniation). The six patients relevant to this topic were very severely injured with

low admission Glasgow Coma Scale scores, evidence of herniation, or severe secondary insults common among them. For these six patients, three of the four who received postoperative ICP monitoring had sustained ICP values <20 mm Hg. The fourth had intracranial hypertension requiring further treatment. Five of the six patients died.

A study by Rutigliano et al (10) was performed which was a retrospective case series of six patients with TBI of age <20 yrs who underwent DC for elevated ICP (without a specified definition), which was refractory to guidelines-based treatment. Five of these patients were <18 yrs of age and could be analyzed separately. They performed wide bifrontal/biparietal craniectomies with duraplasty. Four of the five had no postoperative ICP eleva-

tions. The fifth patient required a return to surgery for intracranial hypertension whereupon débridement of the contused brain resulted in resolution.

A study by Jagannathan et al (7) was performed as a retrospective case series of 23 patients with TBI of age <20 yrs who underwent DC for initial mass lesion requiring evacuation or elevated ICP (>20 mm Hg), which was refractory to guidelines-based treatment. Twenty-one of these patients were <18 yrs of age and could be analyzed separately. They performed wide bifrontal/biparietal craniectomies with duraplasty and sectioning of the falx or unilateral DC if there was a mass lesion or unilateral swelling. Ten of the 23 patients underwent early DC, 11 had later DC, and two even later as a result of medical instability. Mean ICP

reduced from 30 mm Hg preoperatively to 18 mm Hg postoperatively. Nineteen of 23 patients had control of postoperative ICP elevations with maximal medical management. Two patients continued to have refractory ICP.

A study by Cho et al (4) was a case series of 23 children <2 yrs of age presenting with nonaccidental trauma. Children were included based on their ICP regardless of their presenting level of consciousness. A subgroup of 13 patients with a Children's Coma Score equivalent to severe on the Glasgow Coma Scale, and ICP values >30 mm Hg, were treated medically (n = 4) or with DC (n = 9) based on either family wishes or being admitted before DC became a routine part of treatment for this disease. On the nine surgical patients, bifrontal DC was performed for diffuse swelling or large unilateral frontotemporoparietal DCs for unilateral hemispheric swelling. They included a section of the anterior sagittal sinus and an expansive duraplasty. The decompression was performed within 24 hrs of injury in the majority. In the surgical group, DC lowered the mean ICP measurements from 54.9 mm Hg to 11.9 mm Hg.

In summary, it appears that DC may be effective in lowering ICP to below the threshold for treatment in patients refractory to medical management. This limited conclusion would add some support to choosing to perform DC for ICP control when intracranial hypertension is resistant to nonsurgical management and the ICP levels maintained are considered hazardous to the patient.

Does Decompressive Craniectomy Improve Clinical Outcomes?

This section focuses on whether DC performed for severe or intractable intracranial hypertension or clinical herniation is associated with a beneficial influence on outcome.

All of the studies in this section are retrospective case series. All used retrospectively collected data, except for the Rutigliano et al (10) study that used a prospectively collected database, which was not designed specific to the question of DC. None of them have internal or matched external controls and there were no randomized controlled trials. Common to all of these studies is the absence of sufficient data on the injury characteristics of the study group to predict their

outcomes independent of the surgical decompression using predictive modeling.

A study by Hejazi et al (6) reported that all of the patients with early DC had a "complete recovery" although this is not defined. There was no mortality and complication rate was low with only subdural effusions in four of seven.

A study by Figaji et al (5) reported "early [postoperative] clinical improvement" in their decompressed patients. All five cases had Glasgow Outcome Scale scores of 4–5 at 14- to 40-month follow-up. The patients had not had preoperative ICP monitoring and had DC performed for clinical deterioration. The authors felt that the outcomes were better than expected given that each of the patients had an initial Glasgow Coma Scale score ≤ 8 , each had a documented secondary deterioration, which was believed to be the result of raised ICP, pupillary abnormalities were seen in four, and all demonstrated obliteration of the perimesencephalic cisterns (diffuse injury III and IV).

A study by Ruf et al (9) studied six pediatric patients with TBI undergoing DC for refractory ICP >20 mm Hg. One of the six was a posterior fossa DC to treat swelling from a cerebellar contusion. At 6 months, all patients had survived, three being described as "normal" and the others having mild-to-moderate residual deficits.

A study by Rutigliano et al (10) described six pediatric patients with TBI who underwent DC. Five of these patients were <18 yrs of age. A large bilateral frontoparietal DC with duraplasty was performed for "elevated ICP" refractory to tier 1 and tier 2 medical management. They reported early signs of clinical improvement and discharge Functional Independence Measurement scores of independent or minimal assistance for all five patients.

A study by Jagannathan et al (7) described 21 pediatric patients with TBI after undergoing DC either incidentally after evacuation of a mass lesion or for diffuse swelling refractory ICP to medical management. Eighteen of 23 were done for refractory ICP to maximal medical management, three of whom had pupillary changes and did not survive DC. They reported an overall 22% mortality rate despite ICP ≤ 20 mm Hg in two of the five patients who died. Mean follow-up was 62 months (range, 11–126 months) and the mean Glasgow Outcome Scale score was 4.2 (range, 1–5). The

mean score on the quality-of-life questionnaires was 4 (maximum, 5) in the ability to perform activities of daily living, general cognition, interpersonal behavior, and emotional behavior (range, 1–4.75).

In the Cho et al (4) case series, children <2 yrs of age with severe TBI from nonaccidental trauma and ICP values >30 mm Hg were treated with medically (n = 4) or with decompressive craniotomy (n = 9). For the medically treated group, scores on the Children's Outcome Scale (COS), measured at a mean of 3.2 yrs (range, 6 months to 6 yrs), revealed two dead (COS 5) and two vegetative (COS 4). For the surgical group, two patients had an "excellent" recovery (COS 1), two had a moderate recovery (COS 2), four had severe disability (COS 3), and one was vegetative. Notably, although DC was performed based on ICP elevation alone, a mean of 32 mL of subdural blood was removed during the surgery.

Two studies reported less favorable outcomes (8, 11). A study by Skoglund et al (11) studied 19 patients with TBI, of whom eight were <18 yrs, treated with DC for either refractory ICP >20 mm Hg or acute neurologic deterioration immediately after trauma with computed tomography scan showing diffuse edema. All patients were medically managed using the Lund approach. Five of the eight pediatric patients had neurologic deterioration or pupillary changes at the time of surgery. Outcome at ≥ 1 yr after surgery was three patients with Glasgow Outcome Scale score of 5, one with Glasgow Outcome Scale score of 4, three with Glasgow Outcome Scale score of 3, and one death.

A study by Kan et al (8) described 51 pediatric patients with TBI undergoing DC, although the craniectomy was incidental to surgery to evacuate a mass lesion in 45. Five cases were done for refractory ICP >25 mm Hg and the sixth for clinical herniation. These patients were very severely injured. Three were Glasgow Coma Scale score 3 on admission, three were bilaterally fixed and dilated, and two others had a unilateral fixed and dilated pupil. The sixth patient presented with profound hypotension. They reported an 83% mortality rate despite ICP ≤ 20 mm Hg in three of the four patients monitored after surgery. Five of the six patients died.

Given the paucity of descriptive statistics contained within these studies, it is impossible to accurately compare the pa-

tients studied between these various papers. Adding in the differences in trigger criteria for DC, variations in DC technique, and the wide variations in outcome measurements, no more than simple, qualitative summaries may be made. Given the severity of injury of these children and the physiological abnormalities required to become candidates for DC, cautious interpretation of these outcomes suggests that DC may be effective in improving outcome in patients with medically intractable intracranial hypertension.

VI. INFORMATION FROM OTHER SOURCES

A. Indications From the Adult Guidelines

The *Guidelines for the Surgical Management of TBI* (12), published in 2006, found no class I or II evidence on which to base level I or II recommendations. The level III-equivalent recommendations with respect to DC were based on class III literature, the most prominent of which were the reports of Polin et al (13) and Taylor et al (14) (briefly reviewed subsequently).

The recommendations from the adult guidelines regarding DC were:

- Bifrontal DC within 48 hrs of injury is a treatment option for patients with diffuse, medically refractory posttraumatic cerebral edema and resultant intracranial hypertension.
- Decompressive procedures, including subtemporal decompression, temporal lobectomy, and hemispheric DC, are treatment options for patients with refractory intracranial hypertension and diffuse parenchymal injury with clinical and radiographic evidence for impending transtentorial herniation.

Of note, the recently completed DECRA study by Cooper et al (2) for adults with diffuse severe TBI showed that ICP could be effectively reduced with early bifrontotemporoparietal DC but, interestingly, outcomes were worse in the surgery group than the clinical management group alone.

B. Information Not Included as Evidence

Indications From the 2009 Cochrane Review on Decompressive Craniectomy. In the 2009 update of the Cochrane Review on DC (15), the author found only one publication of sufficient rigor to include, that of Taylor et al (14), which

studied a pediatric TBI group. It was concluded that “despite the wide confidence interval for death and the small sample size of this one identified study, the treatment may be justified in patients below the age of 18 yrs when maximal medical treatment has failed to control ICP.” With respect to the current evidence report, however, this paper must be excluded as a result of its inclusion of patients with admissions scores above the cutoff (≤ 8).

VII. SUMMARY

Eight small class III case series suggest that large decompressive surgeries with duraplasty may be effective in reversing early signs of neurologic deterioration or herniation, and in treating intracranial hypertension refractory to medical management, and that these effects may be correlated with improving outcomes in the critically ill pediatric patients who develop such indications. Limited evidence suggests that duraplasties, when done, should be large, and consideration should be given to removing the bone rather than “floating” it *in situ*. There is insufficient evidence to allow defining the patient characteristics that either 1) optimize the beneficial effects of these procedures or 2) render them ineffective.

VIII. KEY ISSUES FOR FUTURE INVESTIGATION

- A primary focus on future research should be performing a randomized controlled trial on DC as a method of controlling increased ICP in pediatric patients with TBI.
- Given the infrequency with which pediatric patients with TBI are admitted to any individual center, it would be very useful to develop a prospective pediatric TBI database to facilitate class II investigations into many of the variables relevant to DC (such as timing, size and placement, and technique), which are unlikely to ever be subject to class I study.
- It would be very useful if the investigators involved in the two adult DC trials, the DECRA trial (1) and the Rescue ICP trial (3), both of which enrolled patients overlapping with the pediatric age group, would parse out this group for separate subgroup analysis of efficacy and technical details. It would be valuable to design or determine standardized and practical techniques to quantify the physiological changes induced by DC, both as a clinically useful measure of efficacy and as a research parameter.

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Chapter 13. Hyperventilation

I. RECOMMENDATIONS

Strength of Recommendations: Weak.

Quality of Evidence: Low, from one poor-quality study and one moderate-quality class III study.

A. Level I

There are insufficient data to support a level I recommendation for this topic.

B. Level II

There are insufficient data to support a level II recommendation for this topic.

C. Level III

Avoidance of prophylactic severe hyperventilation to a $\text{Paco}_2 < 30$ mm Hg may be considered in the initial 48 hrs after injury.

If hyperventilation is used in the management of refractory intracranial hypertension, advanced neuromonitoring for evaluation of cerebral ischemia may be considered.

II. EVIDENCE TABLE (see Table 1)

III. OVERVIEW

Hyperventilation has been used in the management of severe pediatric traumatic brain injury (TBI) for the rapid reduction of ICP since the 1970s. This approach was based on the assumption that hyperemia was common after pediatric TBI. Hyperventilation therapy was thought to benefit the injured brain primarily through an increase in perfusion to ischemic brain regions and a decrease in ICP. More recent pediatric studies have shown that hyperemia is uncommon and also have raised concerns about the safety of hyperventilation therapy (1–6).

Research on the effect of hyperventilation in children has focused on assessment of cerebral physiological variables. The effect of hyperventilation therapy on

outcome in infants and children with severe TBI has not been directly compared with other therapies such as hyperosmolar agents, barbiturates, hypothermia, or early decompressive craniectomy.

Hyperventilation reduces ICP by producing hypocapnia-induced cerebral vasoconstriction and a reduction in cerebral blood flow (CBF) and cerebral blood volume, resulting in a decrease in ICP. Recent clinical studies in mixed adult and pediatric populations have demonstrated that hyperventilation may decrease cerebral oxygenation and may induce brain ischemia (5, 7–9). In addition, after TBI, the CBF response to changes in Paco_2 can be unpredictable. A study by Stringer et al (10) studied regional CBF using xenon computed tomography and vascular reactivity before and after hyperventilation in 12 patients including three children with severe TBI. Hyperventilation-induced CBF reductions affected both injured and apparently intact areas of the brain. The ischemic threshold was defined as a CBF of 23 mL/100 g/min in gray matter and this occurred in four of 12 patients after hyperventilation. Changes in ICP, cerebral perfusion pressure, and mean arterial pressure were variable in these patients after hyperventilation. The level of hyperventilation used in this study was profound with end-tidal CO_2 values of 20–26 mm Hg before and 8–19 mm Hg after hyperventilation. In addition to reducing CBF, prophylactic hypocarbia after TBI has been shown experimentally to reduce the buffering capacity of cerebrospinal fluid (CSF), an effect that may be as or more important than its effect on CBF (5).

Despite a prior recommendation in the 2003 guidelines against prophylactic hyperventilation, it remains a commonly used therapy in children (11–13). For example, >40% of the children in the recent Canadian multicentered trial of hypothermia in severe pediatric TBI had $\text{Paco}_2 < 30$ mm Hg (12). Similarly, in the study by Curry et al (11), 50% of patients with severe TBI had severe hypocarbia ($\text{Paco}_2 < 30$ mm Hg) by arterial blood gas in the first 48 hrs of admission. This finding parallels another recent report that

mild hyperventilation was the most commonly used therapy, having been applied in >90% of patients in the data bank of >500 children with severe TBI from the United Kingdom and Ireland (14).

IV. PROCESS

For this update, MEDLINE was searched from 1996 through 2010 (Appendix B for search strategy), and results were supplemented with literature recommended by peers or identified from reference lists. Of 15 potentially relevant studies, one was added to the existing table and used as evidence for this topic.

V. SCIENTIFIC FOUNDATION

Two class III studies met the inclusion criteria for this topic and provide evidence to support the recommendations (11, 15). Neither represented a comparison of hyperventilation vs. normal ventilation or to any other therapy targeting control of ICP. Similarly, there were no reports in children specifically addressing the effects of varying levels of hyperventilation on ICP or outcome or studies of the transient application of hyperventilation in the setting of impending herniation or ICP crisis. Lastly, neither study had a standardized protocol to assess Paco_2 , measuring it only intermittently.

One report described the effects of hyperventilation on CBF, brain physiology, and Glasgow Outcome Scale at 6 months (15). A study by Skippen et al (15) was carried out as a prospective nonrandomized, selected case series of 23 children (3 months to 16 yrs of age) with isolated severe TBI. CBF was measured by xenon computed tomography during Paco_2 adjustments to >35, 25–35, and <25 mm Hg. The ischemic threshold was defined as $\text{CBF} < 18$ mL/100 g/min. However, the ischemic threshold in children is not defined and may vary with age. CO_2 reactivity of CBF was also assessed. Management included CSF drainage and hyperosmolar therapy but not steroids or barbiturates. As Paco_2 was reduced with hyperventilation, CBF decreased in almost all patients despite decreased ICP and increased cerebral perfusion pressure. A relationship

Table 1. Evidence table

Reference	Study Description	Data Class, Quality, and Reasons	Results and Conclusion
Study from previous guidelines Skippen et al, 1997 (15)	Design: case series N = 23 Age: mean 11 yrs (range, 3 months to 16 yrs) Protocol: CBF measured by xenon-enhanced computed tomography during partial pressure of arterial carbon dioxide adjustments to >35, 25–35, and <25 mm Hg Outcome: ischemic threshold defined as <18 mL/100 g/min; Glasgow Outcome Scale score at 6 months	Class III Poor quality: no control for confounders	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 arterial carbon dioxide (range, –2.3% to 7.1%) 52.2% had good or moderate outcome; 43.5% were severe or vegetative; 4.3% died (no analysis)
New study Curry et al, 2008 (11)	Design: retrospective cohort study (trauma registry) before and after 2003 pediatric Brain Trauma Foundation guidelines N = 464 Age: mean 8.0 yrs (range, 0–14 yrs) Protocol: all children had controlled mechanical ventilation Outcome: incidence of severe hypocarbia (arterial carbon dioxide <30 mm Hg) during the initial 48 hrs and risk of inpatient mortality Analysis: chi square and logistic regression	Class III Moderate quality: unclear if outcome assessment methods unbiased; otherwise met all criteria	Severe hypocarbia 60% patients before and 52% after ($p = .19$) Severe hypocarbia on initial measurement was more common in infants (≤ 2 yrs) vs. older children (30.8% vs. 19.3%, respectively, $p = .02$) Incidence of severe hypocarbia in the first 48 hrs was similar between age groups (58.9% for infants vs. 58.0% for older children; $p = .91$) Mortality adjusted odds ratio (95% confidence interval) of 1.44 (0.56–3.73) for 1 episode, 4.18 (1.58–11.03) for 2 episodes of severe hypocarbia, and 3.93 (1.61–9.62) for ≥ 3 episodes

CBF, cerebral blood flow.

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 <25 mm Hg, respectively. However, no statistical analysis was done. Fifty-two percent had a good or moderate outcome, 43.5% were severely disabled or vegetative, and 4.3% died. Again, no analysis was conducted.

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 (11). A study by Curry et al (11) was carried out as a retrospective cohort study of 464 patients <15 yrs of age with an admission Glasgow Coma Scale score ≤ 9 and a head Abbreviated Injury Score ≥ 3 with a Paco_2 recorded in the first 48 hrs of admission for the years 2000–2005. The authors examined the incidence of severe hypocarbia (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 (16). They found a nonsignificant change in the incidence of severe hypocarbia from 60% of patients before to 52% after ($p = .19$). Patients with one documented episode of severe hypocarbia, controlling for emergency department Glasgow Coma Scale score, lowest emergency department systolic blood pressure, Injury Severity Score, Paco_2 sampling frequency, and year of admission, had an adjusted odds ratio (95% confidence interval) for mortality of 1.44 (0.56–3.73) for one episode of severe hypocarbia, 4.18 (1.58–11.03) for two episodes, and 3.93 (1.61–9.62) for three or more episodes compared with patients with mild or no hypocarbia. These findings, although retrospective, show a strong association of severe hypocarbia with poor outcomes. However, there might be other contributors to hypocarbia such as marked reduction in metabolic rates or acidosis from systemic shock. Thus, the exact contribution of induced hyperventilation to

poor outcome cannot be clearly defined from this study.

VI. INFORMATION FROM OTHER SOURCES

A. Indications From the Adult Guidelines

The most recent adult guidelines (17) had one level II recommendation: “prophylactic hyperventilation (Paco_2 of 25 mm Hg or less) is not recommended.” The authors also had several level III recommendations: 1) “hyperventilation is recommended as a temporizing measure for the reduction of elevated ICP”; 2) “hyperventilation should be avoided during the first 24 hrs after injury when CBF is often critically reduced”; and 3) “if hyperventilation is used, jugular venous oxygenation saturation or brain tissue oxygen tension measurements are recommended to monitor oxygen delivery.”

VII. SUMMARY

Despite a lack of published evidence supporting the use of hyperventilation in the management of pediatric patients with severe TBI, it continues to be used commonly worldwide. No randomized controlled trial has been carried out to study the impact of hyperventilation on any aspect of the management of severe TBI in children such as in the setting of refractory intracranial hypertension or herniation. The limited evidence, however, supports that prophylactic severe hyperventilation to a $\text{Paco}_2 < 30$ mm Hg should be avoided in the initial 48 hrs after injury. Arguing against the use of prophylactic hyperventilation, published evidence discussed in this report indicates that the use of hyperventilation is associated with CBF reductions and that prolonged and/or significant hypocarbia is associated with poor outcome in pediatric patients with severe TBI. As a result, advanced neuromonitoring for evaluation of cerebral ischemia may be considered if hyperventilation is to be used in the management of refractory intracranial hypertension.

VIII. KEY ISSUES FOR FUTURE INVESTIGATION

- In the setting of refractory intracranial hypertension or brain herniation, studies are needed to determine the efficacy of hyperventilation in comparison to other second-tier therapies.
- Studies are needed to determine the optimal monitoring technique in patients treated with hyperventilation, including assessments of markers of cerebral ischemia, such as CBF, brain tissue oxygen

tension, jugular venous oxygenation saturation, transcranial Doppler, near-infrared spectroscopy, serum biomarkers of brain injury, or other advanced neuromonitoring.

- The effects of hyperventilation on long-term outcome should be addressed.

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Chapter 14. Corticosteroids

I. RECOMMENDATIONS

Strength of the Recommendation: Weak.

Quality of the Evidence: Low, from two reports of one small, moderate-quality class II study.

A. Level I

There are insufficient data to support a level I recommendation for this topic.

B. Level II

The use of corticosteroids is not recommended to improve outcome or reduce intracranial pressure (ICP) for children with severe traumatic brain injury (TBI).

C. Level III

There are insufficient data to support a level III recommendation for this topic.

II. EVIDENCE TABLE (see Table 1)

III. OVERVIEW

Corticosteroids are widely used in treatment of a variety of pediatric illnesses, including neurologic conditions such as brain tumors and meningitis. Steroids are thought to restore altered vascular permeability (1), inhibit tumor induced angiogenesis (2), and decrease edema and cerebrospinal fluid production (3, 4) as well as diminish free radical production (3). These mechanisms of action provide a rationale for potential benefit in neurologic diseases. Administration of steroids to patients with symptomatic brain tumors is standard care and preoperative administration is beneficial for patients undergoing resection. However, the efficacy of steroids to attenuate morbidity among pediatric patients with acute bacterial meningitis remains controversial (5). A number of corticosteroids are available; however, only dexamethasone has been reported in

studies of pediatric TBI. This chapter addresses the use of corticosteroids as a neuroprotective agent to treat cerebral edema and improve Glasgow Outcome Scale in pediatric TBI. The question of the use of corticosteroids in the treatment of refractory hypotension was not addressed by the studies. Finally, the role of steroid therapy, both efficacy and toxicity, remains less well known in children compared with adults.

IV. PROCESS

For this update, MEDLINE was searched 1996 through 2010 (Appendix B for search strategy), and results were supplemented with literature recommended by peers or identified from reference lists. Of 20 potentially relevant studies, none were added as evidence for this topic.

V. SCIENTIFIC FOUNDATION

Two reports of one moderate-quality class II trial met the inclusion criteria for this topic and provide evidence to support the recommendation (6, 7).

A study by Fanconi et al (6) was a randomized, prospective, placebo-controlled clinical trial on 25 pediatric patients with severe TBI using dexamethasone at 1 mg/kg/day for 3 days ($n = 13$) vs. placebo ($n = 12$). Baseline characteristics did not differ between groups. Dexamethasone treatment did not influence ICP (mean of 14 mm Hg in both groups), cerebral perfusion pressure, number of interventions required, duration of intubation, or 6-month Glasgow Outcome Scale vs. placebo. However, steroid treatment vs. placebo significantly suppressed endogenous-free cortisol levels up to day 6. In addition, steroid treatment resulted in a trend toward increased bacterial pneumonia vs. placebo (seven of 13 vs. two of 12, respectively, $p = .097$). Although this study appeared to be carefully performed, 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.

The study by Kloti et al (7) reported on 24 of the same 25 patients from the study

described previously. Additional outcomes in this report included duration of ICP monitoring; steroid treatment produced no difference between groups. The small sample size for this trial limits the ability to make definitive conclusions regarding neurologic outcomes or complications. However, suppression of cortisol production by steroid treatment was clearly documented.

VI. INFORMATION FROM OTHER SOURCES

A. Indications From the Adult Guidelines

The most recent *Guidelines for the Management of [Adult] Severe Traumatic Brain Injury* (8) summarize studies of corticosteroid administration in adults and found that it did not improve functional outcome or mortality or lower ICP. They provide a strong class I recommendation against administration of steroids to improve outcome or lower ICP and caution that use is associated with increased risk of mortality and thus contraindicated. However, the studies in the adult guidelines do not specifically report on steroids use for pediatric patients after severe TBI.

B. Information Not Included as Evidence

Children with severe TBI have been observed to have higher rates of generalized hyperemia and more diffuse swelling after injury compared with adults, which could, theoretically, serve as a basis for the possible need for different approaches to the management of brain edema (9, 10). One report of steroid therapy in patients with severe TBI indicated better outcomes for children vs. adults (11); however, this difference may be the result of age and cannot be directly attributed to steroid-associated benefit. Several reports included in the 2003 pediatric TBI guidelines were excluded from this document because they failed to meet the more rigorous inclusion criteria. A study by Cooper et al (12) looked at a combined group

Table 1. Evidence table

Reference	Study Description	Data Class, Quality, and Reasons	Results and Conclusion
Studies from previous guidelines Fanconi et al, 1988 (6); Kloti et al, 1987 (7)	Design: randomized prospective, placebo controlled trial N = 25; 13 steroid, 12 placebo (Fanconi) N = 24; 12/12 (Kloti) Age: range 1.4–15.8 yrs Glasgow Coma Scale score: ≤ 7 Protocol: dexamethasone at 1 mg/kg/day vs. placebo Outcome: 6-month Glasgow Outcome Scale, ICP, duration of ICP monitoring, duration of intubation, cerebral perfusion pressure, free cortisol levels, and complications	Class II Moderate quality: randomization and allocation concealment methods not described; unclear if outcome assessors were blinded	Steroid treatment resulted in no differences vs. placebo in ICP, cerebral perfusion pressure, 6-month Glasgow Outcome Scale, duration of ICP monitoring, or duration of intubation Steroid treatment vs. placebo significantly suppressed endogenous free cortisol levels from day 1 to day 6 Steroid treatment resulted in a trend to ward increased bacterial pneumonia (7 of 13 vs. 2 of 12 vs. placebo, respectively, $p = .097$)

ICP, intracranial pressure.

of children and adults with severe and moderate TBI. Only ten patients were ≤ 10 yrs of age. In this subgroup, two of four (50%) in the placebo group compared with five of six (83%) in a combined low- and high-dose steroid group had a good outcome, which did not reach statistical significance. A study by Gobiet (13) compared two cohorts, one from 1972–1974 without steroid treatment and a second from 1975–1976 with steroid treatment, and suggested a reduction in mortality. However, important differences between groups in ICP monitoring and intensive care unit care were also described, making it impossible to determine the effect of steroids on outcome. A study by James et al (14) reported a case series of nine children with severe TBI and compared two doses of dexamethasone (1 mg/kg or 0.25 mg/kg) vs. no steroid in groups with sample sizes of only two in some groups, limiting any ability to assess for a treatment effect. A study by Kretschmer (15) reported a case series of 107 children in 1983 with TBI. Fifty-six received steroids and 51 received dexamethasone in addition to standard therapy. Reasons for exclusion of this study were the inclusion of 29 cases of penetrating injury, selection bias—24 of 29 cases of penetrating injury were in the no steroid group, and inclusion of patients with mild or moderate TBI. Overall mortality did not differ with treatment (24% vs. 23%). The authors reported a trend toward reduced mortality with steroid use in the subgroup of children with intracranial hematoma: from 36.8% to 11.8% in the placebo vs. steroid groups,

respectively. Although no significant beneficial effect of steroids was reported, the exclusion violations in the overall study, small sample size, and major limitations in the study design preclude the ability to make meaningful conclusions with regard to corticosteroid therapy in pediatric TBI.

VII. SUMMARY

The recommendation regarding steroid administration to treat severe TBI in pediatrics is based on two reports of one class II trial, which indicates that steroid treatment is not associated with improved functional outcome, decreased mortality, or reduced ICP. Significant suppression of endogenous cortisol levels was documented with dexamethasone treatment and trends toward increased incidence of pneumonia were observed.

Given the lack of evidence for benefit in children and the potential for harm from infectious complications and known suppression of the pituitary adrenal axis, the routine use of steroids to treat children with severe TBI to lower ICP or improve functional outcomes or mortality is not recommended.

VIII. KEY ISSUES FOR FUTURE INVESTIGATION

- Further studies are needed to determine risk factors for pituitary dysfunction and appropriate screening in the acute and chronic phases after severe TBI in children because alterations in the endogenous steroid response could

have important implications on management, complications, and outcome (16).

- Future research should consider testing the efficacy of the use of corticosteroids for treatment of severe TBI in pediatric patients as distinct from adults. However, if a corticosteroid trial is considered, preliminary data are needed for careful assessment of potential toxicities, including infectious complications, hyperglycemia, and detrimental effects on nutritional status.

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Chapter 15. Analgesics, sedatives, and neuromuscular blockade

I. RECOMMENDATIONS

Strength of Recommendations: Weak.
Quality of Evidence: Low, from poor-quality class III studies.

A. Level I

There are insufficient data to support a level I recommendation for this topic.

B. Level II

There are insufficient data to support a level II recommendation for this topic.

C. Level III*

Etomidate may be considered to control severe intracranial hypertension; however, the risks resulting from adrenal suppression must be considered.

Thiopental may be considered to control intracranial hypertension.

*In the absence of outcome data, the specific indications, choice and dosing of analgesics, sedatives, and neuromuscular-blocking agents used in the management of infants and children with severe traumatic brain injury (TBI) should be left to the treating physician.

*As stated by the Food and Drug Administration, continuous infusion of propofol for either sedation or the management of refractory intracranial hypertension in infants and children with severe TBI is not recommended.

II. EVIDENCE TABLE (see Table 1)

III. OVERVIEW

Analgesics, sedatives, and neuromuscular-blocking agents are commonly used in the management severe pediatric TBI. Use of these agents can be divided into two major categories: 1) for emergency intubation; and 2) for management including control of elevated intracranial pressure (ICP) in the intensive care unit (ICU). This chapter evaluates these agents during ICU treatment.

Analgesics and sedatives are believed to favorably treat a number of important pathophysiological derangements in se-

vere TBI. They can facilitate necessary general aspects of patient care such as the ability to maintain the airway, vascular catheters, and other monitors. They can also facilitate patient transport for diagnostic procedures and mechanical ventilatory support. Other proposed benefits of sedatives after severe TBI include anti-convulsant and antiemetic actions, the prevention of shivering, and attenuating the long-term psychological trauma of pain and stress. Analgesics and sedatives also are believed to be useful by mitigating aspects of secondary damage. Pain and stress markedly increase cerebral metabolic demands and can pathologically increase cerebral blood volume and raise ICP. Studies in experimental models showed that a two- to threefold increase in cerebral metabolic rate for oxygen accompanies painful stimuli (1, 2). Noxious stimuli such as suctioning can also increase ICP (3–6). Painful and noxious stimuli and stress can also contribute to increases in sympathetic tone with hypertension and bleeding from operative sites (7). However, analgesic or sedative-induced reductions in arterial blood pressure can lead to cerebral ischemia as well as vasodilation and can exacerbate increases in cerebral blood volume and ICP. In the absence of advanced neuromonitoring, care must be taken to avoid this complication.

The ideal sedative for patients with severe TBI has been described as one that is rapid in onset and offset, easily titrated to effect, has well-defined metabolism (preferably independent of end-organ function), neither accumulates nor has active metabolites, exhibits anticonvulsant actions, has no adverse cardiovascular or immune actions, and lacks drug-drug interactions while preserving the neurologic examination (8).

Neuromuscular-blocking agents have been suggested to reduce ICP by a variety of mechanisms including a reduction in airway and intrathoracic pressure with facilitation of cerebral venous outflow and by prevention of shivering, posturing, or breathing against the ventilator (9). Reduction in metabolic demands by elimination of skeletal muscle contraction has also

been suggested to represent a benefit. Risks of neuromuscular blockade include the potential devastating effect of hypoxemia secondary to inadvertent extubation, risks of masking seizures, increased incidence of nosocomial pneumonia (shown in adults with severe TBI) (9), cardiovascular side effects, immobilization stress (if neuromuscular blockade is used without adequate sedation/analgesia), and increased ICU length of stay (9, 10). Myopathy is most commonly seen with the combined use of nondepolarizing agents and corticosteroids. Incidence of this complication varies between 1% and over 30% of cases (5, 11, 12). Monitoring of the depth of neuromuscular blockade can shorten duration of its use in the ICU (13).

IV. PROCESS

For this update, MEDLINE was searched from 1996 through 2010 (Appendix B for search strategy), and results were supplemented with literature recommended by peers or identified from reference lists. Of 46 potentially relevant studies, two were included as evidence for this topic.

V. SCIENTIFIC FOUNDATION

The recommendations on the use of analgesics, sedatives, and neuromuscular-blocking agents in this chapter are for patients with a secure airway who are receiving mechanical ventilatory support yielding the desired arterial blood gas values and who have stable systemic hemodynamics and intravascular volume status.

Two class III studies of the use of analgesics or sedatives met inclusion criteria for this topic and provide evidence to support the recommendations: one study about etomidate and one about thiopental. These studies only addressed ICP as the outcome (14, 15). No study addressed the most commonly used analgesics and sedatives (narcotics and benzodiazepines).

Etomidate

A study by Bramwell et al (14) carried out a prospective unblinded class III study of the effect of a single dose of

Table 1. Evidence table

Reference	Study Description	Data Class, Quality, and Reasons	Results and Conclusion
New studies			
Bramwell et al, 2006 (14)	Design: prospective case series N = 8 Age: <15 yrs Protocol: single IV dose of etomidate (0.3 mg/kg) Purpose: determine if etomidate reduces ICP in the setting of intracranial hypertension (ICP >20 mm Hg) Outcome: ICP	Class III Poor quality: no control for confounders; very small sample size	Etomidate administration resulted in a decrease in ICP vs. baseline ($p < .05$) without change in mean arterial pressure, thereby increasing cerebral perfusion pressure at each 5-min interval; at 6 hrs after etomidate administration, adrenocorticotrophic hormone stimulation tests showed adrenal suppression in 4 of the 8 patients; however, no patient required treatment with steroids
de Bray et al, 1993 (15)	Design: prospective case series N = 10 TBI and 10 orthopedic controls Age: 4–14 yrs Protocol: IV administration of thiopental and Doppler assessment of middle cerebral artery flow velocity Purpose: assess the effect of thiopental (5 mg/kg, IV) on ICP and middle cerebral artery flow velocity Outcome: middle cerebral artery flow velocity blood velocity, measured at the time of greatest decrease of mean arterial pressure after thiopental administration, compared with baseline	Class III Poor quality: no control for confounders; unclear if selection was unbiased; unclear if missing data	Thiopental reduced mean ICP, measured in 6 of the 10 patients with TBI, by 48% ($p < .01$), with no significant correlation with middle cerebral artery flow velocity; thiopental also reduced middle cerebral artery flow velocity (systolic velocities $-15\% \pm 6.9\%$, $p < .01$) and diastolic velocities ($-21\% \pm 6.5\%$, $p < .01$) in cases, not controls; reduction in middle cerebral artery flow velocity occurred in 90% cases compared with 10% controls; mean ICP, measured in 6 of the 10 patients with TBI, was reduced by 48% ($p < .01$) with no significant correlation with middle cerebral artery flow velocity

IV, intravenous; ICP, intracranial pressure; TBI, traumatic brain injury.

etomidate (0.3 mg/kg, intravenously) on ICP >20 mm Hg in eight children with severe TBI. Etomidate reduced ICP vs. baseline in each 5-min interval during the 30-min study period. The patients in this study had severe intracranial hypertension and etomidate reduced ICP from 32.8 ± 6.6 mm Hg to 21.2 ± 5.2 mm Hg. An increase in cerebral perfusion pressure was also seen that was significant for the initial 25 mins after etomidate administration. Every patient in the study exhibited a reduction in ICP with treatment. No data were presented on cortisol levels in these patients. However, in the discussion section of the manuscript, the authors indicated that at 6 hrs after etomidate administration, adrenocorticotrophic hormone stimulation tests were performed on each patient; four of the eight showed adrenal suppression. It is unclear if this degree of adrenal suppression is different from that normally observed in pediatric TBI (16). No patient showed clinical signs of adrenal insufficiency such as electrolyte disturbances or blood pressure lability, and no patient received steroid therapy.

The availability of other sedatives and analgesics that do not suppress adrenal function, small sample size and single-

dose administration in the study discussed previously, and limited safety profile in pediatric TBI limit the ability to endorse the general use of etomidate as a sedative other than as an option for single-dose administration in the setting of raised ICP.

Barbiturates

Barbiturates can be given as a sedative at doses lower than those required to induce or maintain barbiturate coma. No report specifically addressed their use in that capacity in pediatric TBI. One report did, however, address the effects of barbiturate administration outside of the setting of refractory raised ICP. A study by de Bray et al (15) was a prospective study of the effect of a single dose of thiopental (5 mg/kg, intravenously) on middle cerebral artery flow velocity in ten children with severe TBI and compared the findings with those seen with thiopental administration in ten children under general anesthesia for orthopedic procedures. In this small study, effects on ICP were assessed in only six of the ten children with severe TBI. In those six, thiopental reduced ICP by 48%. Flow velocity was reduced by approximately 15%

to 21% in the pediatric patients with TBI. Baseline ICP was 16.5 mm Hg. Cerebral perfusion pressure was not significantly changed. At the class III level, this study supports the ability of thiopental, administered as a single dose, to reduce ICP, even when only moderately increased. The effects on flow velocity are also consistent with the reduction in cerebral blood volume that would be expected to mediate the reduction in ICP produced by thiopental. No study was identified, however, that specifically addressed barbiturate use as a sedative on any other outcome parameter.

VI. INFORMATION FROM OTHER SOURCES

A. Indications From the Adult Guidelines

In the most recent adult guidelines, a chapter on "Anesthetics, Analgesics, and Sedatives" identified a class II study to recommend continuous infusion of propofol as the agent of choice.

Only case reports or mixed adult and pediatric case series have been published supporting propofol use in pediatric TBI

(17, 18). However, a number of reports (in cases not restricted to TBI) suggest that continuous infusion of propofol is associated with an unexplained increase in mortality risk in critically ill children. A syndrome of lethal metabolic acidosis ("propofol syndrome") can occur (19–24). In light of these risks, and with alternative therapies available, continuous infusion of propofol for either sedation or management of refractory intracranial hypertension in severe pediatric TBI is not recommended. The Center for Drug Evaluation and Research Web site of the Food and Drug Administration (25) states, "Propofol is not indicated for pediatric ICU sedation as safety has not been established." Based on the Food and Drug Administration recommendations against the continuous infusion of propofol for sedation in pediatric critical care medicine, the recommendation from the adult guidelines cannot be translated to pediatric TBI management and represents an important discontinuity between pediatric and adult TBI management.

Neuromuscular-blocking agents were not addressed in the "Anesthetics, Analgesics, and Sedatives" chapter of the most recent adult guidelines. In the 2000 adult guidelines (26), the initial management section cited a study that examined 514 entries in the Traumatic Coma Data Bank and reported no beneficial effects of neuromuscular blockade and an increased incidence of nosocomial pneumonia and prolonged ICU stay associated with prophylactic neuromuscular blockade (9). It was suggested that use of neuromuscular-blocking agents be reserved for specific indications (intracranial hypertension, transport).

B. Information Not Included as Evidence

Ketamine exhibits neuroprotective effects in experimental models of TBI; however, concerns over its vasodilatory effects and their impact on ICP have long limited its consideration as a sedative in TBI. Recently, a study by Bar-Joseph et al (27) was carried out, which was a prospective study in 30 children with raised ICP, 24 with nonpenetrating TBI. A single dose of ketamine (1–1.5 mg/kg, intravenously) was evaluated for its ability to either 1) prevent further increases in ICP during a stressful procedure (i.e., suctioning); or 2) treat refractory intracranial hypertension. Ketamine reduced ICP in both settings. These patients had se-

vere intracranial hypertension with an overall mean ICP of 25.8 mm Hg. The study did not meet inclusion criteria for these guidelines for two reasons. First, it fell just below the cutoff of 85% of TBI cases, and second, Glasgow Coma Scale score was not provided—although it is likely that the children had severe TBI given the ICP data.

Regarding the use of etomidate in critical care, including severe TBI and multiple trauma victims (28–31), there are general concerns over adrenal suppression. As stated earlier, the availability of other sedatives and analgesics that do not suppress adrenal function, along with the small sample size and single-dose administration in the single study in the evidence table (Table 1) and limited safety profile in pediatric TBI, limit the ability to endorse the general use of etomidate as a sedative other than as an option for single-dose administration in the setting of raised ICP.

VII. SUMMARY

Two studies were identified that met inclusion criteria, rendering reserved class III recommendations that 1) etomidate may be considered to decrease intracranial hypertension, although the risks resulting from adrenal suppression must be considered; and 2) thiopental, given as a single dose, may be considered to control intracranial hypertension.

Despite the common use of analgesics and sedatives in TBI management, there have been few studies of these drugs focused on pediatric patients with severe TBI, and studies meeting inclusion criteria for the most commonly used agents were lacking. Similarly, no studies were identified meeting inclusion criteria that addressed the use of neuromuscular blockade in pediatric patients with severe TBI. Until experimental comparisons among these agents are carried out, the choice and dosing of analgesics, sedatives, and neuromuscular-blocking agents used should be left to the treating physician. Based on recommendations of the Food and Drug Administration, continuous infusion of propofol is not recommended in the treatment of pediatric TBI.

VIII. KEY ISSUES FOR FUTURE INVESTIGATION

- Studies are needed comparing the various sedatives and analgesics in pediatric patients with severe TBI, examining

sedative and analgesic efficacy, effects on ICP, other surrogate markers, and functional outcome.

- Studies are needed to assess the toxicities, including hypotension, adrenal suppression, effects on long-term cognitive outcomes, and other adverse effects.
- Studies are needed on dosing, duration, and interaction effects with other concurrent therapies.
- Optimal sedation after severe TBI may differ between infants and older children and requires investigation. Specifically, given concerns over the effects of various anesthetics and sedatives on neuronal death in the developing brain (32, 33), studies of various analgesic and sedative regimens in infants with TBI are needed, including infants who are victims of abusive head trauma.
- The specific role of neuromuscular-blocking agents in infants and children with severe TBI needs to be defined.

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Chapter 16. Glucose and nutrition

I. RECOMMENDATIONS

Strength of the Recommendation: Weak.

Quality of Evidence: Moderate, from one moderate-quality class II study.

A. Level 1

There are insufficient data to support a level I recommendation for this topic.

B. Level II

The evidence does not support the use of an immune-modulating diet for the treatment of severe traumatic brain injury (TBI) to improve outcome.

C. Level III

In the absence of outcome data, the specific approach to glycemic control in the management of infants and children with severe TBI should be left to the treating physician.

II. EVIDENCE TABLE (see Table 1)

III. OVERVIEW

Providing nutritional support to children after TBI is a decision with wide-ranging implications. Similar to adults, traumatically injured children require energy for wound healing, repair, alterations in normal organ function, and other pathologic processes initiated by the injury. However, 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 profound effects on short- and long-term outcome, and results from studies in adults may not be applicable to infants and children.

IV. PROCESS

For this update, MEDLINE was searched from 1996 through 2010 (Appendix B for search strategy), and results were supplemented with literature recommended by peers or identified from reference lists. Of the 104 potentially relevant studies, one was added to the existing table and used as evidence for this topic.

V. SCIENTIFIC FOUNDATION

One class II randomized controlled trial met the inclusion criteria for this topic and provides evidence to support the recommendation (1). A study by Briassoulis et al (1) prospectively studied the effect of an immune-enhancing formula on various outcomes after TBI in a cohort of 40 children in a single center. Subjects with severe TBI (Glasgow Coma Scale [GCS] score ≤ 8) without renal or gastrointestinal disease were eligible. Enteral nutrition was initiated within 12 hrs of TBI. Children were randomized within a block design to either a specialized formula (Stresson, including supplemental glutamine, arginine, antioxidants, and omega-3 fatty acids) or a more standard formula (Tentrini) through a nasogastric tube. For each 100 mL, the specialized formulation contained greater amounts of protein (7.5 g vs. 3.3 g), fat (13.2 g vs. 11.1 g), glutamine (1.3 g vs. 0 g), arginine (0.89 g vs. 0 g), docosahexaenoic acid (0.028 g vs. 0 g), eicosapentaenoic acid (0.072 g vs. 0 g), selenium (14.1 mg vs. 4.9 mg), copper (338 μ g vs. 0 μ g), vitamin E (12.5 mg vs. 1.3 mg), carotenoids (0.38 mg vs. 0.15 mg), and carnitine (7.5 mg vs. 3 mg). Furthermore, the experimental formula demonstrated an increased osmolality (420 mOsm/L vs. 245 mOsm/L) compared with the standard preparation. Administration of feedings was targeted based on predicted energy expenditure (PEE) that included compensatory increases for various injury factors. The amount of nutritional support from each formula was escalated over the first 5 days after TBI based on PEE (0.5%, 100%, 125%, 150%, and 150%, respectively). In both groups, feeding intolerance was treated with gastric-emptying

agents and diarrhea was treated with temporary discontinuation of feedings. Failure of a regimen was defined as inability to follow the prescription outlined here. Nitrogen balance, serum nutritional indices, and cytokines were determined in each group as the primary outcome parameters. The mean age of enrolled children was 120 months with a majority being male (71.4%). There were five deaths (12.5%). There were no significant differences in outcomes between the two feeding groups for survival (enhanced vs. standard: 80% vs. 95%), length of stay (16.7 vs. 12.2 days), or length of mechanical ventilation (11 vs. 8 days). Nitrogen balance was achieved in a greater percentage of children receiving the enhanced formula by day 5 (69.2% vs. 30.8%), but zinc, copper, retinol-binding protein, and transthyretin were not different between the groups throughout the study period. The only cytokine measured that was independently associated with the enhanced diet was interleukin-8. Levels were lower in the immune enhanced vs. standard treatment group.

VI. INFORMATION FROM OTHER SOURCES

A. Indications From the Adult Guidelines

Based on three class II and 11 class III studies (2), a recommendation to obtain full caloric replacement by 7 days postinjury was made in the adult guidelines. Overall, studies included within this guideline addressed the manner of feeding, the quantity of calories administered/expended, hyperglycemia, and mineral supplementation.

In comparing the manner in which nutrition is administered, a class II study by Rapp et al (3) randomized 38 subjects to total parenteral nutrition (TPN) or enteral nutrition (EN) and found that the TPN group had decreased mortality (zero vs. eight subjects, $p < .001$). They also found that the TPN group achieved higher caloric intake and reached full nutritional replacement by 7 days postinjury (compared with 14 days postinjury for EN

Table 1. Evidence table

Reference	Study Description	Data Class, Quality, and Reasons	Results and Conclusion
New study Briassoulis et al, 2006 (1)	Design: randomized controlled trial N = 40 GCS: mean 6.2 (SEM 0.5) Age: mean 127 month $\pm$ 7.9 for immune-modulating group; 112 months $\pm$ 14.5 for standard group Protocol: children randomized to immune-enhancing diet containing supplementation with glutamine, arginine, and antioxidants vs. a regular formula from 12 hrs after admission Purpose: determine if an immune-enhanced diet would alter mortality Outcomes: hospital mortality, length of stay, nutritional indices, and cytokine concentrations	Class II Moderate quality: attrition not reported; unclear if intention-to-treat analysis conducted; otherwise met all criteria	Immune-enhancing vs. regular formula Survival: 80% vs. 95% Length of stay: 16.7 vs. 12.2 days Length of mechanical ventilation: 11 vs. 8 days <i>P</i> values not reported; no significant differences between groups Fewer positive gastric cultures in immune-enhancing group ($p < .02$), but infections did not differ The group fed an immune-modulating diet; was more likely to have positive nitrogen balance at 5 days (69% vs. 31%, $p < .05$)

GCS, Glasgow Coma Scale; SEM, standard error of mean.

group). Class III studies provided complementary information regarding this issue. Specifically, a study by Hadley et al (4) demonstrated that subjects randomized to TPN had higher mean daily nitrogen intakes and losses, resulting ultimately in no difference in nitrogen balance between the intervention groups. A study by Young et al (5) randomized 51 subjects with severe to moderate TBI (GCS 4–10) to TPN or EN and found the TPN group had increased protein intake, improved nitrogen balance, and improved outcome at 3 months postinjury. Finally, a study by Borzotta et al (6) found that TPN and EN were equally effective when prescribed based on measured energy expenditure (MEE). They found that MEE remained between 135% and 146% of predicted for the first 4 wks postinjury and neither feeding regimen was associated with differences in infection rates or hospital costs.

In comparing various EN strategies, a class II study by Taylor et al (7) demonstrated that an accelerated EN regimen to meet goals within the first week postinjury in mechanically ventilated TBI victims was associated with improved outcome at 3 months (yet no difference at 6 months). Furthermore, fewer infections were also observed in the accelerated EN group. Other class III studies demonstrated that 1) percutaneously placed feeding tubes could safely administer calories after TBI (8, 9); 2) continuously fed subjects demonstrated less feeding intolerance and reached caloric goals more quickly (10); and 3) nasojunal feedings

permitted increased delivery of calories (11). A study by Clifton et al (12) recommended that a nomogram be used to estimate energy requirements to guide caloric intake, whereas other recent studies suggest that published formulas poorly predict the energy requirements of adults (13) or children (14).

Regarding supplementation of feedings, a class II study showed a nonsignificant trend ($p = .09$) toward decreased mortality in subjects randomized to receive 12 mg elemental zinc in parenteral nutrition for 15 days followed by 22 mg oral zinc for an additional 15 days (15). Improvements in nutritional markers (albumin, prealbumin, and retinol-binding protein) were observed in this treatment group compared with the standard subjects. Finally, two class III studies demonstrated that hyperglycemia early after TBI was associated with poor outcome (16, 17), although this effect may reflect a stress response after injury rather than a nutritional effect.

In summary, the adult guidelines (2) suggest that starved patients with TBI lose sufficient nitrogen to reduce weight by 15% per week and support administration of 100% to 140% replacement of resting energy expenditure with 15% to 20% nitrogen calories, which may reduce nitrogen loss. The data support full feeding at least by the end of the first week. It has not been established that any method of feeding is better than another or that early feeding before 7 days improves outcome. Based on the level of nitrogen-wasting documented in patients with

TBI and the nitrogen-sparing effect of feeding, it is a level II recommendation that full nutritional replacement be instituted by day 7 postinjury for adult patients.

B. Information Not Included as Evidence

A number of studies have been reported on this topic that failed to meet inclusion criteria because they did not compare specific nutritional regimens. There have been several studies addressing the effect of TBI on metabolism with a focus on the amount of consumed calories in the immediate post-TBI time period. This information is thought to be an important precursor to studies that would target the amount of calories required after TBI and the possible effect of different nutritional support strategies on overall outcome. Evidence suggests that underfed critically ill, nontrauma pediatric patients have increased mortality, infections, and poor wound healing (14). However, overfeeding is associated with increased carbon dioxide production and respiratory complications. Caloric needs can be measured using indirect calorimetry (MEE) or estimated by various mathematical formulae (PEE). Because many factors after TBI can affect caloric expenditure (including sedation, neuromuscular blockade, hemodynamic support, seizures, temperature, other injuries, and others), MEE currently represents the most accurate method for determining energy requirements (18).

Two studies have reported MEE after severe TBI in children. Phillips et al (19) studied the effect of TBI on energy expenditure (measured by indirect calorimetry), nitrogen excretion, and serum markers of nutritional adequacy in children with GCS 3–8. This observational study followed 12 children (aged 2–17 yrs) for the first 2 wks after TBI. There was one case of penetrating TBI, whereas all others had closed TBI. Multiple other injuries are described, yet the “major injury” was to the brain. Six children developed intracranial hypertension that was treated with hyperventilation, neuromuscular blockade ($n = 4$), cerebrospinal fluid diversion, mannitol, or barbiturates ($n = 4$). Phenytoin was administered only when seizures were observed. All children received antibiotics and antipyretics (aspirin/acetaminophen). Nutrition was administered enterally starting 3–12 days after injury ($n = 5$) or parenterally starting 2–6 days after injury ($n = 7$). MEE was performed on nine children, 1–14 days after TBI. The mean MEE was 130% of PEE derived from the Harris/Benedict formula, and the lowest MEE/PEE was 94%.

Diarrhea ($n = 5$) and gastric residuals ($n = 2$) were noted as limitations to enteral feeding regimen. Mean nitrogen excretion was 307 mg/kg/day for adolescents and 160 mg/kg/day for younger children, and nitrogen balance remained negative throughout the 2-wk period. Mean serum albumin decreased during the 2-wk study period (2.9 g/dL to 2.4 g/dL), whereas mean serum protein increased (5.4–6.0 g/dL) with both being below laboratory normals for the first week after TBI. Other nutritional markers (retinol binding protein and prealbumin) were slightly increased in week 2 compared with week 1. Weight loss was prominent, ranging 2–26 pounds among all subjects. This represents 9% loss of body weight for adolescents and 4% loss of body weight for children. The possible effects of neuromuscular blockade, sedation, temperature, and seizures were not addressed.

In another study, Moore et al (20) measured MEE within the first 48 hrs after TBI in 20 subjects with severe TBI, including seven children. Entry into this study was limited to patients with an Injury Severity Score for head injury greater than all other organ systems. All subjects underwent pulmonary artery catheterization for cardiac output monitoring, 17 received intracranial pressure

monitoring, and two received corticosteroids. Within the pediatric group (age, 3–16 yrs), oxygen consumption was 180% of predicted and energy expenditure was 173% of predicted. None of the values were <100% of predicted. The average respiratory quotient was 0.68, indicating consumption of lipids as a predominant fuel. The mean rectal temperature at the time of the metabolic testing was 38.2°C. Nutritional support started within 48 hrs after TBI, but information regarding the administration of enteral or parenteral nutrition, neuromuscular blockade, and barbiturates was not reported.

Two additional manuscripts, comprising some of the same patient population, were reported regarding MEE measurements (21, 22). Eighteen children after severe TBI (GCS <8) were studied and all received standard therapies including sedation and paralysis during the study period. Nasogastric feedings were begun on day 2 and MEE was determined serially for the first several days after TBI using the Douglas bag method. A total of 107 MEE measurements were obtained, with 1) 82% within the normal reference ranges for resting children (85% to 115% PEE); 2) 4% at >115% PEE; and 3) 14% at <85% PEE. Logistic regression demonstrated a significant association between MEE and rectal temperature with an increase of 1°C corresponding to an increase in MEE by 7.4%. Furthermore, MEE was significantly associated with plasma epinephrine, triiodothyronine, and glucagon concentrations.

Although the precise mechanism underlying the association between hyperglycemia and outcome is still unclear, the possibility exists that it may be related in part to nutrient delivery. Two studies regarding hyperglycemia and TBI included admission glucose concentrations among children with TBI. A study by Michaud et al (23) retrospectively studied 54 children (age, <16 yrs) with severe TBI (GCS ≤8) treated in a single center. Children who died in the emergency department, those with gunshot wounds to the head, and those who had fatal outcomes from multiple or extracranial injuries ($n = 8$) were excluded. Children who received dextrose-containing solutions at another institution before serum glucose testing were separately analyzed. Discharge Glasgow Outcome Scale (GOS) scores were recorded. In the 16 children who died or remained in a vegetative state, mean admission glucose concentration was 288 mg/dL compared with 194 mg/dL for

those with more favorable outcome ($p = .01$). Increases in blood glucose were also associated with hypotension, acidosis, abnormal pupillary responses, lower GCS, and cerebral edema on initial computed tomography scan.

A study by Cochran et al (24) was of 170 children with both moderate and severe TBI (Abbreviated Injury Score of the head at admission ≥3) who had admission serum glucose concentration measured. GOS scores were obtained at hospital discharge and mortality rate was 9.4%. Children who died had greater mean serum admission glucose concentration (267 mg/dL) compared with those with severe (GOS = 3; 249 mg/dL), moderate (GOS = 4; 168 mg/dL), or mild disability (GOS = 1; 128 mg/dL).

A study by Chiaretti et al (25) retrospectively analyzed 122 children after severe TBI (GCS ≤8) for various factors that might be associated with an adverse neurologic outcome. Inclusive in these factors was hyperglycemia, defined as blood glucose concentration >150 mg/dL. Glucose measurements were obtained at hospital admission and at least twice daily during the admission. Other factors considered in the analysis were hypoxia ($\text{PaO}_2 < 60$ mm Hg or $\text{SaO}_2 < 90\%$ for at least 15 mins or apnea/cyanosis noted on examination), hypotension (arterial pressure less than the fifth percent for age for at least 15 mins), radiologic findings (cerebral hemorrhages, cerebral edema, and other findings as interpreted by an independent radiologist), hematologic, coagulation, metabolic and seizures. Outcomes were assessed by GOS scores at 6 months after TBI and dichotomized into favorable (GOS 4–5) and unfavorable (GOS 1–3). Of the children enrolled, the mean age was 122 months, 74 had isolated head injury, whereas 48 had multiple trauma. There were 47 children with a poor outcome (38.5%) at 6 months. All children had admission glucose concentrations obtained and initial GCS and blood glucose were highly correlated ($p = .001$). Mean admission serum glucose varied by outcomes that included some overlap between the groups (GOS 4–5, 221 mg/dL ± 70; GOS 3–4, 261 mg/dL ± 102; GOS 1–2, 290 mg/dL ± 88). Hyperglycemia after TBI was associated with poor outcome based on bivariate analysis, which remained significant in multivariate analysis adjusting for GCS, type of trauma (isolated vs. multi-trauma), hypoxia, hypotension, disseminated intravascular coagulation, and

early posttraumatic seizures. Administration of glucose, insulin, and other nutritional support was not reported.

VII. SUMMARY

Although multiple studies examined the timing, quantity, manner, and composition of nutritional support for patients with TBI, only one met the inclusion criteria for this topic. That class II randomized controlled trial showed no difference in outcomes for children provided an immune-enhancing diet vs. regular formula. There is insufficient evidence to recommend the use of glycemic control after severe pediatric TBI to improve outcome despite evidence indicating that posttraumatic hyperglycemia is associated with poor outcome.

VIII. KEY ISSUES FOR FUTURE INVESTIGATION

- Prospective trials of nutritional support, either enteral or parenteral, to determine the superiority of various potential strategies.
- Measurement of caloric expenditure and other nutritional indices in larger studies to gain a broader understanding of the role of nutrition after TBI so that novel strategies, including the possible targeting of caloric expenditure, can be tested.
- Prospective trials of glycemic control with protocolized administration of nutrition and insulin.
- More complete reporting of nutritional strategies used in large, randomized controlled trials of other therapies in TBI that would increase our understanding of the effect of nutrition on important outcomes.
- Fundamental observational studies of the effect of TBI on nutritional markers (including standard indices and metabolomics) for the design of rational clinical trials.

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Chapter 17. Antiseizure prophylaxis

I. RECOMMENDATIONS

Strength of Recommendation: Weak.

Quality of Evidence: Low, from one poor-quality class III study.

A. Level I

There are insufficient data to support a level I recommendation for this topic.

B. Level II

There are insufficient data to support a level II recommendation for this topic.

C. Level III

Prophylactic treatment with phenytoin may be considered to reduce the incidence of early posttraumatic seizures (PTS) in pediatric patients with severe traumatic brain injury (TBI).

II. EVIDENCE TABLE (see Table 1)

III. OVERVIEW

Posttraumatic seizures are defined as occurring early, within 7 days of injury, or late, beyond 8 days of recovery (1). 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, Glasgow Coma Scale (GCS) score <10, severity of injury, length of posttraumatic amnesia, subdural or epidural hematoma, penetrating injury, chronic alcoholism, and age. Infants and children have lower seizure thresholds (2), adding to the challenge of recognition of subtle clinical seizures (3) in critically ill children.

IV. PROCESS

For this update, MEDLINE was searched from 1996 through 2010 (Appendix B for search strategy), and re-

sults were supplemented with literature recommended by peers or identified from reference lists. Of 15 potentially relevant new studies, no new studies were used as evidence for this topic.

V. SCIENTIFIC FOUNDATION

One class III study met the inclusion criteria for this topic and provides evidence to support the recommendation. Data from a single center retrospective cohort study of children ages 3 months to 15 yrs identified by International Classification of Diseases, 9th Revision code were reported by Lewis et al (4). This study reported a significant reduction in early PTS rate in the severe TBI cases treated with prophylactic phenytoin compared with patients with severe TBI who were not treated prophylactically (15% vs. 53%, $p = .04$, one-tailed Fisher's exact test). Limitations of this study include the small size of the severe TBI group, the decision to treat based on individual physician preference, and the absence of data on long-term outcome, phenytoin levels, or complications of anticonvulsant therapy.

VI. INFORMATION FROM OTHER SOURCES

A. Indications From the Adult Guidelines

Based on data from five studies, the adult guidelines for the prevention of PTS provide a level II recommendation for the use of anticonvulsants to decrease the incidence of early PTS (3). Among these studies, three compared phenytoin with placebo, one compared phenobarbital with placebo, and one compared phenytoin with valproate. The use of either phenytoin or valproic acid as prophylaxis to reduce the incidence of late PTS is not recommended. Similar recommendations have been published elsewhere (5). There are no data to show that early PTS are associated with worse outcomes.

A prospective study by Temkin et al (6) was performed as a double-blind,

placebo-controlled study to determine the effect of treatment with phenytoin on early and late PTS in 404 patients. Importantly, dosages were adjusted to maintain therapeutic levels. In the treated group, the incidence of early PTS was 3.6%, a significant reduction ($p < .001$) compared with placebo (14.2%) (risk ratio, 0.27; 95% confidence interval [CI], 0.12–0.62). Treatment with phenytoin had no effect on either late PTS or survival compared with placebo.

A randomized, double-blind trial to evaluate the effect of valproic acid on the incidence of PTS compared phenytoin with valproic acid (7). One hundred thirty-two patients were randomized to 1-wk treatment with phenytoin, 120 to 1 month of valproic acid, and 126 to 6 months of valproic acid. The rates of early PTS did not differ between treatment groups (1.5% for the phenytoin group and 4.5% for both arms of the valproic acid group) and there were also no differences in the rate of late PTS. There was a trend toward higher mortality rate in patients treated with valproic acid compared with phenytoin (13.4% vs. 7.2%, $p = .07$; risk ratio, 2.0; 95% CI, 0.9–4.1).

B. Information Not Included as Evidence

To address the question about whether prophylactic treatment reduces seizures, various questions/issues need to be considered. For example: 1) What is the incidence of PTS? 2) What is the right anticonvulsant medication? 3) What is the appropriate dose? 4) What is the risk–benefit of the drug in the context of other morbidities after TBI? 5) Can and should the drug therapy be targeted to a high-risk group?

The following studies provide information about these questions but do not constitute evidence. It is important to keep in mind that the various studies have different case definitions when discussing PTS: 0–24 hrs, 0–48 hrs, 0–7 days, or 0–2 yrs.

Frequency of posttraumatic seizures in pediatric TBI. A number of studies that report the inclusion of pediatric

Table 1. Evidence table

Reference	Study Description	Data Class, Quality, and Reasons	Results and Conclusion
Study from previous guidelines Lewis et al, 1993 (4)	Design: retrospective cohort study N = 194; 31 with severe traumatic brain injury Age: ranged from 3 months to 15 yrs; median, 6 yrs GCS: 3–8 (31 [16%]); 9–15 (163 [84%]) Protocol: phenytoin within 24 hrs of hospital admission or no prophylactic anticonvulsant medication Purpose: to determine factors associated with early PTS Outcome: occurrence of any seizure during hospitalization	Class III Poor quality: for comparison of groups based on anticonvulsant medication use; moderate for prognostic factor analysis: control for confounders only in analysis of predictors of seizure, not for comparison of groups based on seizure prophylaxis	For children with GCS 3–8, treatment with prophylactic phenytoin was associated with a reduced rate of seizures (2 of 13 [15%]) compared with patients not treated with prophylactic medication (9 of 17 [53%]) ($p = .04$ one-tailed Fisher's; $p = .057$ two-tailed) Rate of seizures in total group of 194 was 9.3% In 14 of these 18 cases (78%), seizures occurred within 24 hrs of injury GCS of 3–8 ($p < .01$) and abnormal computed tomography ($p = .02$) associated with increased risk of early PTS Logistic regression performed to account for contribution of abnormal computed tomography, loss of consciousness, and GCS score to risk for PTS showed only association with GCS of 3–8 ($p < .001$)

GCS, Glasgow Coma Scale; PTS, posttraumatic seizures.

cases have examined the frequency of early and late PTS after severe TBI.

In a four-center study, subjects >6 yrs admitted between 1993 and 1998 with computed tomography evidence of TBI or a GCS less ≤ 10 24 hrs postinjury with negative computed tomography were studied to determine the natural history of later PTS in moderate and severe TBI (8). The subjects were followed for 2 yrs or until the first seizure >8 days after TBI, death, or treatment with an anticonvulsant. Among the 647 subjects, 43% were <30 yrs. Sixty-six (10%) of subjects had a late PTS, although 26% of the total were lost to follow-up. The probability of developing late PTS at 2 yrs after TBI was 13.8% (66 of 480). The majority (79%) of these seizures were generalized. The length of initial anticonvulsant prophylaxis correlated with a greater frequency of late PTS. The relative risk of seizures at 2 yrs after treatment with phenytoin on days 1–7 was 1.56 compared with 4.27 in the subjects treated up to 30 days after injury. It is possible this difference reflects differences in the severity of injury between these groups.

The incidence of late PTS was examined in two populations in Italy, a retrospective study of 55 cases and a prospective study of 82 subject all with severe TBI (9). In the retrospective group (age range, 14–62 yrs), ten patients (18%) had PTS of whom half had been treated with an anticonvulsant

(phenobarbital) and half had not. In the prospective part of the study, 84% of the subjects were treated with prophylactic anticonvulsants during 2-yr follow-up and 39% experienced PTS. There were no PTS in the subjects who were not treated with an anticonvulsant. This counterintuitive finding may again reflect the clinical assessment of the need for treatment in the more severely impaired subjects.

A retrospective study from two hospitals in Turkey examined the risk factors for PTS in children <16 yrs (10). There were 149 cases of PTS (8.4%) in the 1785 patients in this series. Young age (<3 yrs), severity of injury, cerebral edema, depressed skull fracture, and hemorrhage were more common in the cases with PTS. A retrospective review of traumatic intracranial hemorrhage confirmed by computed tomography scan at three centers in Israel identified 52 cases (mean age, 50 yrs; range, 8–85 yrs) with recurrent seizures (11). Only five cases were <19 yrs, all of whom were reported as mentally handicapped. The patients with seizures or epilepsy were identified only by International Classification of Diseases, 9th Revision code and the majority of cases (44) were male. This study did not define risk factors for seizures after traumatic intracranial hemorrhage, but rather provided a description of the characteristics of patients with traumatic

intracranial hemorrhage leading to recurrent seizures.

A study of 102 children aged 1.3–15.2 yrs with severe TBI, of which 85% required mechanical ventilation, all of whom received inpatient rehabilitation therapy between 1991 and 1998, examined the prevalence of posttraumatic epilepsy (12). Follow-up in this study ranged from 19 months to 7 yrs, during which nine subjects (9%) developed posttraumatic epilepsy. The interval from insult to first seizure onset ranged from 0.7 to 5.2 yrs (median, 2.9 yrs). The presence of early (within the first week post-TBI) seizures ($p = .002$) and GCS score ($p = .043$) were the only factors at the time of injury related to the development of posttraumatic epilepsy. A series of 318 children ages 1 month to 17 yrs treated between 1965 and 1991—with an average follow-up of 8 yrs, 9 months—reported early seizures in 19.8% and an incidence of late seizures of 29.6% after open head injury compared with 20.2% after closed head injury (13).

Effects of treatment with anticonvulsants. In a randomized, double-blind, placebo-controlled study of the efficacy of phenytoin in preventing late PTS in 41 patients, Young et al (14) found no difference in rate of PTS in the treated group (12%) compared with control subjects (6.2%). All seizures occurred within the first year after injury. Compliance was poor, and by 6 months,

serum levels of phenytoin were available on only 15 (60%) of the treatment group. Among this group, six subjects (40%) had a measured serum drug level of ≤ 10 $\mu\text{g/mL}$. Notably, no patients with a serum level >10 $\mu\text{g/mL}$ had a seizure. The study is limited by the small size, poor compliance, unclear criteria for randomization, and lack of clarity over association between GCS and outcome. Sixteen (39%) of the subjects had a GCS of ≤ 7 . Because the analysis combined severe and moderate patients, it did not meet criteria for inclusion as evidence for this topic.

In a prospective cohort study of children admitted to the pediatric intensive care units at three centers, Tilford et al (15) identified 138 cases of severe TBI among the 477 children admitted with a diagnosis of head trauma. There was a significant variation in anticonvulsant use (range, 10% to 35%) among the three centers with an overall incidence of early PTS of 9.4%. The type of anticonvulsant used was not specified. The indications for such use, either prophylaxis or in response to a clinical or electrographic seizure, were also not specified. In a stepwise logistic regression model (accounting for GCS, the participating site, other therapies), the use of an anticonvulsant medication was associated with a significant reduction in risk of mortality ($p = .014$; odds ratio, 0.17; 95% CI, 0.04–0.70), but the analysis was not limited to patients in the severe TBI group.

A study by Young et al (16) reported no reduction in the rate of PTS within 48 hrs of injury in a randomized, double-blind, placebo-controlled trial of phenytoin in children with moderate to severe blunt head injury. Children <16 yrs with a GCS of ≤ 9 (<4 yrs) or ≤ 10 (>4 yrs) were enrolled by deferred consent within 40 mins of presentation to the emergency department and drug or placebo administered within 60 mins of presentation. Phenytoin dose was 18 mg/kg followed by 2 mg/kg every 8 hrs for the 48 hrs of the study. Subjects were stratified by age and GCS. One hundred three subjects were randomized with 33% lost at 48-hr follow-up and 36% lost at 30-day follow-up. In the phenytoin-treated group, three patients (7%) had a seizure during the 48-hr observation period compared with three (5%) in the placebo group. Six patients (one phenytoin, five placebo) had an electroencephalogram performed. None

showed nonconvulsive seizures. Over 30 days recovery, there was no difference in mortality in the treatment group (20% [six of 30]) compared with placebo (39% [14 of 36]). The major limitations of this study are the low seizure rate and the small sample size resulting from early loss of subjects and decrease in enrollment after ceasing to waive consent.

A study of 318 cases of severe TBI from a single center in Germany with mean follow-up of 8 yrs, 9 months identified 68 cases (21%) of late seizures with a mean latency of 2 yrs, 5 months (17). Approximately half of these cases were resistant to anticonvulsant therapy, although the details of therapy are not given. The children with PTS had a worse outcome in this series with 60% having disabilities compared with 17% in the other patients.

In a single-center, prospective study during the war in Bosnia, 310 patients between 0 and 18 yrs with severe TBI were treated with either intravenous phenytoin or phenobarbital, depending on the availability of each drug (18). The primary outcome was the frequency of seizure in the first 24 hrs after admission. This was low, occurring only in two cases (0.64%). Although the criteria for classification of cases as severe are not specified, skull fracture was present in 85% of cases. The frequency of seizures is low and there is no detail on the process for monitoring for seizures, suggesting this may be an underestimate.

Pharmacokinetic considerations. TBI results in an increase in hepatic metabolism and decrease in protein binding of drugs including anticonvulsants (19), resulting in an increase in plasma clearance. The free fraction of phenytoin is elevated (20). The altered pharmacokinetics of phenytoin and other drugs may result in levels considered to be subtherapeutic. As part of a clinical trial evaluating the use of valproic acid for prophylaxis of posttraumatic seizures, the time-dependent effects of TBI on the pharmacokinetics of total and unbound valproic acid were evaluated (21). In the trial, 158 adult TBI cases (mean age, 36 yrs; mean GCS, 10; range, 3–15) were treated with a loading dose of valproic acid (20 mg/kg) followed by a maintenance dose. TBI resulted in an average 75% increase in drug clearance by 2 and 3 wks of recovery, which was associated with in-

creased TBI severity, lower albumin concentration, tube feeding, and the presence of ethanol on admission. In general, there are limited data (22) on the effect of early age, genetic factors, and other drug interactions affecting pharmacokinetics of anticonvulsants after TBI and the contribution of these factors to neurologic outcomes.

Mechanisms of epileptogenesis relevant to pediatric TBI. Studies of the mechanisms of posttraumatic epilepsy traditionally were limited by the lack of animal models; however, recent studies have begun to focus on PTS in developing animals after experimental TBI (23–25). A number of mechanisms of posttraumatic epilepsy have been investigated; many focused on pathophysiological changes in the hippocampus including axonal sprouting, impaired K^+ buffering by glia, saturation of synaptic long-term potentiation of Schaffer collaterals, hilar neuron loss, and activation of hippocampal TrkB-ERK1/2-CREB/ELK-1 pathways (23, 26). Recent studies have suggested a role for albumin-induced changes in the electrophysiological properties of astrocytes mediated by the transforming growth factor- β receptor and leading to accumulation of extracellular potassium (27, 28).

VII. SUMMARY

The incidence of early PTS in pediatric patients with TBI is approximately 10% given the limitations of the available data. Based on a single class III study (4), prophylactic anticonvulsant therapy with phenytoin may be considered to reduce the incidence of early posttraumatic seizures in pediatric patients with severe TBI. Concomitant monitoring of drug levels is appropriate given the potential alterations in drug metabolism described in the context of TBI. Stronger class II evidence is available supporting the use of prophylactic anticonvulsant treatment to reduce the risk of early PTS in adults. There are no compelling data in the pediatric TBI literature to show that such treatment reduces the long-term risk of PTS or improves long-term neurologic outcome.

VIII. KEY ISSUES FOR FUTURE INVESTIGATION

- Investigation of the frequency of early PTS in the setting of contemporary

management and their association with acute pathophysiology and long-term neurologic sequelae.

- Investigation of the efficacy, safety, and drug levels required for the prevention of early posttraumatic seizures.
- Investigation of the efficacy and safety of new anticonvulsants for the treatment of early and late posttraumatic seizures.
- Identification of neuroimaging, electroencephalography, or serum biomarkers, which serve to predict patients at increased risk for late posttraumatic seizures.
- Elucidation of the mechanisms of epileptogenesis after TBI and identification of new therapeutic targets based on understanding these mechanisms.
- Improvement in the classification of early and late seizures, including the use of electroencephalography, to detect and classify posttraumatic seizures.
- Evaluation of the effect of TBI on changes in dosage requirements for anticonvulsant drugs and the contribution of age and genetically determined differences in hepatic and renal drug metabolism to the efficacy of anticonvulsants in the treatment of posttraumatic seizures.

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APPENDIX A

Publications from the First Edition Not Included in the Second Edition

Topic	Reference	Reason(s) for Exclusion
Indications for ICP monitoring	Cho, 1995 Taylor, 2001 Sharples part I, 1995 Eder, 2000 Peterson, 2000	Data not relevant to this topic GCS range exceeds 8 with no separate analysis of severe No direct correlation between ICP and outcome Retrospective, N = 21 Treatment study about effect of hypertonic saline on ICP
ICP thresholds	Cho, 1995 Shapiro and Marmarou, 1982 Sharples part I, 1995	Data not relevant to this topic Data not relevant to this topic No direct correlation between ICP and outcome
Cerebral perfusion pressure thresholds	Elias-Jones, 1992 Sharples part III, 1995	GCS range exceeds 8 with no separate analysis of severe No association between ICP/ CPP and outcome
Hyperosmolar therapy	James, 1980 Miller, 1993 Khanna, 2000	Mean age 42 yrs, with no separate analysis of pediatric patients 4 of 16 patients are children and relevant data are not provided by age Prospective cohort, N = 10
Temperature control	Gruszkiewicz, 1973	Randomized controlled trial, N = 20
Decompressive craniectomy	Polin, 1997 Taylor, 2001	Average age 18.7 ± 12.6 yrs with no separate analysis of pediatric patients GCS range >8 with no separate analysis of severe
Hyperventilation	Stringer, 1993	Case series, N = 3
Corticosteroids	Gobiet, 1977, Advances in . . . Gobiet, 1977, Monitoring of . . . Hoppe, 1981 Kretschmer, 1983 James, 1979 Cooper, 1979	GCS not reported Sample includes adults with no separate analysis of pediatric patients No comparison group 27% penetrating brain injury without separate analysis Retrospective, N = 9 Prospective cohort, N = 10
Analgesics, sedatives, and neuromuscular blockade	Vernon and Witte, 2000	Includes patients with pathologies other than traumatic brain injury without separate analysis
Glucose and nutrition	Phillips, 1987 Moore, 1989	No analysis of association between any nutritional parameter and any clinical outcome Age range is 3–67 yrs with no separate analysis of pediatric patients
Antiseizure prophylaxis	Tilford, 2001 Young, 1983	Does not analyze the effect of anticonvulsants within the severe group GCS range >8 with no separate analysis of severe

ICP, intracranial pressure; GCS, Glasgow Coma Scale; CPP, cerebral perfusion pressure.

APPENDIX B

Literature Search Strategies

Indications for Intracerebral Pressure Monitoring

Database: Ovid Medline <1996 to 2010>
Search Strategy

Line Search

- 1 exp Craniocerebral Trauma/
- 2 head injur\$.mp. [mp = title, original title, abstract, name of substance word, subject heading word]
- 3 brain Injur\$.mp. [mp = title, original title, abstract, name of substance word, subject heading word]
- 4 1 or 2 or 3
- 5 intracranial pressure.mp. or Exp Intracranial Pressure/
- 6 intracranial hypertension.mp. or exp Intracranial Hypertension/
- 7 5 or 6
- 8 4 and 7
- 9 Limit 8 to "all Child (0 to 18 Yrs)"
- 10 (2001\$ or 2002\$ or 2003\$ or 2004\$ or 2005\$ or 2006\$ or 2007\$ or 2008\$ or 2009\$).ed.
- 11 10 and 9

Intracerebral Pressure Thresholds

Database: Ovid Medline <1996 to 2010>
Search Strategy

Line Search

- 1 exp Craniocerebral Trauma/
- 2 head injur\$.mp. [mp = title, original title, abstract, name of substance word, subject heading word]
- 3 brain injur\$.mp. [mp = title, original title, abstract, name of substance word, subject heading word]
- 4 1 or 2 or 3
- 5 intracranial pressure.mp. or exp Intracranial Pressure/
- 6 intracranial hypertension.mp. or exp Intracranial Hypertension/
- 7 5 or 6
- 8 4 and 7
- 9 limit 8 to "all child (0 to 18 yrs)"
- 10 (2001\$ or 2002\$ or 2003\$ or 2004\$ or 2005\$ or 2006\$ or 2007\$ or 2008\$ or 2009\$).ed.
- 11 10 and 9

Cerebral Perfusion Pressure Thresholds

Database: Ovid Medline <1996 to 2010>
Search Strategy

Line Search

- 1 exp Craniocerebral Trauma/
- 2 head injur\$.mp. [mp = title, original title, abstract, name of substance word, subject heading word]
- 3 brain injur\$.mp. [mp = title, original title, abstract, name of substance word, subject heading word]
- 4 1 or 2 or 3
- 5 cerebral perfusion pressure.mp.
- 6 cerebrovascular circulation/and blood pressure/
- 7 5 or 6
- 8 4 and 7
- 9 Limit 8 to "all child (0 to 18 Yrs)"
- 10 (2001\$ or 2002\$ or 2003\$ or 2004\$ or 2005\$ or 2006\$ or 2007\$ or 2008\$ or 2009\$).ed.
- 11 10 and 9

Advanced Neuromonitoring

Database: Ovid Medline <1950 to 2010>
Search Strategy

Line Search

- 1 Exp Craniocerebral Trauma/
- 2 ((head or brain\$ or cereb\$ or cerebell\$) adj3 (wound\$ or traum\$ or injur\$ or damag\$)).mp. [mp = title, original title, abstract, name of substance word, subject heading word]
- 3 1 or 2
- 4 exp Monitoring, Physiologic/
- 5 exp Intensive Care Units/or Exp Intensive Care/
- 6 4 and 3 and 5
- 7 exp Oxygen/bl, an [Blood, Analysis]
- 8 licox.mp.
- 9 pbto2.mp.
- 10 ((oxygen\$ or o2 or hypoxi\$) adj3 (concentrat\$ or level\$ or monitor\$ or pressur\$)).mp.
- 11 exp Oximetry/
- 12 8 or 11 or 7 or 10 or 9
- 13 ((transcrani\$ adj3 (doppler or ultrasono\$) or tcd).mp. [mp = title, original title, abstract, name of substance word, subject heading word]
- 14 ((near infrared adj3 spectrosc\$) or nirs).mp. [mp = title, original title, abstract, name of substance word, subject heading word]
- 15 exp Phosphopyruvate Hydratase/
- 16 exp Nervous System/
- 17 exp Nervous System Diseases/
- 18 17 or 16
- 19 18 and 15
- 20 neuron specific enolase\$.mp.

- 21 nse.mp.
- 22 21 or 20 or 19
- 23 exp S100 Proteins/
- 24 (s100b or S100 β).mp. [mp = title, original title, abstract, name of substance word, subject heading word]
- 25 24 or 23
- 26 exp Myelin Basic Proteins/
- 27 (Myelin basic protein\$ or mbp).mp. [mp = title, original title, abstract, name of substance word, subject heading word]
- 28 26 or 27
- 29 glutamat\$.mp.
- 30 xenon.mp. or exp Xenon/
- 31 ((brain\$ or cereb\$ or cerebell\$) adj5 ((interstitial\$ or extracellul\$) adj3 (fluid\$ or space\$))).mp. [mp = title, original title, abstract, name of substance word, subject heading word]
- 32 exp Extracellular Space/or exp Extracellular Fluid/
- 33 exp Brain/
- 34 32 and 33
- 35 34 or 31
- 36 microdialysis.mp. [mp = title, original title, abstract, name of substance word, subject heading word]
- 37 exp Biological Markers/
- 38 (biomarker\$ or biological marker\$).mp. [mp = title, original title, abstract, name of substance word, subject heading word]
- 39 37 or 38
- 40 3 and 5
- 41 40 and 12
- 42 13 and 40
- 43 14 and 40
- 44 22 and 40
- 45 25 and 40
- 46 28 and 40
- 47 29 and 40
- 48 30 and 40
- 49 35 and 40
- 50 36 and 40
- 51 39 and 40
- 52 50 or 51 or 41 or 48 or 47 or 42 or 49 or 46 or 45 or 43 or 44
- 53 52 or 6 (333)
- 54 limit 53 to "all child (0 to 18 yrs)"
- 55 limit 54 to English language

Neuroimaging

Database: Ovid Medline <1950 to 2010>
Search Strategy

Line Search

- 1 exp Craniocerebral Trauma/
- 2 ((head or brain\$ or cereb\$ or cerebell\$) adj3 (wound\$ or traum\$ or

injur\$ or damag\$)).mp. [mp = title, original title, abstract, name of substance word, subject heading word]
 3 1 or 2
 4 exp Tomography, X-Ray Computed/
 5 exp Magnetic Resonance Imaging/
 6 ((t2 or t1 or diffusion or susceptibility) adj weight\$ adj3 imag\$).mp. [mp = title, original title, abstract, name of substance word, subject heading word]
 7 exp Magnetic Resonance Spectroscopy/
 8 (magnetic\$ adj resonan\$ adj2 spectroscop\$).mp. [mp = title, original title, abstract, name of substance word, subject heading word]
 9 8 or 7
 10 apparent diffusion coefficient\$.mp.
 11 exp Tomography, Emission-Computed/
 12 (positron\$ adj emission\$ adj2 spectroscop\$).mp. [mp = title, original title, abstract, name of substance word, subject heading word]
 13 (positron\$ adj emission\$ adj3 tomogra\$).mp. [mp = title, original title, abstract, name of substance word, subject heading word]
 14 pet scan\$.mp.
 15 11 or 13 or 12 or 14
 16 6 or 4 or 10 or 9 or 15 or 5
 17 3 and 16
 18 Limit 17 to (English Language and Humans)
 19 Limit 18 to "all child (0 to 18 yrs)"
 20 exp Intensive Care Units/or exp Intensive Care/
 21 ((intensiv\$ or critical\$) adj2 (care or cared or caring or treat\$ or therap\$)).mp. [mp = title, original title, abstract, name of substance word, subject heading word]
 22 (icu or ccu).mp. [mp = title, original title, abstract, name of substance word, subject heading word]
 23 22 or 21 or 20
 24 23 and 19
 25 exp Emergency Treatment/
 26 exp Emergency Service, Hospital/
 27 25 or 26
 28 27 and 19
 29 28 or 24

Hyperosmolar Therapy
 Database: Ovid Medline <1996 to 2010>
 Search Strategy

Line Search

1 exp Craniocerebral Trauma/
 2 head injur\$.mp. [mp = title, original title, abstract, name of substance word, subject heading word]
 3 brain injur\$.mp. [mp = title, original title, abstract, name of substance word, subject heading word]
 4 1 or 2 or 3
 5 hyperosmolar therapy.mp.
 6 hyperosmolar treatment.mp.
 7 fluid therapy.mp. or exp Fluid Therapy/
 8 Saline Solution, Hypertonic/
 9 Osmolar Concentration/
 10 5 or 6 or 7 or 8 or 9
 11 4 and 10
 12 limit 11 to (English language and humans)
 13 limit 12 to "all child (0 to 18 yrs)"
 14 (2001\$ or 2002\$ or 2003\$ or 2004\$ or 2005\$ or 2006\$ or 2007\$ or 2008\$ or 2009\$).ed.
 15 13 and 14

Temperature Control

Database: Ovid Medline <1996 to 2010>
 Search Strategy

Line Search

1 exp Craniocerebral Trauma/
 2 head injur\$.mp. [mp = title, original title, abstract, name of substance word, subject heading word]
 3 brain injur\$.mp. [mp = title, original title, abstract, name of substance word, subject heading word]
 4 1 or 2 or 3
 5 Hypothermia, Induced/
 6 4 and 5
 7 limit 6 to "all child (0 to 18 yrs)"
 8 (2001\$ or 2002\$ or 2003\$ or 2004\$ or 2005\$ or 2006\$ or 2007\$ or 2008\$ or 2009\$).ed.
 9 8 and 7

Line Search

1 Exp Craniocerebral Trauma/
 2 ((brain\$ or cereb\$ or cerebell\$ or head) adj3 (traum\$ or damag\$ or injur\$ or wound\$)).mp. [mp = title, original title, abstract, name of substance word, subject heading word, unique identifier]
 3 1 or 2
 4 exp Fever/
 5 Fever\$.mp.
 6 4 or 5

7 3 and 6
 8 limit 7 to "all child (0 to 18 yrs)"
 9 limit 8 to English language
 10 hypertherm\$.mp.
 11 1 and 10
 12 limit 11 to "all child (0 to 18 yrs)"
 13 limit 12 to English language
 14 9 or 13

Cerebrospinal Fluid Drainage

Database: Ovid Medline <1996 to 2010>
 Search Strategy

Line Search

1 exp Craniocerebral Trauma/
 2 head injur\$.mp. [mp = title, original title, abstract, name of substance word, subject heading word]
 3 brain injur\$.mp. [mp = title, original title, abstract, name of substance word, subject heading word]
 4 1 or 2 or 3
 5 lumbar drain\$.mp.
 6 lumbar shunt\$.mp.
 7 exp Cerebrospinal Fluid Shunts/
 8 *Drainage/
 9 5 or 6 or 7 or 8
 10 4 and 9
 11 limit 10 to "all child (0 to 18 yrs)"
 12 (2001\$ or 2002\$ or 2003\$ or 2004\$ or 2005\$ or 2006\$ or 2007\$ or 2008\$ or 2009\$).ed.

Decompressive Craniotomy

Database: Ovid Medline <1996 to 2010>
 Search Strategy

Line Search

1 exp Craniocerebral Trauma/
 2 head injur\$.mp. [mp = title, original title, abstract, name of substance word, subject heading word]
 3 brain injur\$.mp. [mp = title, original title, abstract, name of substance word, subject heading word]
 4 1 or 2 or 3
 5 intracranial hypertension.mp. or Exp Intracranial Hypertension/
 6 4 and 5
 7 limit 6 to "all child (0 to 18 yrs)"
 8 limit 7 to English language
 9 su.fs.
 10 drain\$.mp.
 11 cerebrospinal fluid shunts.mp. or exp Cerebrospinal Fluid Shunts/
 12 neurosurgery.mp. Or Neurosurgery/
 13 shunt\$.mp.
 14 9 or 10 or 11 or 12 or 13

- 15 8 and 14
- 16 (2001\$ or 2002\$ or 2003\$ or 2004\$ or 2005\$ or 2006\$ or 2007\$ or 2008\$ or 2009\$).ed.
- 17 16 and 15

Hyperventilation

Database: Ovid Medline <1950 to 2010>
Search Strategy

Line Search

- 1 exp Craniocerebral Trauma/
- 2 exp ISCHEMIA/
- 3 exp Jugular Veins/
- 4 exp Regional Blood Flow/
- 5 exp PERFUSION/
- 6 Exp HYPERVENTILATION/
- 7 2 or 3 or 4 or 5 or 6
- 8 1 and 7
- 9 limit 8 to "all child (0 to 18 yrs)"
- 10 (2001\$ or 2002\$ or 2003\$ or 2004\$ or 2005\$ or 2006\$ or 2007\$ or 2008\$ or 2009\$).ed.

Corticosteroids

Database: Ovid Medline <1996 to 2010>
Search Strategy

Line Search

- 1 exp Craniocerebral Trauma/
- 2 head injur\$.mp. [mp = title, original title, abstract, name of substance word, subject heading word]
- 3 brain injur\$.mp. [mp = title, original title, abstract, name of substance word, subject heading word]
- 4 1 or 2 or 3
- 5 exp Steroids/or steroids.mp.
- 6 synthetic glucocorticoids.mp.
- 7 5 or 6
- 8 4 and 7
- 9 limit 8 to "all child (0 to 18 yrs)"
- 10 (2001\$ or 2002\$ or 2003\$ or 2004\$ or 2005\$ or 2006\$ or 2007\$ or 2008\$ or 2009\$).ed.
- 11 10 and 9

Analgesics, Sedatives, and Neuromuscular Blockade

Database: Ovid Medline <1950 to 2010>
Search Strategy

Line Search

- 1 exp Analgesics/
- 2 exp "Hypnotics and Sedatives"/
- 3 propofol.mp. [mp = title, original title, abstract, name of substance word, subject heading word]
- 4 exp phenothiazines/
- 5 exp central nervous system depressants/
- 6 1 or 2 or 4 or 5
- 7 exp Craniocerebral Trauma/
- 8 6 and 7
- 9 Limit 8 to (English language and humans)
- 10 limit 9 to "all child (0 to 18 yrs)"

Glucose and Nutrition

Database: Ovid Medline <1950 to 2010>
Search Strategy

Line Search

- 1 exp Craniocerebral Trauma/
- 2 ((head or brain\$ or cereb\$ or cerebell\$) adj3 (wound\$ or traum\$ or injur\$ or damag\$)).mp. [mp = title, original title, abstract, name of substance word, subject heading word]
- 3 1 or 2
- 4 exp Glucose/
- 5 exp hyperglycemia/or exp hypoglycemia/
- 6 exp Insulin/
- 7 exp diet/
- 8 exp Nutrition Therapy/
- 9 exp nutritional status/
- 10 exp nutritional requirements/
- 11 exp Enteral Nutrition/
- 12 exp Intubation, Gastrointestinal/
- 13 exp Feeding Methods/
- 14 exp Gastrostomy/
- 15 exp Energy Metabolism/
- 16 Exp Energy Intake/
- 17 harris-benedict equation.mp.
- 18 exp Nutritional Requirements/
- 19 intralipid.mp. or exp Fat Emulsions, Intravenous/
- 20 (metaboli\$ adj3 (cart or carts)).mp. [mp = title, original title, abstract, name of substance word, subject heading word]
- 21 4 and 3
- 22 3 and 5
- 23 6 and 3
- 24 3 and 7

- 25 3 and 8
- 26 3 and 9
- 27 3 and 10
- 28 3 and 11
- 29 12 and 3
- 30 3 and 13
- 31 3 and 14
- 32 15 and 3
- 33 3 and 16
- 34 3 and 17
- 35 3 and 18
- 36 3 and 19
- 37 3 and 20
- 38 24 or 25 or 26 or 27 or 35 or 33 or 36 or 29 or 34 or 21 or 28 or 30 or 22 or 32 or 23 or 31 or 37
- 39 limit 38 to English language
- 40 limit 39 to humans
- 41 limit 40 to "all child (0 to 18 yrs)"

Antiseizure Prophylaxis

Database: Ovid Medline <1996 to 2010>
Search Strategy

Line Search

- 1 exp Craniocerebral Trauma/
- 2 head injur\$.mp. [mp = title, original title, abstract, name of substance word, subject heading word]
- 3 brain injur\$.mp. [mp = title, original title, abstract, name of substance word, subject heading word]
- 4 1 or 2 or 3
- 5 exp Seizures/or Seizures.mp.
- 6 exp Epilepsy/
- 7 exp convulsions/or convulsions.mp.
- 8 5 or 6 or 7
- 9 4 and 8
- 10 limit 9 to "all child (0 to 18 yrs)"
- 11 exp seizures/dt, pc or exp epilepsy/dt, pc or convulsions/dt, pc
- 12 4 and 11
- 13 limit 12 to "all child (0 to 18 yrs)"
- 14 exp Clinical Trials as Topic/
- 15 Exp Practice Guidelines as Topic/or practice guidelines.mp.
- 16 14 or 15
- 17 10 and 16
- 18 13 or 17
- 19 (2001\$ or 2002\$ or 2003\$ or 2004\$ or 2005\$ or 2006\$ or 2007\$ or 2008\$ or 2009\$).ed.
- 20 18 and 19

APPENDIX C

Literature Search Yield

Topic	Search Results	Abstracts Read	Publications Read	Included First Edition Studies	Included New Studies
Indications for intracranial pressure monitoring	756	422	35	9	7
Intracranial pressure treatment threshold	756	422	60	6	5
Cerebral perfusion pressure thresholds	219	161	78	3	8
Advanced neuromonitoring	121	74	44	N/A	2
Neuroimaging	344	161	89	N/A	1
Hyperosmolar therapy	213	31	9	3	0
Temperature control	228	53	17	2	2
Cerebrospinal fluid drainage	136	32	6	3	1
Barbiturates	212	87	47	2	0
Decompressive craniectomy	160	83	18	1	7
Hyperventilation	295	141	16	1	1
Steroids	138	20	19	2	0
Analgesics, sedatives	699	121	44	0	2
Neuromuscular blockade					
Nutrition	593	182	113	0	1
Antiseizure prophylaxis	68	17	10	1	0

N/A, not applicable.

APPENDIX D

Mixed Patient Samples

Criteria for including a study in which the sample includes patients with TBI and patients with other pathologies, or pediatric and adult patients

If:

- the sample for a study includes patients with TBI as well as patients with other pathologies, pediatric as well as adult patients, or mild/moderate as well as patients with severe TBI,
- and the data are not reported separately,
- and there is an effect of the study,

then it cannot be known if the effect existed for the TBI group or if it was large in the non-TBI group and small in the TBI group. Similarly, it cannot be known if the effect existed for the pediatric group or if it was large in the adult group and small in the pediatric group. Therefore, we cannot know with confidence that the intervention had an effect for TBI in pediatric patients.

We have established the following criteria to minimize the uncertainty when including publications with mixed samples:

1. Sample size must be ≥ 25 patients.
2. $\geq 85\%$ of the patients must have severe TBI.
3. $\geq 85\%$ of the patients must be ≤ 18 yrs of age.

4. Such a study could never be used to support a level I recommendation.
5. Such a study can only support a level II or III recommendation. It cannot be used to support a level II recommendation if it is the only class II study available.
6. If a publication mixes the results of pediatric patients with those of adults, and the mean and standard deviation for age are provided, the mean and standard deviation can be used to calculate the proportion of pediatric patients, and if the proportion is $\geq 85\%$, the study can be used as evidence.
7. If the study does not report the percent of patients with TBI, it cannot be used as evidence at any level.

APPENDIX E

Evidence Table Template

Source	Study Design	Setting/Population	Sample	Intervention	Cointerventions	Confounding Variables
Length of Follow-Up	Measures	Analysis	Results		Caveats	Level of Evidence