

Guidelines for the Management of Severe Traumatic Brain Injury

4th Edition

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Preface

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Conflict of Interest Disclosure

There are no conflicts of interest. The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this publication.

Authors' Preface

The scope and purpose of this work is two-fold: to synthesize the available evidence and to translate it into recommendations. This document provides recommendations only when there is evidence to support them. As such, they do not constitute a complete protocol for clinical use. Our intention is that these recommendations be used by others to develop treatment protocols, which necessarily need to incorporate consensus and clinical judgment in areas where current evidence is lacking or insufficient. We believe it is important to have *evidence-based* recommendations in order to clarify what aspects of practice currently can and cannot be supported by evidence, to encourage use of evidence-based treatments that exist, and to encourage creativity in treatment and research in areas where evidence does not exist. The communities of neurosurgery and neuro-intensive care have been early pioneers and supporters of evidence-based medicine and plan to continue in this endeavor.

Guidelines for the Management of Severe Traumatic Brain Injury

Introduction

In this 4th Edition of the Brain Trauma Foundation’s guidelines, there are 189 publications used for evidence—5 Class 1, 46 Class 2, 136 Class 3 studies, and 2 meta-analyses. Over the past 20 years, our community has evolved along with the science and application of evidence-based medicine in general. As a consequence, with each new iteration of the guidelines, we have applied the most current methodological standards and established more rigorous procedures for future work. This approach resulted in changes in the evaluation of previous work, an increase in the quality of the included studies, and essential improvements in the precision of the recommendations.

The size of the literature base is a reflection of the rate at which new studies are being conducted that can be used as evidence for guideline recommendations. During the 7 years between the 3rd¹ and 4th Editions of this work, 94 new studies were added to the library of evidence. Although there have been numerous new publications, many of them repeat the same methodological flaws found in previous research. The following is an examination of the current condition of brain trauma clinical research, our view of how this condition is defining and shaping our future, and a proposed solution in establishing a formal evidence-based consortium.

Brain Trauma Research: Current Conditions

Clinical Trials in TBI. Failure to establish intervention effectiveness for brain trauma in clinical trials is a primary feature of the current condition of our work. Fourteen years ago, the Clinical Trials in Head Injury Study Group published a thoughtful summary of recommendations to improve the design and conduct of clinical trials in TBI.² They encouraged (in part):

- Identification and testing of specific (appropriate) subgroups of TBI patients
- Standardized clinical management across centers
- Independent monitoring of patient management and data quality

- Parsimonious data collection
- Identification of relevant outcome measures and adequate time to follow-up
- Identification of clinically relevant effect size

A useful exercise might be to examine the extent to which our community is adhering to these recommendations, and to fundamental tenets of evidence-based medicine, in the design and conduct of our current work.

New Research Approaches. It is reasonable to consider how different research designs might be used to identify which treatments work best, for whom, and under what circumstances. This is the possibility of Comparative Effective Research (CER), which is being promoted by funding agencies and adopted by large consortium efforts in the brain trauma research community. However, at the operational level, CER is still subject to many of the same vulnerabilities as traditional research, because it is accomplished using randomized controlled trials (RCTs) and observational studies. A transition to a new focus on CER must be accompanied by consistent adherence to evidence-based protocols.

Collaborations. There is a need for investigators to work together, share data, and pool resources in order to improve our efficiency at finding answers. Currently, funding agencies are requiring collaborative efforts among their grantees as a prerequisite to funding. In our efforts to successfully collaborate, we need to account for institutional barriers to financial collaborations, and for barriers in the mechanics of collaborations. Pooling data into large repositories requires resources, time, and cooperation across investigators, institutions, and disciplines that often exceed the scope of the project. Building the platform for the repository becomes the deliverable, rather than using the platform to enable answering the questions.

The Brain Trauma Foundation's Position

The Role of the Brain Trauma Foundation. The Brain Trauma Foundation is a service organization dedicated to improving outcomes from TBI. Our core—our DNA—is evidence-based guidelines. Our job is to:

- Identify topics requiring evidence-based analysis that are relevant and specific to populations and subgroups of TBI patients

- Access, systematically review, assess, and synthesize the literature
- Make recommendations based on this evidence
- Identify information gaps and priorities for future research
- Promote a new generation of high-quality studies that can contribute to the evidence base

Specialty societies, health care delivery systems, and clinicians that treat TBI patients generate demand for complete treatment protocols. The mandate is to give clinicians what they need to be able to make decisions in practice. Development of rigorous and comprehensive evidence-based protocols is essential to the appropriate utilization of guidelines. Such protocols merge evidence, consensus, and standards for general good practice in clinical care. The Brain Trauma Foundation's role is to provide the evidence and related recommendations; currently, delineating specific, comprehensive protocols is beyond the scope of these guidelines.

The Scope of the Guidelines. The guidelines address treatment interventions, monitoring, and treatment thresholds that are particular to TBI or that address a risk that is higher in TBI patients. The scope of the guidelines is not intended to cover all topics relevant to the care of patients with severe TBI. Topics related to general good care for all patients, or all trauma patients, are not included. In the future, new topics will be added only if they are TBI-specific. Topics included in prior editions that cover general medical care needs by many patients, such as infection and deep vein thrombosis prophylaxis, have been narrowed to focus on TBI-specific risks or issues. As stated, the recommendations are limited to those areas for which an evidence base was identified. Developing protocols that incorporate general best practices for trauma patients (not TBI-specific) and that provide guidance, suggestions, or options in areas of TBI management where the evidence is insufficient is outside the scope of this endeavor.

The Future of the Guidelines. We are committed to improving the quality of the guidelines and the efficiency of their delivery into the community. The following outlines the major changes we initiated with this update. More detail is provided in the Methods section.

1. **Evaluation of the Evidence.** We added a summary table of the quality of the body of evidence and a discussion of applicability to each topic. This provides more transparency than prior editions about the steps necessary to develop recommendations from a

synthesis of individual studies. In this edition of the guidelines, whether the available evidence was sufficient to merit a recommendation required:

- a. An assessment of the quality of the individual studies
- b. Consideration of the applicability of the individual studies
- c. A synthesis across the studies into an assessment of the quality of the “body of evidence”

In the quality of the body of evidence tables, we indicated how many studies were included and how many patients were in those studies; we summarized the quality across the individual studies, the directness of the included evidence, and the precision of the estimates of results; and we indicated the level of consistency across studies. Additionally, in accompanying text we described characteristics that could impact the applicability of individual studies and how they influence the recommendations.

2. **Criteria for Determining Level of Recommendation.** Another change is that the level of a recommendation is constrained, but not wholly determined, by the class of the included studies. While in past guidelines editions, Class 1 evidence corresponded to a Level I recommendation, in this edition we focused on the quality of the body of evidence, and we took into consideration applicability, in deciding whether a recommendation was warranted, and then what level it should be. Given this approach, a single Class 1 study would be included in the evidence synthesis, and it could contribute to a Level 1 recommendation; however, it may only contribute to a Level 2 recommendation, or no recommendation, if the quality of the body of evidence was moderate or if there are concerns about limited applicability. Once a recommendation was deemed to be appropriate, the *quality of the body of evidence, combined with the class of the studies*, determined the *recommendation level*. This is described in more detail in the Methods section.
3. **The Living Guidelines.** This 4th Edition of the guidelines is transitional. We do not intend to produce a 5th Edition. Rather, we are moving to a model of continuous monitoring of the literature, rapid updates to the evidence review, and revisions to the Recommendations as the evidence warrants. We call this the Living Guidelines model. This is driven by several trends, including advances in technology, the increasing volume

of available information, and the corresponding changes in expectations among clinicians and other stakeholders. A static document that is updated after several years no longer responds to the demands of the community we serve.

More details on the changes within each topic from the 3rd to the 4th Edition are in Appendix A.

The Brain Trauma Evidence-Based Consortium

The Brain Trauma Foundation recognizes that our responsibility extends beyond gathering, assimilating, and reporting the existing evidence. We also have a responsibility to actively promote the generation of new, strong evidence that addresses critical questions identified in our guidelines documents. To that end, we created the Brain Trauma Evidence-Based Consortium (B-TEC), which is currently supported by the U.S. Army Contracting Command, Aberdeen Proving Ground, Natick Contracting Division, under Contract No. W911QY-14-C-0086. This is a multi-center program with a contract to Stanford University in collaboration with the Brain Trauma Foundation, and with subcontracts to Oregon Health & Science University, Portland State University, and other institutions. The key core functions are:

- **Priority Research Topics.** In this function, we bring evidence-based methods to pre-specified priority research topics. Current topics include:
 - Evidence-based guidelines for concussion
 - Secondary analysis of existing datasets
 - Development of a clinically useful classification system for TBI, using dynamic, non-linear modeling.
- **Living Guidelines.** The model of continuous literature review and rapid recommendations updates will be applied to the Brain Trauma Foundation's compendium of evidence-based guidelines, including Prehospital Management, Hospital Management, Pediatric TBI, and Prognosis.
- **Evidence-Based Clinical Research Coordinating and Training Center (CTC).** The CTC of B-TEC will provide an infrastructure for conducting clinical trials that will include specific research project coordination, investigator training and education, data management, and data analytics.

REFERENCES

1. Brain Trauma Foundation, American Association of Neurological Surgeons, Congress of Neurological Surgeons, Joint Section on Neurotrauma Critical Care--AANS CNS, Bratton SL, Chestnut RM, Ghajar J, McConnell Hammond FF, Harris OA, Hartl R, Manley GT, Nemecek A, Newell DW, Rosenthal G, Schouten J, Shutter L, Timmons SD, Ullman JS, Videtta W, Wilberger J E, Wright DW. Guidelines for the management of severe traumatic brain injury. *J Neurotrauma*. 2007;24 Suppl 1:S1-106. PMID: 17511554.
2. Narayan RK, Michel ME, Ansell B, et al. Clinical trials in head injury. *J Neurotrauma*. May 2002;19(5):503-557. PMID: 12042091.

Methods

The development of guidelines encompasses two major activities: first, a systematic review and synthesis of evidence, and second, the derivation of recommendations. These guidelines do not include earlier steps such as the development of a research agenda or primary research on specific questions. Nor do they include the subsequent steps of translating recommendations into comprehensive protocols or algorithms that clinicians can use to guide all steps of treatment or develop quality measures that can be used to monitor care. A comprehensive protocol must integrate aspects of good critical care *in general* with the care that is specific to traumatic brain injury (TBI). These later steps may be done at the local level by hospitals or nationally by professional associations or other organizations interested in improving TBI care. The goals of these guidelines are to identify key questions, review the literature for evidence, assess and assimilate the evidence, derive recommendations, identify research gaps, and deliver the information to the brain trauma community for integration into its various activities and environments.

In the following sections, we describe the methods for the Systematic Evidence Review and Synthesis, followed by the methods for the Development of the Recommendations. Subgroups of the Research Team included the Methods Team and the Clinical Investigators (see Appendix B).

Systematic Evidence Review and Synthesis

We describe below our approach to the scope of the review (topic refinement, topics included in this edition, major changes for this edition, and analytic frameworks) and study selection and compilation of evidence (literature search strategies, abstract and full-text review, use of indirect evidence, use of intermediate outcomes, quality assessment of individual studies, data abstraction, synthesis, identification of subtopics and synthesis, quality of the body of evidence, and applicability).

Scope of the Review

Topic Refinement

Topics for inclusion in this edition were primarily carried forward from the 3rd Edition. Two topics were added (Decompressive Craniectomy and Cerebrospinal Fluid Drainage), and the

questions within topics were revised based on input from the Clinical Investigators. Topics related to good clinical care that are not TBI-specific were excluded. For example, general procedures for reducing hospital-acquired infections are not included. However, measures designed to prevent ventilator-associated pneumonia (VAP) are included based on data suggesting the rate of VAP is higher for TBI patients than for other critical care patients.

Topics Included in This Edition

The topics are organized in three categories that are specific to severe TBI in adults: treatments, monitoring, and thresholds.

Treatments

1. Decompressive Craniectomy
2. Prophylactic Hypothermia
3. Hyperosmolar Therapy
4. Cerebrospinal Fluid Drainage
5. Ventilation Therapies
6. Anesthetics, Analgesics, and Sedatives
7. Steroids
8. Nutrition
9. Infection Prophylaxis
10. Deep Vein Thrombosis Prophylaxis
11. Seizure Prophylaxis

Monitoring

12. Intracranial Pressure
13. Cerebral Perfusion Pressure
14. Advanced Cerebral Monitoring

Thresholds

15. Blood Pressure
16. Intracranial Pressure
17. Cerebral Perfusion Pressure
18. Advanced Cerebral Monitoring

Major Changes for This Edition

Major changes for this edition are summarized here, and details are presented in Appendix A.

- *Cerebral Fluid Drainage*. New topic.
- *Decompressive Craniectomy*. New topic.
- *Deep Vein Thrombosis*. For risks that are traumatic brain injury-specific, direct evidence was not identified. Indirect evidence was identified and included.
- *Intracranial Pressure Technology*. Technology assessment is outside the scope of management guidelines and no longer included.
- *Hyperventilation*. Renamed Ventilation Therapies.
- *Brain Oxygen Monitoring*. Renamed Advanced Cerebral Monitoring.
- *Infection Prophylaxis*. Focus on Ventilator Associated Pneumonia and External Ventricular Drain infections. Indirect evidence was identified and used.
- *Intracranial Pressure Monitoring, Cerebral Perfusion Pressure Monitoring, Advanced Cerebral Monitoring*. Divided into (a) benefits and risks of monitoring (Monitoring) and (b) values to be targeted or avoided (Thresholds).

Analytic Frameworks

Analytic frameworks are tools developed to help guide systematic reviews. They show the relationships between the variables specific to each key question within each topic. They identify the relevant populations, interventions, intermediate outcomes, harms, clinical outcomes, and other factors, and they help clarify what is and is not outside the scope of the review. Three analytic frameworks were developed, one each for Treatments, Monitoring, and Thresholds (see Appendix C). These were used by the Methods Team and the Clinical Investigators to establish the scope of the literature search and to clarify the distinction between studies of treatments, monitoring, and thresholds.

Study Selection and Compilation of Evidence

Literature Search Strategies

The research librarian from the 3rd Edition reviewed the search strategies for that edition, updated them as needed, and executed the searches for this 4th Edition. For all topics continued from the 3rd Edition, Ovid/MEDLINE was searched from 2006 through July 2013, and an

update was performed to include articles published and indexed by the third week of November 2013. For Cerebrospinal Fluid Drainage, the search included literature from 1980 through November 2013. Decompressive Craniectomy had previously been included in the surgical guidelines, so the search was conducted as an update from 2001 through November 2013. Relevant studies referred to us that were published after the November 2013 update were also included. The search strategies are in Appendix D.

Abstract and Full-Text Review

Studies were reviewed in a two-step process. The titles and abstracts were reviewed independently by two members of the Methods Team. Articles were retained for full-text review if at least one person considered them relevant based on the abstract. Two Methods Team members read each full-text article and determined whether it met the inclusion criteria (see Appendix E). The included and excluded full-text articles for each topic were also reviewed by one or more Clinical Investigators who took the lead on each topic, and full-text articles were available for review by all authors. The key criteria for inclusion were: the study population was adult patients with severe TBI (defined as Glasgow Coma Scale [GCS] Score of 3 to 8), and the study assessed an included outcome. Differences were resolved via consensus or by a third reviewer. A list of studies excluded after full-text review is in Appendix F.

Use of Indirect Evidence

Evidence can be defined as indirect when (1) head-to-head comparisons of treatments are not made (e.g., A is compared with placebo and B is compared with placebo but A is not compared with B) or (2) the evidence comes from studies with differences from the pre-specified inclusion criteria, but may be useful in deriving conclusions (e.g., evidence from a study that includes mixed severities or mixed pathologies).¹ This second type of indirect evidence was used in a limited way in these guidelines.

When direct evidence was available, indirect evidence was not used. For most topics, direct evidence was available. However, for some topics in TBI management, no direct evidence was found. In these situations we searched for indirect evidence.

When indirect evidence was considered, we required the same interventions, outcomes, and comparators, but relaxed the criteria related to the population. We considered studies that

included patients with moderate as well as severe TBI, mixed ages, or mixed pathologies using the following criteria:

1. How relevant to (or different from) our target population is the population in the indirect study?
2. To what extent does the relevant physiology of the population in the indirect study approximate the relevant physiology of the population of interest?
3. To what extent are differences in physiology expected to influence the outcome?
4. In what direction would these differences influence the observed effect?

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

Use of Intermediate Outcomes

Direct health outcomes, specifically mortality and neurologic function, are always the priority for our recommendation development. If there were no data about direct health outcomes for a particular topic, we considered use of intermediate outcomes if there was evidence to suggest an association between improvement in intermediate outcomes and improvement in direct health outcomes. In this edition, we explicitly indicated when an intermediate outcome was the target of a recommendation, and in some cases we qualified the recommendation by stating the treatment was indicated *when the overall benefit was felt to outweigh the complications associated with such treatment*. We specified when we included indirect evidence and intermediate outcomes in the assessment of the quality of the body of evidence. (See Quality of the Body of Evidence tables in each topic section.)

Quality Assessment of Individual Studies

All included studies were assessed for potential for bias, which is an approach to assessing the internal validity or quality of the study. This assessment is a core component of systematic review methods. It is an approach to considering and rating studies in terms of how the study design and conduct addressed issues such as selection bias, confounding, and attrition. The criteria used in the 3rd Edition were maintained and applied to the newly identified studies of monitoring and treatments. The criteria for threshold studies were revised to be specific to the

structure of studies of thresholds. (See Appendix G for a complete list of the quality criteria used for individual studies.)

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

Data Abstraction

Data were abstracted from studies by a member of the Methods Team and checked for errors by a second member. Information was recorded about the study population, design, and results. For topics on which meta-analysis was considered, the study characteristics and results were independently abstracted by two people and verified by a third.

Key elements of each included study are presented in the Summary of Evidence tables for each topic section.

Synthesis

The final phase of the evidence review is the synthesis of individual studies into information that the Clinical Investigators and the Methods Team use to develop recommendations. This synthesis is described for each topic in the section titled Evaluation of the Evidence, following the Recommendations and preceding the Evidence Summary.

Identification of Subtopics and Synthesis

For each treatment, monitoring, or thresholds topic, the Clinical Investigators identified important subtopics. For example, for Nutrition, there are questions about the route or mode of feeding, the timing of feeding, glycemic control, and supplements. The studies in each topic were reviewed to determine if quantitative synthesis—meta-analysis was feasible. This involved determining if the patient populations, specifics of the intervention, and the outcomes were similar enough that the study results could be combined. The result of this assessment is included

in the Quality of the Body of Evidence table for each subtopic. For this edition, we did not identify any topics for which quantitative synthesis was appropriate according to current standards. For this reason, the evidence was synthesized qualitatively.

Quality of the Body of Evidence

Assessing the quality of the body of evidence involves four domains: the aggregate quality of the studies, the consistency of the results, whether the evidence provided is direct or indirect, and the precision of the evidence. The criteria and ratings are outlined below, and more detailed definitions are in Appendix H. In addition, the number of studies and number of included subjects are considered. Based on these, an overall assessment is made as to whether the quality of the body of evidence is high, moderate, low, or insufficient. The assessment of the body of evidence for each subtopic is included in a table in each section.

Criteria

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

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

Directness: We define directness as whether the study population is the same as the population of interest and if the outcomes are clinical rather than intermediate outcomes. Evidence is labelled as Direct, Indirect, or Mixed.

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

Ratings

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

The ratings are defined as follows:

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

- Moderate—Moderate confidence that the evidence reflects the true effect. Further research may change the confidence in the estimate of effect and may change the estimate.
- Low—Low confidence that the evidence reflects the true effect. Further research is likely to change the confidence in the estimate of effect and is likely to change the estimate.
- Insufficient— Evidence is unavailable or does not permit a conclusion.

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

Applicability

Applicability is the extent to which research findings are useful for informing recommendations for a broader population (usually the population that is the target of the recommendations). What is important to consider when assessing applicability will vary depending upon the topic, and the assessment is context-specific. Consequently, there is currently no generally accepted universal rating system for applicability. Common considerations focus on the characteristics of the patient population (e.g., to which patients are the results applicable?) and the settings for care delivery (e.g., where could a similar result be expected?). Even if the patient population meets the inclusion criteria established for the review, there may be specific characteristics that affect applicability. The characteristics of the setting in which a study was conducted may also be important to consider. For example, a study conducted in a Veterans Administration (VA) Medical Center may or may not be applicable to other

settings, depending upon how similar the Veterans are to the population of interest, or how similar the context of the VA is to the care setting of interest. Additional characteristics to be considered may include the geographic location (e.g., country, state, urban, or rural) and the type of hospital (e.g., level of trauma center). The geographic area and type of hospital are considered because it is possible that the patients, practice patterns, and available services are different across environments. In this edition, we consider the applicability of individual studies in the *Quality of the Body of Evidence and Applicability* section immediately following the recommendations.

Development of Recommendations

Inclusion of Recommendations

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

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

Level of Recommendation

Recommendations in this edition are designated as Level I, Level II A, Level II B, or Level III. The Level of Recommendation is determined by the assessment of the quality of the body of evidence, rather than the class of the included studies.

The levels were *primarily* based on the quality of the body of evidence as follows:

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

The Class of studies in the body of evidence was the basis for making a Level II B or III recommendation: Level II B recommendations were based on a body of evidence with Class 2 studies, with direct evidence but of overall low quality, and Level III recommendations were based on Class 3 studies, or on Class 2 studies providing only indirect evidence.

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

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

Recommendation Review and Revision

Preliminary Topic Reviews

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

Clinical Investigator Review Meeting

In a two-day meeting in 2014, each topic was presented and discussed by the group. Based on these discussions, the Methods Team revised the searches and recommendations.

Review of Complete Draft

The complete draft of all topics as well as the other sections of the guidelines (e.g., Methods, Appendices) was sent to all Clinical Investigators for review and comment. Phone conferences were held to answer questions, discuss the draft, and finalize the document throughout 2015.

Peer Review

After revisions were made based on input from the Clinical Investigators, the 4th Edition was sent out for peer review. The Peer Review Committee was comprised of topic-specific TBI clinicians, methodologists, representatives of specialty societies, and related stakeholders. Their input was reviewed and incorporated as appropriate. A comprehensive review was also conducted by members of the American Association of Neurological Surgeons/Congress of Neurological Surgeons Joint Guidelines Committee, in collaboration with the Clinical Investigators and Methods Team.

REFERENCE

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Evidence Synthesis and Recommendations, Part I: Treatments

This section contains the evidence synthesis and recommendations for 11 treatments that are either specific to the in-hospital management of severe traumatic brain injury (TBI) or are related to risks experienced by TBI patients. This does not include treatments or procedures that are considered good hospital and trauma care for all patients.

Topics that are included reflect current practice but are expected to change as new treatments are developed that may replace or complement existing treatments.

1. Decompressive Craniectomy

INTRODUCTION

Cerebral edema can result from a combination of several pathological mechanisms associated with primary and secondary injury patterns in traumatic brain injury (TBI).¹ As pressure within the skull increases, brain tissue displacement can lead to cerebral herniation, resulting in disability or death.²⁻⁴

Surgical removal of a portion of the skull, known as decompressive craniectomy (DC), has been performed for the purpose of relieving elevated intracranial pressure with outcome improvement in specific TBI patients.^{5,6} Most of the debate surrounding the role of decompressive craniectomy in the management of severe TBI results from a paucity of data coming from randomized controlled trials (RCTs) assessing this intervention.⁷⁻⁹

There have been variations in surgical techniques, timing, and patient populations in most of the observational studies published in the last 2 decades.⁸⁻¹¹ A new RCT, pending publication, will evaluate decompressive craniectomy as a secondary procedure after intracranial pressure (ICP) targeted medical therapies have failed,¹² and will hopefully lend further evidence to support or not support this intervention.

RECOMMENDATIONS*

Level I

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

Level II A

- Bifrontal DC is not recommended to improve outcomes as measured by the Glasgow Outcome Scale–Extended (GOS-E) score at 6 months post-injury in severe TBI patients with diffuse injury (without mass lesions), and with ICP elevation to values >20 mm Hg for more than 15 minutes within a 1-hour period that are refractory to first-tier therapies. However, this procedure has been demonstrated to reduce ICP and to minimize days in the intensive care unit (ICU).

- A large frontotemporoparietal DC (not less than 12 x 15 cm or 15 cm diameter) is recommended over a small frontotemporoparietal DC for reduced mortality and improved neurologic outcomes in patients with severe TBI.

*The committee is aware that the results of the RESCUEicp trial¹³ may be released soon after the publication of these Guidelines. The results of this trial may affect these recommendations and may need to be considered by treating physicians and other users of these Guidelines. We intend to update these recommendations after the results are published if needed. Updates will be available at <https://braintrauma.org/coma/guidelines>.

Changes from Prior Edition

DC is a new topic for this 4th Edition. DC had been included in the surgical guidelines.

EVALUATION OF THE EVIDENCE

Quality of the Body of Evidence

Studies of DC covered several questions (Table 1-1). The Class 2 studies either (1) compared DC to medical management or (2) compared DCs of different sizes, in terms of their effect on patient mortality and functional outcomes. Class 3 studies addressed these questions, and also (3) comparison of DC to craniotomy and (4) assessment of the use of DC earlier or later in the course of treatment.

For the first two questions addressed by Class 2 evidence, the quality of the body of evidence was moderate. The RCT that compared DC to initial medical management was rated Class 1.¹⁴ This study was high quality but was a single study, and replication is needed for high confidence in the results. Both RCTs that compared size of DCs were rated Class 2.^{15,16} The Class 3 studies on these two questions were not incorporated into the recommendations and are not included in Table 2, given there was higher-level evidence available. These Class 3 studies are included in Table 1-3 and in the text in the Evidence Tables and Summary section below.

For the third and fourth questions for which only Class 3 evidence was identified, the body of evidence was rated as insufficient, primarily because the results were inconsistent, with different studies reporting positive, negative, and no effects. As the studies were of poor quality, it was not possible to reconcile these differing results or to use the studies to support Level III recommendations.

Table 1-1. Quality of the Body of Evidence (Depressive Craniectomy)

| COMPONENTS OF OVERALL QUALITY – Class 1 and 2 | | | | | | | | |
|---|-------------------|------------------------|--------------------|------------------|-----------------------------------|---------------------------------|---------------------------------|--|
| Topic | Number of Studies | Meta-Analysis | Number of Subjects | Class of Studies | Consistency (High, Moderate, Low) | Directness (Direct or indirect) | Precision (High, Moderate, Low) | Quality of Evidence (High, Moderate, Low, or Insufficient) |
| DC vs. initial medical management ¹⁴ | 1 RCT | NA | 155 | 1 | NA | Direct | Low | Moderate |
| Larger DC vs. smaller DC ^{15,16} | 2 RCTs | No: Different outcomes | 560 | 2 | Moderate | Direct | Moderate | Moderate |
| COMPONENTS OF OVERALL QUALITY – Class 3 | | | | | | | | |
| DC vs. craniotomy ^{17,18} | 2 Observational | No | 174 | 3 | Moderate | Direct | Low | Insufficient |
| Timing of DC ^{19,20} | 2 Observational | No | 160 | 3 | Low | Direct | Low | Insufficient |

Abbreviations: DC=decompressive craniectomy, NA=not applicable, RCT=randomized controlled trial.

Applicability

The applicability differs across questions and studies. The Class 1 study comparing DC to initial medical management was conducted in three countries over an 8-year period, and included 15 centers.¹⁴ While this diversity may have limited the ability to detect an effect, it could increase the applicability of the study. The two studies rated Class 2 that compare size of DCs were both conducted in one country (China).^{15, 16} Incomplete reporting about these studies limited the ability to fully understand key elements such as the standard of care and characteristics of the populations.

SUMMARY OF THE EVIDENCE

Process

Of the 31 potentially relevant studies reviewed, 21 were excluded because they did not meet the inclusion criteria. Of the remaining 10 studies, one Class 1¹⁴ and two Class 2^{15, 16} studies were included as evidence to support recommendations for this topic. The remaining seven were rated Class 3.¹⁷⁻²³

Class 1 and 2 Studies

The evidence from Class 1 and 2 studies of depressive craniectomy is summarized in Table 1-2.

Table 1-2. Summary of Evidence – Class 1 and 2 Studies (Depressive Craniectomy)

| Reference, Study Topic | Study Design, N, and Outcomes | Data Class | Results Conclusion |
|---|--|---|--|
| DC compared with Medical Management | | | |
| Cooper, 2011* ¹⁴ Comparison of bifrontotemporoparietal DC treatment vs. initial medical management without DC | RCT N=155 DC=73 No DC=82 Extended GOS at 6 months; favorable outcome | Class 1 | <u>Odds ratios for worse outcome in DC group:</u> GOS-E at 6 months 1.84 (95% CI 1.05 to 3.24), p=0.03. Unfavorable outcomes 2.21 (95% CI 1.1.4 to 4.26), p=0.02. Mortality at 6 months DC 19% vs. standard care 18%. Post hoc adjustment for pupil reactivity at baseline resulted in differences that were no longer significant. DC vs. initial medical management Mean ICP after randomization (mm Hg) 14.4 ± 6.8 vs. 19.1 ± 8.9, p<0.001. Fewer ICU Days 13(10-18) vs. 18 (13-24), p<0.001. DC resulted in lower ICP and fewer ICU days, but more unfavorable outcomes. |
| Size of DC | | | |
| Jiang, 2005* ¹⁵ Comparison of the influence of standard, larger trauma craniectomy (unilateral frontotemporoparietal bone flap [12x15 cm]) vs. a limited, smaller craniectomy (temporoparietal bone flap [6x8 cm]) | RCT N=486 STC=245 LC=241 GOS at 6 months; Complications | Class 2 Concern about baseline differences between eligible/excluded and eligible/included | STC vs. LC GOS 4 or 5: Good recovery or moderate deficit 96 (39.8%) vs. 70 (28.6%), p=0.05. GOS 2 or 3: Severe deficit or vegetative state 82 (34.0%) vs. 89 (36.3%), p=0.05. GOS 1: Death 63 (26.2%) vs. 86 (35.1%), p<0.05. Significantly greater mortality in LC group. Incidence of delayed hematoma and incision CSF fistula significantly lower in STC group, while other complications did not differ. |

| Reference, Study Topic | Study Design, N, and Outcomes | Data Class | Results Conclusion |
|---|--|---|---|
| Qiu, 2009*¹⁶ Unilateral decompressive craniectomy (larger=15 cm diameter) vs. unilateral routine temporoparietal craniectomy | RCT N=74 Unilateral DC=37 Unilateral routine temporoparietal craniectomy (control group)=37 Mortality at 1 month; GOS at 1 year; Complications | Class 2 Concern about baseline differences between eligible/excluded and eligible/included | Mortality at 1 month 27% large DC group 57% in smaller DC control, p=0.010. Good neurological outcome (GOS Score of 4 to 5) at 1 year 56.8% large DC group vs. 32.4% smaller DC control, p=0.035. Incidences of delayed intracranial hematoma 21.6% large DC group vs. 10.8% smaller DC group, p=0.041 Subdural effusion 5.4% large DC group vs. 0 % smaller DC group, p=0.040. Larger DC improved outcomes (mortality and function), but resulted in higher rates of complications. |

Abbreviations: CSF= cerebrospinal fluid, DC=decompressive craniectomy, GOS=Glasgow Outcome Scale, GOS-E=Extended Glasgow Outcome Scale, ICP=intracranial pressure, ICU=intensive care unit, LC=limited, smaller craniectomy, MAP=mean arterial pressure, N=total sample size, RCT=randomized controlled trial, STC=standard, larger traumatic craniectomy.

* **Reference new to the 4th Edition**

The DECRA trial, an RCT that compared bifrontotemporoparietal DC to initial medical management for refractory raised ICP, recruited patients in 15 tertiary care hospitals in Australia, New Zealand, and Saudi Arabia between December 2002 and April 2010.¹⁴ This study found poorer GOS-E scores for patients in the DC group than those in standard care at 6 months post-injury, and lower ICP and fewer ICU days for patients in the DC group. Despite randomization, the proportion of patients in the DC group with reactivity in neither pupil on admission was higher (27% vs. 12%, p=0.04) than in controls. Planned baseline covariate adjustment did not change the results, but post hoc adjustment for this difference in pupil reactivity at admission resulted in outcome differences that were no longer significant. Based on this, the authors reported that “...the overall effect size did not change, although the harmful effect of craniectomy was no longer significant. A beneficial effect of craniectomy was excluded.”

The two studies that compared different sizes of DC were both conducted in China. One¹⁵ was conducted at five medical centers, while the other¹⁶ was conducted at a single site. They differed in the requirements for inclusion; Jiang, 2005 et al.¹⁵ required refractory intracranial hypertension while Qiu, 2009¹⁶ included patients based on a computed tomography (CT) scan showing a swollen hemisphere. Both studies found better outcomes with larger DCs; however,

the differences in patients, procedures, and treatment, as well as the fact that these studies did not adjust for any covariates, limited the ability of these studies to provide a definitive answer to this question. Of importance, these studies did not make a comparison of different sizes with no decompression. Thus, the evidence did not allow an estimate of the effect of decompression compared with no decompression.

Class 3 Studies

The evidence from Class 3 studies of depressive craniectomy is summarized in Table 1-3.

Table 1-3. Summary of Evidence – Class 3 Studies (Depressive Craniectomy)

| Reference Study Topic | Study Design, N and Outcomes | Data Class | Results Conclusion |
|---|---|------------|--|
| New Studies | | | |
| DC compared with Medical Management | | | |
| Olivecrona, 2007* ²² Comparison of DC vs. non-craniectomy | Retrospective Cohort N=93 Treatment craniectomy= 21 Control, non-craniectomy=72 Mortality GOS Scores | Class 3 | DC vs. no DC Mortality 3 (14.4%) vs. 10 (14.1%) GOS 2 1 (4.8%) vs. 3 (4.2%) GOS 3 2 (9.6%) vs. 15 (21.1%) GOS (GOS 5–4) 15 (71%) vs. 43 (61%), p>0.05. No significant difference in mortality or GOS The reduction of ICP was statistically significant in the Craniectomy group 72 hours post-procedure, p<0.001. |
| Soustiel, 2010* ²³ Comparison of DC vs. non-craniectomy (medical management) | Prospective Cohort N=122 DC=36 No DC=86 Mortality GOS ICP CBF | Class 3 | Odds Ratio: DC to no DC Mortality: No difference OR: 0.80 (no CI reported), p=0.4185. Good functional outcome at 6 months (GOS): OR; 0.14, p=0.0000. Patients in DC group are more likely to have a poor functional outcome. Both mortality and GOS were adjusted for Age, CT, GCS at admission, ICP, CBF, CMRO ₂ |

| Reference Study Topic | Study Design, N and Outcomes | Data Class | Results Conclusion |
|---|---|------------|--|
| DC vs. Craniotomy | | | |
| Huang, 2008*¹⁷ Comparison of decompressive craniectomy and duraplasty vs. traditional craniotomy for treatment of hemorrhagic cerebral contusion | Retrospective Cohort N=54 Treatment, craniectomy and duraplasty=38 Control, craniotomy=16 Mortality GOS-E | Class 3 | Treatment vs. Control Mortality 5 (13.2%) vs. 4 (25.0%), p=NS. Reoperation rates 3 (7.9%) vs. 6 (37.5%) vs. p<0.05. GOSE scores 5.55 ± 2.34 vs. 3.56 ± 2.37, p<0.005. |
| Soukiasian, 2002*¹⁸ Comparison of craniectomy vs. craniotomy | Retrospective Cohort N=120 Treatment, craniectomy=24 Control, craniotomy=96 Mortality TBI Complications | Class 3 | Mortality did not differ and there was no difference in survival between groups, with 52% vs. 79%, p=0.08. Complications were more frequent among craniectomy patients vs. craniotomy patients. Complications included collapse of basilar cisterns 30.4% vs. 4.3%, p=0.0001 and herniation, 17.4% vs. 5.4%, p=0.05. |
| Size of DC | | | |
| Lu, 2003*²¹ Comparison of standard large trauma craniotomy vs. routine craniotomy | Observational N=230 Treatment, STC=115 Control, RC=115 Mortality GOS scores Complications | Class 3 | STC vs. RC Mortality 48 (41.7%) vs. 66 (57.74%) p<0.01. GOS good outcomes/moderate disability 27 (23.5%) vs. 21 (18.3%), p=NS. GOS severe disability or vegetative survival 40 (34.8%) vs. 28 (24.3%), p=NS. |
| Timing of DC | | | |
| Akyuz, 2010*¹⁹ Comparison of DC as a second tier, late treatment vs. DC as first tier, early treatment for severe TBI | Observational N=76 2nd Tier, N=36 1st Tier, N=40 Mortality GOS ICP Complications | Class 3 | 2nd Tier vs. 1st Tier Mortality=GOS of 1 16 (44.4%) vs. 5 (12.5%), p=0.0018. GOS of 2 or 3 (negative outcome) 10 (27.0%) vs. 15 (37.5%) GOS 4 + 5 10 (27.8%) vs. 20 (50%), p=0.047. ICP after DC (mm Hg, mean, ± sd) 23.3 ± 3.5 vs. 17.2 ± 3.5 Early DC resulted in better outcomes |

| Reference Study Topic | Study Design, N and Outcomes | Data Class | Results Conclusion |
|--|--|------------|--|
| Wen, 2011* ²⁰ Comparison of early DC vs. late DC | Prospective Cohort N=44 Treatment, early DC=25 Matched comparison late DC=19 Mortality GOS score Complications | Class 3 | Mortality 1 month post-surgery 4 (16%) vs. 3 (15.8%) p=0.985. 6 months post-surgery 5 (20%) vs. 4(21%), p=0.932. Good outcome (GOS 4 or 5)/poor outcome (GOS 1, 2,3) 1 month 7/18 vs. 7/12, p=0.533 6 months 13/12 vs. 12/7, p=0.459 No difference in outcomes |

Abbreviations: CBF=cerebral blood flow, CMRO₂=cerebral metabolic rate of oxygen, CT=computed tomography, DC=decompressive craniectomy, GCS=Glasgow Coma Scale, GOS=Glasgow Outcome Scale, GOS-E=Extended Glasgow Outcome Scale, ICP=intracranial pressure, ICU=intensive care unit, LC=limited, smaller craniectomy, MAP=mean arterial pressure, N=total sample size, NR=not reported, NS=not significant, OR=odds ratio, RC=routine craniotomy, RCT=randomized controlled trial, sd=standard deviation, STBI=severe traumatic brain injury, STC=standard, larger trauma craniectomy.

***References new to the 4th Edition.**

Both of the two Class 3 studies that compared DC to medical management reported no significant difference in mortality; however, one reported poorer functional outcomes with DC²³ while the other found no difference in function.²² The one Class 3 study comparing large and small DC reported lower mortality with larger DC.²¹ These results were similar to the Class 2 studies that addressed this question. For these questions, higher quality Class 2 evidence was available, and the Class 3 evidence was not used to inform the recommendations.

The studies that compared DC to craniotomy reported lower, but not statistically significant, mortality rates and conflicting findings about function and complications.^{17,18} Similarly, the results of two studies of the timing of DC were inconsistent. One reported reduced mortality,¹⁹ and one reported no difference.²⁰ Given the quality of the studies and the inconsistency of the findings, the quality of the body of evidence was rated as insufficient and these studies were not used as the basis for recommendations.

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2. Prophylactic Hypothermia

INTRODUCTION

Hypothermia is well recognized to preserve cells and tissue in the face of metabolic challenge. Evidence supports the administration of hypothermia as standard of care for neuroprotection after cardiac arrest from acute coronary syndromes.^{1,2} There has been long-standing interest in applying hypothermia to reduce the tissue damage associated with central nervous system trauma; however, benefit cannot be presumed. In addition to suggested neuroprotective effects, hypothermia is well known for its ability to reduce intracranial pressure. However, hypothermia bears risks, including coagulopathy and immunosuppression, and profound hypothermia bears the additional risk of cardiac dysrhythmia and death.³

Hypothermia can be administered either early after injury and prior to intracranial pressure elevation, in which case it is termed “prophylactic,” or as a treatment for refractory intracranial pressure elevation, typically referred to as “therapeutic.” Prophylactic hypothermia has been subject to scrutiny in studies that have reported conflicting results.³ Of uncertain relevance to adult traumatic brain injury (TBI), two recent high-quality pediatric trials failed to show benefit and additionally suggested harm related to prophylactic hypothermia for TBI.^{4,5} Interest has thus shifted to exploring how specific aspects of induced hypothermia, such as the duration and depth, relate to clinical effect.³ For instance, it is generally suggested that gradual rewarming can mitigate the inherent risk of rebound intracranial pressure elevation⁶ and there has been interest in localized cerebral cooling in the hopes of obtaining the desired benefits without the systemic side effects.

RECOMMENDATIONS

Level I and II A

- There was insufficient evidence to support a Level I or II A recommendation for this topic.

Level II B

- Early (within 2.5 hours), short-term (48 hours post-injury) prophylactic hypothermia is not recommended to improve outcomes in patients with diffuse injury.

Changes from Prior Edition

In the 3rd Edition, the studies that compared hypothermia to normothermia were summarized in a meta-analysis. For this 4th Edition we re-examined the underlying assumptions of our prior work in light of the current standards for meta-analysis and decided not to repeat the meta-analysis because the hypothermia interventions in the higher-quality studies (Class 2 or better) differed across the studies in clinically important ways. More detail is provided in Appendix I.

EVALUATION OF THE EVIDENCE

Quality of the Body of Evidence

The research identified for prophylactic hypothermia (Table 2-1) included studies that make three types of comparisons: (1) hypothermia versus normothermia, (2) shorter versus longer periods of cooling, and (3) head-only versus systemic cooling.

The quality of the body of evidence for the comparison of hypothermia with normothermia is low because the findings were inconsistent, with some studies reporting benefits and others reporting no difference between treatment and control groups. The Class 1 study found no difference in outcomes between hypothermia and normothermia groups and supported the Level II B recommendation.⁷ Of note, the II B recommendation only applies to the early, short-term protocol used; there is insufficient evidence to make a recommendation outside these conditions.

For the questions addressing length of cooling⁸ and head-only versus systemic cooling,⁹ the evidence was insufficient. In both cases, the evidence consisted of single studies which, although rated Class 2, had limitations that minimized confidence in the findings.

Table 2-1. Quality of the Body of Evidence (Prophylactic Hypothermia)

| COMPONENTS OF OVERALL QUALITY – Class 1 and 2 | | | | | | | | |
|--|-------------------|--------------------------------|--------------------|--------------------------|-----------------------------------|---------------------------------|---------------------------------|--|
| Topic | Number of Studies | Meta-Analysis | Number of Subjects | Class of Studies | Consistency (High, Moderate, Low) | Directness (Direct or indirect) | Precision (High, Moderate, Low) | Quality of Evidence (High, Moderate, Low, or Insufficient) |
| Hypothermia vs. normothermia ^{7, 10-15} | 7 RCTs | No differences in intervention | 816 | One Class 1, six Class 2 | Low | Direct | Low | Low |

| COMPONENTS OF OVERALL QUALITY – Class 1 and 2 | | | | | | | | |
|--|-------------------|---------------|--------------------|------------------|-----------------------------------|---------------------------------|---------------------------------|--|
| Topic | Number of Studies | Meta-Analysis | Number of Subjects | Class of Studies | Consistency (High, Moderate, Low) | Directness (Direct or indirect) | Precision (High, Moderate, Low) | Quality of Evidence (High, Moderate, Low, or Insufficient) |
| Length of cooling (short term—48 hours or less vs. long term) ⁸ | 1 RCT | NA | 215 | 2 | NA | Direct | Low | Insufficient |
| Head vs. systemic cooling ⁹ | 1 RCT | NA | 66 | 2 | NA | Direct | Low | Insufficient |

Abbreviation: NA=not applicable, RCT=randomized controlled trial.

Applicability

Potential applicability concerns vary across sub-topics. For the comparison of hypothermia to normothermia, one Class 1 and three Class 2 studies were conducted in the United States,^{7,11,12,14} two in China,^{13,15} and one in Japan.¹⁰ While practice patterns, resources, and standards may be different across these countries, the different locations could also be a strength. However, the studies conducted in China and Japan reported benefits from hypothermia, while three out of the four U.S. studies found no difference.^{7,11,12} This could reflect differences in the tendency not to publish studies with negative results or that find no benefit. Another difference is that two studies were conducted at multiple sites^{7,12} with comparatively large sample sizes while the others were limited to a single site and fewer patients (sample sizes ranged from 26 to 87). The larger multi-site studies may be considered more applicable.

Details Related to Assessment for Meta-Analysis

Since the publication of the 3rd Edition there has been a proliferation of meta-analyses in the neurosurgery literature as well as in the medical literature in general. While meta-analyses are useful for combining small but similar studies in order to increase precision, issues have been raised about when meta-analysis is appropriate and about the level of rigor required to establish confidence in the findings. These issues have complicated the interpretation of the results of the studies for this topic.^{16, 17}

A fundamental requirement for meta-analysis is that the patient populations, interventions, and outcomes should be similar enough that combining them is logical from a clinical perspective. We re-evaluated the included studies in the 3rd Edition meta-analysis and found that they varied in terms of the target temperature, the length of time hypothermia was maintained, and the rate of rewarming. These differences were used for subgroup analyses in the 3rd Edition but with the caveat that sample sizes were small. However, if these treatment differences are clinically important, combining the studies in order to determine an overall impact is not appropriate. (See Appendix I for detailed information on the differences in hypothermia treatment across studies.) On review, these differences in treatment were considered important and for this reason, we did not repeat the meta-analysis.

SUMMARY OF THE EVIDENCE

Process

Of the 14 new, potentially relevant studies reviewed, five were excluded because they did not meet the inclusion criteria for this topic. One new Class 1 study,⁷ two new Class 2 studies,^{8,9} and six Class 2 studies¹⁰⁻¹⁵ from the 3rd Edition were included as primary evidence for this topic (Table 2-2). Six new studies were rated Class 3 (Table 2-3).

Class 1 and 2 Studies

The evidence from Class 1 and 2 studies of prophylactic hypothermia is summarized in Table 2-2; results from studies included in the 3rd Edition are replicated in the table for continuity and new references are noted.

Table 2-2. Summary of Evidence – Class 1 and 2 Studies (Prophylactic Hypothermia)

| Reference Study Topic | Study Design, N, and Outcomes | Data Class | Results Conclusion |
|--|---|------------|---|
| Hypothermia compared with Normothermia | | | |
| Aibiki, 2000 ¹⁰ Comparing effect of moderate hypothermia (3-4 days, 32-33° C) vs. normothermia | RCT N=26 Hypothermia=15 Normothermia=11 Mortality GOS at 6 months post-injury Japan | Class 2 | Hypothermia vs. normothermia Mortality 1 (6.7%) vs. 3 (27.3%) significance not reported. GOS at 6 months Better outcomes 80% vs. 36.4% Mean GOS 4.2 vs. 2.9, p=0.04. |

| Reference Study Topic | Study Design, N, and Outcomes | Data Class | Results Conclusion |
|--|--|------------|---|
| Clifton, 1993 ¹¹ Comparing effect of hypothermia (2 days, 32-33° C) vs. normothermia | RCT N=46 Hypothermia=24 Normothermia=22 Mortality GOS at 3 months Complications United States | Class 2 | Hypothermia vs. normothermia Mortality 35% (8) vs. 36% (8) not significant. 3-month GOS Good recovery to moderate disability=52.2% vs. 36.4% not significant Significantly fewer seizures in hypothermia group, p=0.019. No significant differences between groups on other complications. |
| Clifton, 2001 ¹² Comparing the effect of hypothermia (2 days, 33° C) vs. normothermia | RCT N=392 Hypothermia=199 Normothermia=193 GOS at 6 months United States, Multi-center | Class 2 | Hypothermia vs. normothermia Mortality 28% vs. 27% p=0.79. 6-month GOS severe disability, vegetative, or dead 57% in both groups. Trend toward poor outcomes for patients hypothermic on arrival and randomized to normothermia. |
| Clifton, 2011*⁷ Comparison of 48 hours of early hypothermia (33° C) vs. normothermia | RCT N=97 Hypothermia=52 Normothermia=45 Mortality Neurological Outcome United States, Multi-center | Class 1 | Hypothermia vs. normothermia Mortality 12/52 vs. 8/45, RR 1.30, 95% CI 0.58 to 2.52; p=0.52. Poor outcomes (severe disability, vegetative state, or death) 31/52 vs. 25/45, RR 1.08, 95% CI 0.76 to 1.53; p=0.67. No significant difference in complications. Poor outcomes: difference by type of injury Diffuse injury: 70% vs. 50% p=0.09. Surgically evacuated hematomas 33% vs. 69% p=0.02. Fewer poor outcomes when patients with surgically evacuated hematomas are treated with hypothermia. |
| Jiang, 2000 ¹³ Comparing of effect of long-term (3-14 days) mild hypothermia (33-35° C) vs. normothermia | RCT N=87 Long-term hypothermia=43 Normothermia=44 Mortality and GOS at 1 year China | Class 2 | Hypothermia vs. normothermia Mortality at 1 year 25.6% vs. 45.5% GOS at 1 year significantly better outcomes (good recovery to moderate disability) 46.5% vs. 27.3%, p<0.05. No significant differences in complications. |

| Reference Study Topic | Study Design, N, and Outcomes | Data Class | Results Conclusion |
|--|--|------------|---|
| Marion, 1997 ¹⁴ Comparing the effect of moderate hypothermia (24 hours, 32-33° C) vs. normothermia | RCT N=82 Hypothermia=40 Normothermia=42 GOS at 3 and 6 months, and 1 year United States | Class 2 | Hypothermia vs. normothermia Good outcomes (GOS 4 or 5) 3 months 38%(15) vs. 17% (7) p=0.03. 1 year 62% (24) vs. 38% (16), p=0.05. In subgroup analysis patients with initial GCS of 3 or 4 did not benefit, those with GCS 5 to 7 did benefit from hypothermia |
| Qiu, 2005 ¹⁵ Comparing the effect of mild hypothermia (3-5 days, 33-35° C) vs. normothermia | RCT N=86 Hypothermia=43 Normothermia=43 Mortality and GOS at 2 years China | Class 2 | Hypothermia vs. normothermia Mortality 25.6% vs. 51.2%, p<0.05. 2 year GOS Better outcomes (good recovery or moderate disability) 65.1% vs. 37.2%, p<0.05. More pulmonary infection 60.5% vs. 32.6%) and more thrombocytopenia 62.8% vs. 39.5% respectively, p<0.05. |
| Longer vs. Shorter Hypothermia | | | |
| Jiang, 2006* ⁸ Comparison of long-term hypothermia (4-6 days) vs. short-term hypothermia (1-3 days) | RCT N=215 Long-term group=108 Short-term group=107 GOS 6 months Complications | Class 2 | Long-term vs. short-term hypothermia 43.5% vs. 29% favorable outcomes p<0.05. Significantly higher rate of favorable outcomes for long-term group. No difference in complications. |
| Head vs. Systemic Cooling | | | |
| Liu, 2006* ⁹ Comparison of Selective brain cooling vs. mild systemic cooling (33-35° C) vs. normothermia | RCT N=66 SBC Group= 22 MSH Group=21 Normothermia(control)=23 GOS at 2 years ICP during treatment | Class 2 | SBC vs. MSH vs. control Mortality 27.3% vs. 28.6% vs. 52.2%. Favorable outcome (GOS 4 or 5) 2 years post injury 72.7% vs. 57.1% vs. 34.8%. Outcomes significantly better for SBC than Control group (p<0.05), but no significant difference in outcomes between SBC and MSH groups. Lower ICP for SBC at all measurements vs. controls, p<0.05. |

Abbreviations: GCS=Glasgow Coma Scale, GOS=Glasgow Outcome Scale, ICP=intracranial pressure, MSH=mild systemic hypothermia, N=total sample size, RCT=randomized controlled trial, SBC=selective brain cooling

*References new to the 4th Edition.

Hypothermia versus normothermia. The studies that compare hypothermia to normothermia represent a body of literature with conflicting results.^{7,10-15} Despite attempts to improve study designs and research questions over time, there are important differences in several aspects of the studies. Clifton et al. conducted three studies over almost 2 decades seeking to evaluate hypothermia for patients with severe TBI by improving the study design and adapting the study protocols based on their own findings and those of other researchers.^{7,11,12}

Clifton, 1993 is described as a Phase II study. The authors reported non-significant trends toward better outcomes and no significant differences in most complications in the hypothermia patients.¹¹ Marion, 1997 conducted a study that randomized 82 patients and compared GOS scores at 3, 6, and 12 months.¹⁴ They found no difference in mortality, but more patients in the hypothermia group had better outcomes. However, adjustments for differences in CT evaluations lowered the precision of the estimate. Analysis by initial severity level revealed that the benefit occurred in the patients who were less severely injured (with initial Glasgow Coma Scale [GCS] scores of 5 to 7) while there was no statistically significant benefit in patients who were more severely injured (those with lower GCS of 3 or 4).

Based on Clifton, 1993¹¹ and Marion, 1997,¹⁴ larger, Phase III studies were recommended. Clifton et al., 2001 responded with a second, much larger (N=392) multi-center trial.¹² This study found no difference in mortality or neurological outcome. Authors suggested that hypothermia was not induced quickly enough to produce a benefit in normothermic patients, and that rewarming patients who arrived hypothermic was detrimental.

This informed the design of Clifton et al., 2011, in which patients had to be enrolled within 2.5 hours of injury.⁷ Enrollment in this study was stopped for futility when interim analyses found no difference in mortality or neurological outcomes and calculated that the hypothesized difference could not be reached even if full enrollment was completed. Follow-up was completed for enrolled patients, and exploratory subgroup analyses revealed that in patients with surgically removed hematomas the hypothermia group had better outcomes, while in patients with diffuse brain injuries there was no significant difference in outcomes. These findings suggest a potential underlying reason for the null finding, but would need to be tested in studies designed to determine if there is a difference in outcome for different types of patients before it could be used to inform evidence-based recommendations. In 2012, Clifton et al. published the results of a

post hoc analysis of the subset of patients who received craniotomies to evacuate hematomas from the 2001 and 2011 studies.¹⁸ While this was stronger than the subgroup analysis from a single study, there were important differences. For example, patients in the later study reached target temperatures earlier than those in the first study, in which the time to target temperature was mixed. For this analysis, the authors compared patients who were cooled more quickly, within 1.5 hours of surgery, to patients who were cooled later and those in the normothermia (control) group. Fewer patients who were cooled quickly had negative outcomes (41%), while more patients who were cooled slowly or treated with normothermia had negative outcomes (62%, $p=0.009$).

While other studies also compared hypothermia to normothermia, they differed in important ways. Aibiki et al., 2000 randomized 26 patients to hypothermia and normothermia primarily to assess the impact of cooling on prostanoids that affect cerebral blood flow.¹⁰ In addition to finding that hypothermia may reduce prostanoid production after TBI, they also reported that GOS scores 6 months after injury were significantly higher for the hypothermia group in this limited number of patients. The study by Qui, 2005 randomized 86 patients. The hypothermia group was kept cool for 3 to 5 days and had lower mortality rates.¹⁵ Although pulmonary infections were higher in the hypothermia group (60.5% vs. 32.6%), there were no significant differences in gastrointestinal hemorrhage, electrolyte disorder, or renal malfunction, and there were no severe complications in heart rate, respiration, blood pressure, or arterial blood gases. Jiang et al., 2000 compared normothermia to an experimental hypothermia group in which patients started to be rewarmed when ICP returned to normal, resulting in hypothermia for 3 to 14 days.¹³ Their findings included significantly lower mortality and better outcomes (GOS score at 1 year) in the hypothermia group.

Longer versus shorter duration. One study randomized 215 patients at three medical centers to long-term and short-term hypothermia.⁸ Their analysis found that patients cooled for 5 days had significantly better outcomes (GOS score at 6 months) than patients cooled for 2 days.

Head only versus systemic cooling. Lui, 2006 conducted a preliminary study that compared head only (selective brain cooling) with full body (systemic cooling) and normothermia.⁹ GOS scores 2 years after the injury were highest in the selective brain cooling group (GOS 4 or 5, 72.7% vs. 57.1% for systemic cooling, 34.8% normothermia), and rates of pneumonia were the

lowest in this group (22.7% vs. 38.1% for systemic cooling and 34.8% for the normothermia group).

Class 3 Studies

The summary of evidence from Class 3 studies of prophylactic hypothermia is summarized in Table 2-3.

Table 2-3. Summary of Evidence—Class 3 Studies (Prophylactic Hypothermia)

| Reference Study Topic | Study Design, N and Outcomes | Data Class | Results Conclusion |
|---|---|------------|--|
| Hypothermia compared with Normothermia | | | |
| Harris, 2009* ¹⁹ Comparison of hypothermia with a cooling cap vs. normothermia | RCT N=25 Treatment=12 Control=13 Mortality Morbidity (GOS & modified FIM scores) Intracranial temperature | Class 3 | Mortality: hypothermia vs. control 6/12 (50.0%) vs. 4/13 (30.8%) of 13, p=0.43. GOS: No statistically significant difference Median maximum change in GOS during 28-days=0 for both the treatment and control groups, p=0.50. No significant difference in outcomes. |
| Lee, 2010* ²⁰ Comparison of hypothermia and hypothermia with CPP management vs. normothermia | RCT N=45 A: Normothermia=16 B: Mild hypothermia (33 to 35 degrees C)=15 C: Hypothermia with CPP management=14 Mortality Complications Length of ICU stay ICP PtiO ₂ GOSc | Class 3 | A vs. B vs. C Mortality 2/16 (12.5%) vs. 1/15 (6.7%) vs. 1/14 (8.5%), p=0.89 GOS percentage of favorable neurologic outcomes 50% vs., 60% vs.71.4% p=0.039. ICP Mean: Days 1 and 2: Not statistically significant . Days 3-5: Significantly lower in B and C vs. A High: Days 1 and 2: Not statistically significant. Days 3-5: Significantly lower in B and C vs. A. ICU stay: mean number of days 9.0 days vs.11.3 days vs. 11.6 days, p=0.017. Complications (pulmonary infection, urinary tract infection, and thrombocytopenia) were not significantly different. Mortality did not differ but GOS was better in the hypothermia group and best in the hypothermia plus CPP group. |

| Reference Study Topic | Study Design, N and Outcomes | Data Class | Results Conclusion |
|---|--|------------|---|
| Qiu, 2007* ²¹ Comparison of hypothermia vs. normothermia | RCT N=80 Treatment=40 Control=40 Neurological outcomes Complications ICP | Class 3 | Treatment vs. control Mortality 22.5% vs. 32.5% (OR 1.66, 95% CI 0.61 to 4.48) Favorable neurologic outcomes at 1 year 70.0% vs. 47.5% for controls, p=0.041. Mean ICP Lower in hypothermia group at 24, 48, and 72 hours after injury, p=0.000, p=0.000, and p=0.003. Complications 57.5% vs. 32.5%; p=0.025. (managed without severe sequelae including pulmonary infections) No difference in mortality, better neurological outcomes, but higher rate of complications though they were managed. |
| Qiu, 2006* ²² Comparison of SBC vs. normothermia | RCT N=90 Treatment=45 Control=45 Neurological outcome (GOS scores) ICP Temperature | Class 3 | SBC vs. Control Mortality 20.0% vs. 28.9% (OR 0.615, 95% CI 0.232 to 1.630) Good neurological outcome (GOS score of 4 to 5) 6 months 68.9% vs. 46.7%, p<0.05. Mean ICP values SBC were lower than normothermia at 24, 48, and 72 hours, p<0.001. No complications resulting in severe sequelae. Hypothermia resulted in better GOS at 6 months. |

| Reference Study Topic | Study Design, N and Outcomes | Data Class | Results Conclusion |
|--|--|------------|---|
| Smrcka, 2005* ²³ Comparison of hypothermia vs. normothermia | RCT N=72 Treatment=37 Control=35 Neurological outcomes: Morbidity and mortality (based on GOS scores) ICP CPP | Class 3 | GOS Not significantly different. Morbidity and mortality (based on GOS scores, 5=good to 1=death) Hypothermia vs. normothermia GOS: n, (%) 5: 18 (51) vs. 13 (35) 4: 12 (34) vs. 5 (13.5) 3: 0 (0) vs. 5 (13.5) 2: 0 (0) vs. 3 (8) 1: 5 (15) vs. 11(30) Hypothermia vs. normothermia ICP 10.81+ 5 vs. 18.88+ 6, p<0.0001. CPP 78.10+ 6 vs. 73.71 + 5, p=0.024. No difference in neurological outcomes. |
| Zhao, 2011* ²⁴ Comparison of hypothermia vs. normothermia | RCT N=81 Treatment=40 Control=41 GOS scores ICP Lactic acid Blood glucose | Class 3 | Hypothermia vs. normothermia Mortality 1 (2.5%) vs. 4 (9.8%) GOS Scores Significantly more patients with GOS 4-5 in hypothermia group than normothermia group =75% vs. 51.2%, p=0.038= Significantly fewer patients with GOS 2-3 in hypothermia group than normothermia group =25% vs. 48.8%, p=0.038= ICP values 24 hours: 19.79 vs. 25.83, p<0.01. 72 hours: 18.74 vs. 27.40, p<0.01. |

Abbreviations: CPP=cerebral perfusion pressure, GOS=Glasgow Outcome Scale, ICP=intracranial pressure, MSH=mild systemic hypothermia, N=total sample size, RCT=randomized controlled trial, SBC=selective brain cooling.

***References new to the 4th Edition.**

Six RCTs with sample sizes ranging from 25 to 81 patients compared hypothermia to normothermia. These all had serious methodological limitations and were rated Class 3. Four employed systemic cooling^{20,21,23,24} while two cooled only the head.^{19,22} None of these studies found any statistically significant difference in mortality. Four reported better neurological

outcomes in patients treated with hypothermia,^{20-22,24} while two found no difference.^{19,23} In combination, this is a very weak body of evidence.

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3. Hyperosmolar Therapy

INTRODUCTION

As early as 1783, ¹Monro, ¹Kellie, ²and other investigators ³advanced the notion that the volume of the brain is constant. The landmark work of Weed and McKibben ⁴disproved this long-held dogma when they demonstrated dramatic changes in the volume of the brain resulting from administration of hypertonic or hypotonic intravenous solutions. Since that time, intravenous administration of hyperosmolar agents has become routine in the management of intracranial hypertension and herniation syndromes. However, the optimal agent, their optimal means of administration (i.e., dose and bolus vs. continuous infusion), and their precise mechanisms of action continue to be investigated.

Mannitol and hypertonic saline are routinely employed hyperosmolar agents in North America. Specific circumstances may prompt selection of a specific agent. Hypertonic saline administration may be hazardous for a hyponatremic patient. ⁵ Although mannitol can be used as a resuscitation fluid, its eventual diuretic effect is undesirable in hypotensive patients and attention needs to be paid to replacing intravascular volume loss. ⁶ While mannitol was previously thought to reduce intracranial pressure through simple brain dehydration, both mannitol and hypertonic saline work to reduce intracranial pressure, at least in part, through reducing blood viscosity, leading to improved microcirculatory flow of blood constituents and consequent constriction of the pial arterioles, resulting in decreased cerebral blood volume and intracranial pressure. ^{5,7,8}

RECOMMENDATIONS

Level I, II, and III

- Although hyperosmolar therapy may lower intracranial pressure, there was insufficient evidence about effects on clinical outcomes to support a specific recommendation, or to support use of any specific hyperosmolar agent, for patients with severe traumatic brain injury.

As noted below, the Level II and III recommendations from the 3rd Edition of these guidelines were not carried forward because they were derived from studies that do not meet

Class 3 criteria for this topic. While there is increasing use of hypertonic saline as an alternative hyperosmotic agent, there is insufficient evidence available from comparative studies to support a formal recommendation. The Committee thus chose to re-state here the 3rd Edition recommendations. The rationale for doing so is to maintain sufficient recognition of the potential need for hyperosmolar therapy to reduce intracranial pressure, while acknowledging that more research is needed to inform more specific recommendations. (Refer to the 3rd Edition for summary of supporting studies.)

Recommendations from the Prior (3rd) Edition Not Supported by Evidence Meeting Current Standards

- Mannitol is effective for control of raised intracranial pressure (ICP) at doses of 0.25 g/kg to 1 g/kg body weight. Arterial hypotension (systolic blood pressure <90 mm Hg) should be avoided.
- Restrict mannitol use prior to ICP monitoring to patients with signs of transtentorial herniation or progressive neurological deterioration not attributable to extracranial causes.

Changes from Prior Edition

The Committee is universal in its belief that hyperosmolar agents are useful in the care of patients with severe TBI. However, the literature does not currently support recommendations that meet the strict criteria for contemporary evidenced-based medicine approaches for guideline development.

The recommendations in the 3rd Edition of these guidelines about administration of hyperosmolar agents were based on one Class 2 study and nine Class 3 studies. The study included as a Class 2 study⁹ was not a comparative study for this topic (it is a Class 2 trial about the use of barbiturates), and six of the studies that were rated as Class 3 studies were not comparative¹⁰⁻¹⁵ and therefore did not meet current inclusion criteria.

In this 4th Edition, we focused the search for new evidence explicitly on the comparative effectiveness of different hyperosmolar agents and means of administration.

EVALUATION OF THE EVIDENCE

Quality of the Body of Evidence

Studies acquired from the search for this 4th Edition about hyperosmolar therapy that address the comparative effectiveness of different hyperosmolar agents are limited to one Class 2 retrospective cohort study¹⁶ and two Class 3 randomized controlled trials (RCTs).^{17,18} The Class 2 study was insufficient for a Level II recommendation because it was a single, non-randomized retrospective study with a relatively small sample size (n=75) with limited matching used to address confounding. Similarly, the low-quality trials were not sufficient to support a Level III recommendation.^{17,18} Given that larger observational studies or an RCT have the potential to produce different results, no Level II or Level III recommendation is made at this time.

Three Class 3 studies from the 3rd Edition compared hypertonic saline with normal saline,¹⁹ hypertonic saline with Lactated Ringers,²⁰ and mannitol with barbiturates.²¹ None provided sufficient evidence to support a recommendation. They are summarized in Table 3-1 and in the text below.

Table 3-1. Quality of the Body of Evidence (Hyperosmolar Therapy)

| Topic | Number of Studies | Meta-Analysis | Number of Subjects | Class of Studies | Consistency (High, Moderate, Low) | Directness (Direct or indirect) | Precision (High, Moderate, Low) | Quality of Evidence (High, Moderate, Low, or Insufficient) |
|--|------------------------|---------------|--------------------|------------------|-----------------------------------|---------------------------------|---------------------------------|--|
| COMPONENTS OF OVERALL QUALITY-Class 2 | | | | | | | | |
| Hypertonic saline vs. mannitol ¹⁶ | 1 Cohort 0 RCT | NA | 73 | 2 | NA | Direct | Low | Insufficient |
| COMPONENTS OF OVERALL QUALITY-Class 3 | | | | | | | | |
| Hypertonic saline vs. mannitol ¹⁷ | 1 RCT | NA | 47 | 3 | NA | Direct | Low | Insufficient |
| Concentration (2% or 3% vs. 0.9%). ¹⁹ | 1 Retrospective cohort | NA | 82 | 3 | NA | Direct | Low | Insufficient |
| Hypertonic saline vs. lactated ringers ²⁰ | 1 RCT | NA | 34 | 3 | NA | Direct | Low | Insufficient |
| Mannitol vs. barbiturates ²¹ | 1 RCT | NA | 59 | 3 | NA | Direct | Low | Insufficient |
| Sodium lactate vs. mannitol ¹⁸ | 1 RCT | NA | 34 | 3 | NA | Direct | Low | Insufficient |

Abbreviations: NA=not applicable, RCT=randomized controlled trial.

Applicability

The included Class 2 study was conducted using a database of information collected from 22 trauma centers.¹⁶ However, all of the trauma centers were in one state (New York), raising the possibility of some limits to applicability if practice patterns or patient populations in New York State differ significantly from those in other geographic areas. One Class 3 study was conducted in two university hospitals, one in France and one in Israel,¹⁷ and the other in a single center in France.¹⁸

SUMMARY OF THE EVIDENCE

Process

Of the eight new, potentially relevant studies reviewed, five were excluded because they did not meet the inclusion criteria. Of the remaining three, one was rated Class 2¹⁶ and two Class 3.^{17,18} Three Class 3 studies from the 3rd Edition were retained,¹⁹⁻²¹ but they each addressed different subtopics and did not constitute a body of evidence on these topics.

Class 2 Study

The evidence from the Class 2 study of hyperosmolar therapy is summarized in Table 3-2.

Table 3-2. Summary of Evidence - Class 2 (Hyperosmolar Therapy)

| Reference Study Topic | Study Design, N, and Outcomes | Data Class | Results Conclusion |
|--|--|------------|--|
| Hypertonic Saline vs. Mannitol | | | |
| Mangat, 2014* ¹⁶ Comparison of the effectiveness of HTS vs. mannitol in treating ICP after severe TBI | Retrospective Cohort N=73 HTS=25 Mannitol=25 for 1:1 matching; 48 for 2:1 2-week mortality ICP Burden ICU days ICP Monitoring days | 2 | HTS vs. mannitol Two-week mortality not statistically significant, p=0.56. Cumulative ICP burden 15.52% vs. 36.5%, p=0.003. Daily ICP burden 0.3 ± 0.6 hours/day vs. 1.3 ± 1.3 hours/day, p=0.001. ICU days 8.5 ± 2.1 vs. 9.8 ± 0.6, p=0.004; p=0.06 for 1:2 comparison. HTS was more effective in lowering ICP burden but did not have a significant effect on mortality. |

Abbreviations: GOS=Glasgow Outcome Scale, HTS=hypertonic saline, ICP=intracranial pressure, ICU=intensive care unit, N=total sample size, RCT=randomized controlled trial, TBI=traumatic brain injury

***Reference new to the 4th Edition.**

Mangat et al. used the Brain Trauma Foundation's TBI-trac[®] New York State Database to conduct a retrospective study comparing the effectiveness of mannitol to hypertonic saline.¹⁶ The overall findings are that hypertonic saline may be more effective than mannitol in lowering intracranial pressure but no difference was found in short-term mortality.

Patients who received both agents were excluded as data were not available about the reason for the use of the second drug. All patients over 16 years of age admitted between June 6, 2000, and August 21, 2008, with a severe TBI and who stayed in the hospital for at least 5 days were included. Patients with missing data were dropped. Exact matching was used to match patients who received mannitol with those who received hypertonic saline (HTS) in terms of the Glasgow Coma Scale (GCS), hypotension, and pupil reactivity. Age and CT were not used in the matching because they were balanced between the groups. One-to-one matching was used for the primary analysis and 1:2 matching was used for a sensitivity analysis, resulting in the inclusion of 24 patients who were given HTS compared with 48 who were given mannitol.

Mortality at 2 weeks was not significantly different (1:1 match common odds ratio 0.50, 95% CI 0.05 to 5.51, $p=0.56$). Intensive care unit (ICU) stays were shorter for the HTS group, but the difference was not significant in the 2:1 comparison. The number of days intracranial pressure (ICP) was recorded did not differ between the groups. Cumulative ICP burden, defined as the number of days with an ICP spike >25 mm Hg as a percentage of the total number of days monitored, was significantly lower in the HTS group ($15.2 \pm 19.9\%$ vs. $36.5 \pm 30.9\%$, $p=0.003$, HTS vs. mannitol). Daily ICP burden (hours/day of ICP >25 mm Hg) was also significantly lower in the HTS group (0.3 ± 0.6 vs. 1.3 ± 1.3 hours/day, $p=0.001$, HTS vs. mannitol). These results suggest that HTS may have advantages over mannitol, but additional research is needed to confirm this finding and compare short- and long-term clinical outcomes, including mortality and neurological function.

Class 3 Studies

The evidence from the Class 3 study of hyperosmolar therapy is summarized in Table 3-3.

Table 3-3. Summary of Evidence—Class 3 Studies (Hyperosmolar Therapy)

| Reference Study Topic | Study Design, N and Outcomes | Data Class | Results |
|--|--|------------|---|
| New Studies | | | |
| Cottenceau 2011* ¹⁷ HTS vs. MAN | RCT N=47 HTS=22 MAN=25 ICP GOS at 6 months | Class 3 | MAN vs. HTS Average time of ICP > 20 (11.1 + 7.9 h) vs. (8.4+ 5.9h) NS GOS at 6 months: no significant difference |
| Ichai, 2009* ¹⁸ LAC vs. MAN | RCT N=34 LAC=17 MAN=17 ICP GOS at 1 year post-injury | Class 3 | ICP significantly lower in LAC than MAN (p=0.016). Better 1-year GOS scores for LAC, but study not powered to test this question. |
| Studies from 3rd Edition | | | |
| Qureshi, 1999 ¹⁹ 2% or 3% solution of saline vs. 0.9%. | Retrospective Cohort N=82 Analysis comparing continuous administration of 2% or 3% sodium chloride/acetate solution at 75-150 ml/hour (N=36 – HTS Group) to 0.9% saline (N=46 – NS Group) in TBI patients with GCS <8. | Class 3 | More penetrating TBI and mass lesions in HTS group. HTS group had higher in-hospital mortality. Patients treated with HTS were more likely to receive barbiturate treatment. |
| Shackford, 1998 ²⁰ HTS vs. lactated Ringers | RCT N=34 Comparing 1.6% saline to lactated Ringer's for hemodynamic instability in pre and in-hospital phase in patients with TBI and GCS <13. | Class 3 | Baseline ICP higher and GCS lower in HS group. Despite this, HTS effectively lowered ICP; ICP course was not different between groups. Cumulative fluid balance greater in LR group. Daily serum sodium, osmolarity and ICP interventions greater in HTS group. GOS was not different between groups. |
| Schwartz, 1984 ²¹ MAN vs. barbiturates | RCT N=59 Comparing MAN with barbiturates for ICP control. Crossover permitted. Sequential analysis. | Class 3 | Pentobarbital was not significantly better than MAN. The MAN group had lower mortality 41% vs. 77%. CPP much better with MAN than barbiturates (75 mm Hg vs. 45 mm Hg). |

Abbreviations: CPP=cerebral perfusion pressure, GCS=Glasgow Coma Scale, GOS=Glasgow Outcome Scale, HTS=hypertonic saline, ICP=intracranial pressure, LAC=sodium lactate, MAN=mannitol, NS= Normal Saline, RCT=randomized controlled trial, TBI=traumatic brain injury.

One new, small Class 3 RCT compared hypertonic saline to mannitol.¹⁷ This study reported no significant differences in either the average time with elevated ICP or GOS at 6 months. A second small Class 3 RCT compared sodium lactate to mannitol and reported that ICP was significantly lower for patients who received sodium lactate than for those who received

mannitol.¹⁸ Of the three Class 3 studies maintained from the 3rd Edition, one compared hypertonic saline (2% to 3%) to normal saline (0.9%),¹⁹ one compared hypertonic saline to lactated ringers,²⁰ and one compared mannitol to barbiturates.²¹ Because these are single, Class 3 studies, they were not used to support a recommendation.

The additional studies presented in the 3rd Edition as support for the Level III recommendations included descriptive, non-comparative studies that constituted a body of evidence that provided a basic understanding of the mechanisms and effects of mannitol, but did not provide definitive evidence about its comparative effectiveness or about different regimens of administration. As these studies were not comparative, they were not included in this edition.

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4. Cerebrospinal Fluid Drainage

INTRODUCTION

Management of external ventricular drainage (EVD) systems in patients with severe traumatic brain injury (TBI) remains a controversial topic. An EVD in a closed position allows for monitoring of intracranial pressure (ICP), while in an open position drainage of cerebrospinal fluid (CSF) can occur. Practice patterns regarding whether the EVD should be maintained in a closed or open position vary widely based on a number of variables, including patient age, institutional resources, and physician preferences. The goal of this chapter is to present current EVD management options and review the available evidence that can be used to guide decision-making on this topic.

A key variable in EVD management appears to be related to patient age. In the pediatric population continuous CSF drainage is a relatively common practice with evidence to support improvements in both ICP management and injury biomarkers.¹ Practice patterns are more variable for those patients who are triaged to adult trauma centers. In that setting some physicians prefer to continuously monitor ICP and only intermittently drain for ICP elevations. Others prefer continuous drainage of CSF with intermittent ICP measurements. A third option is to place both an EVD for continuous drainage and an intraparenchymal fiberoptic pressure monitor for continuous ICP measurements. Specific recommendations regarding this topic have not been discussed in prior editions of these guidelines, yet it is a key aspect of patient care with potential to significantly impact patient care and protocol development.

RECOMMENDATIONS

Level I and II

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

Level III

- An EVD system zeroed at the midbrain with continuous drainage of CSF may be considered to lower ICP burden more effectively than intermittent use.
- Use of CSF drainage to lower ICP in patients with an initial Glasgow Coma Scale (GCS) <6 during the first 12 hours after injury may be considered.

Changes from Prior Edition

This new topic, which was added to the 4th Edition as Cerebrospinal Fluid (CSF) drainage, is a potential treatment to lower intracranial pressure.

EVALUATION OF THE EVIDENCE

Quality of the Body of Evidence

The two Class 3 studies included for this topic addressed two different questions: (1) whether continuous or intermittent CSF drainage is superior at reducing ICP² and (2) whether use of CSF drainage is associated with lower mortality.³ Both studies were retrospective and conducted in single sites.

The question of whether EVD use reduces mortality remains uncertain,² as the quality of evidence was low and consisted of a single study with low precision. The single included study supported the Level III recommendation that CSF may be considered for patients with GCS <6 but should be avoided in patients with GCS \geq 6 due to potentially higher mortality rates.

Table 4-1. Quality of the Body of Evidence (Cerebrospinal Fluid Drainage)

| COMPONENTS OF OVERALL QUALITY – Class 3 | | | | | | | | |
|---|------------------------|---------------|--------------------|------------------|-----------------------------------|---------------------------------|---------------------------------|--|
| Topic | Number of Studies | Meta-Analysis | Number of Subjects | Class of Studies | Consistency (High, Moderate, Low) | Directness (Direct or indirect) | Precision (High, Moderate, Low) | Quality of Evidence (High, Moderate, Low, or Insufficient) |
| Continuous vs. intermittent CSF drainage ³ | 1 Retrospective cohort | NA | 62 | 3 | NA | Direct | Low | Low |
| Use of CSF drainage ² | 1 Retrospective cohort | NA | 171 | 3 | NA | Direct | Low | Low |

Abbreviations: CSF=cerebrospinal fluid, NA=not applicable.

Applicability

Both studies were from single centers. EVDs drain cerebrospinal fluid and may decrease ICP; however, presently the evidence that EVD use either improves survival or lowers morbidity in adults with severe TBI is not established. Continuous CSF drainage may be superior to lower ICP compared with intermittent drainage, but this would need to be verified by a multi-institutional study and complications would need to be assessed.

SUMMARY OF THE EVIDENCE

Process

Of 12 new, potentially relevant studies reviewed, 10 were excluded because they did not meet the inclusion criteria for this topic (see Appendix F). No Class 1 or 2 evidence was identified; two new Class 3 studies were included.^{2,3}

Class 3 Studies

The evidence from the Class 3 studies of cerebrospinal fluid drainage is summarized in Table 4-2.

Table 4-2. Summary of Evidence – Class 3 Studies (Cerebrospinal Fluid Drainage)

| Reference Study Topic* | Study Design, N, and Outcomes | Data Class | Results Conclusion |
|--|---|---------------|---|
| Continuous vs. Intermittent EVD | | | |
| Nwachuka, 2013* ³ Assessed continuous vs. intermittent EVD on intracranial pressure | Retrospective Cohort N=62 Continuous=31 Intermittent=31+ (+matched on key characteristics from earlier time period when this was standard of care) 6 month Mortality 6 month GOS ICP | Class 3 | Closed vs. Open n (%) p-value 6-month survival 22 (71.0) vs. 24 (77.4), p=0.56. 6-month favorable GOS 13 (42.0) vs. 8 (26.0), p=0.35. Area under ICP curve (overall ICP values) (mean ± SD; median) 962.7 ± 228.7; 979.0 vs. 608.8 ± 277.3; 519.2 p<0.0001. Area under ICP curve (above 20 mm Hg) (mean ± SD; median) 59.7 ± 72.9; 43.3 vs. 17.2 ± 36.8; 0.0 p=0.0002. Patients managed with a closed, intermittently draining EVD had significantly higher ICP burden than the patients treated with an open EVD, continuous CSF drainage approach. |

| CSF Drainage and Mortality | | | |
|---|--|---------|--|
| Griesdale, 2010^{*2} Examined the relationship between external ventricular drain use and mortality | Retrospective Cohort N=171 EVD=93 Comparison (no EVD)=73 In hospital mortality 28-day mortality | Class 3 | In hospital mortality All OR 2.76 (95% CI 1.07 to 7.08) p=0.04 GCS<6, OR 0.76 (95% CI 0.18 to 3.2) p=0.71 GCS≥6, OR 5.6 (95% CI 1.7 to 18.4), p<0.01. 28-day mortality All OR 2.12 (95% CI 0.80 to 5.62) p=0.13 GCS <6, OR 0.47, (95% CI 0.11 to 2.1) p=0.32 GCS ≥6, OR 5.0, (95% CI 1.5 to 16.7), p<0.01. EVD use was associated with higher in hospital and 28-day mortality for patients with a GCS ≥6 assessed during initial 12 hours of admission. |

Abbreviations: CSF=cerebrospinal fluid, EVD=external ventricular drain, GCS= Glasgow Coma Scale, GOS=Glasgow Outcome Scale, ICS=intracranial pressure.

*** Reference new to the 4th Edition**

Both Class 3 studies were retrospective cohorts. Nwachuka et al. conducted a retrospective study, comparing open EVD to a closed system that allowed intermittent draining.³ In the study hospital, the management protocol changed to open EVD from closed. The patients from the study were selected from the pre- and post-protocol change periods and were matched on age, sex, and injury severity. The primary outcome was ICP burden (mortality and GOS were reported as characteristics demonstrating similarity between the patient groups). Patients with closed EVD had higher mean ICP (15.8 vs. 10.14 mm Hg for closed EVD and open EVD, respectively) than patients managed with open EVD, and this was significantly different after adjusting for initial GCS and whether the patient had a craniectomy.³ The study was not sufficiently robust for strong conclusions. The sample size was small, elements of the study design suggested that it was likely to have a high risk of bias, and it was under powered to detect infrequent potential complications.³

Griesdale et al. identified 171 patients admitted with severe TBI treated in a single university-affiliated tertiary care hospital in British Columbia, Canada, between May 2000 and March 2006.² Patients were excluded if they died within 12 hours of admission or had a high cervical spine injury or non-traumatic reason for level of consciousness. Whether EVD was used or not was examined in the context of a larger inquiry about the extent to which clinicians adhered to patient management guidelines.² The finding that EVD use was associated with

higher ICU but not hospital mortality led the researchers to examine subgroups. They found that mortality was only associated with the EVD use for patients with an initial GCS ≥ 6 , while use in more severely comatose patients demonstrated a statistically insignificant trend for lower mortality. Authors state that additional research is needed to confirm this finding, given the possibility the results are due to unidentified confounding, which is difficult to control for in a retrospective study.

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5. Ventilation Therapies

INTRODUCTION

Patients with severe traumatic brain injury (TBI) require definitive airway protection because they are at risk of pulmonary aspiration or compromised respiratory drive and function. They may also require transient hyperventilation to treat cerebral herniation. Normal ventilation is currently the goal for severe TBI patients in the absence of cerebral herniation and normal partial pressure of carbon dioxide in arterial blood (PaCO_2) ranges from 35-45 mm Hg. PaCO_2 is the measure of arterial levels of carbon dioxide levels and heavily depends on metabolic rate. Exhalation of PaCO_2 results in removal of metabolic waste, and, during times of high metabolism, respiratory rate normally increases to lower PaCO_2 levels. Under normal conditions, PaCO_2 is the most powerful determinant of cerebral blood flow (CBF) and, between a range of 20 mm Hg and 80 mm Hg, CBF is linearly responsive to PaCO_2 . Cerebral blood flow is important in meeting the brain's metabolic demands. Low PaCO_2 , therefore, results in low CBF and may result in cerebral ischemia while high PaCO_2 levels can result in cerebral hyperemia and high intracranial pressure (ICP). Therefore, providing optimal CBF is important under normal and abnormal conditions.

Severe TBI patients receive mechanical ventilation, which can tightly regulate PaCO_2 levels through rate and tidal volume adjustments. Older studies suggested that cerebral hyperemia was more common than cerebral ischemia, and hyperventilation was recommended in the care of patients with TBI.¹⁻³ However, more recent studies have shown that after severe TBI, cerebral metabolic rate is not always low and can be variable. In fact, cerebral ischemia has been documented in a number of studies after severe TBI, changing longstanding recommendations concerning ventilation therapy.⁴⁻⁷ Since cerebral metabolic rate is not universally measured after TBI, it is not possible to provide point of care CBF therapy to these patients. Therefore, the high prevalence of cerebral ischemia in this patient population suggests safety in providing normo-ventilation so as to prevent further cerebral ischemia and cerebral infarction.

RECOMMENDATIONS

Level I and II A

- There was insufficient evidence to support a Level I or II A recommendation for this topic.

Level II B

- Prolonged prophylactic hyperventilation with partial pressure of carbon dioxide in arterial blood (PaCO₂) of 25 mm Hg or less is not recommended.

As noted below, the Level III recommendations from the 3rd Edition of these guidelines were not carried forward because they were derived from case series studies. While no evidence is available from comparative studies to support a formal recommendation, the Committee chose to re-state here the 3rd Edition Level III recommendations. The rationale for doing so is to maintain sufficient recognition of the potential need for hyperventilation as a temporizing measure. (Refer to the 3rd Edition for summary of supporting studies.)

Recommendations from the Prior (3rd) Edition Not Supported by Evidence Meeting Current Standards

- Hyperventilation is recommended as a temporizing measure for the reduction of elevated intracranial pressure (ICP).
- Hyperventilation should be avoided during the first 24 hours after injury when cerebral blood flow (CBF) is often critically reduced.
- If hyperventilation is used, jugular venous oxygen saturation (SjO₂) or brain tissue O₂ partial pressure (BtpO₂) measurements are recommended to monitor oxygen delivery.

Changes from Prior Edition

The title of this section was changed from Hyperventilation to Ventilation Therapies for the 4th Edition.

EVALUATION OF THE EVIDENCE

Quality of the Body of Evidence

The scope of this topic was expanded to allow for inclusion of other related treatments. Despite this, the body of evidence remains an RCT rated Class 2, and the quality of the body of evidence to support a recommendation is low⁸ (Table 5-1).

Table 5-1. Quality of the Body of Evidence (Ventilation Therapies)

| Topic | COMPONENTS OF OVERALL QUALITY | | | | | | | Quality of Evidence (High, Moderate, Low, or Insufficient) |
|--|-------------------------------|---------------|--------------------|------------------|-----------------------------------|---------------------------------|---------------------------------|--|
| | Number of Studies | Meta-Analysis | Number of Subjects | Class of Studies | Consistency (High, Moderate, Low) | Directness (Direct or indirect) | Precision (High, Moderate, Low) | |
| Influence of hyperventilation on outcomes ⁸ | 1 RCT | NA | 113 | 2 | NA | Direct | Low | Low |

Abbreviations: NA=not applicable, RCT=randomized controlled trial.

Applicability

The single study cited in the table and text below was conducted at one U.S. site. Given the data are over 25 years old,⁸ the results may be less applicable than those from a more current study.

SUMMARY OF THE EVIDENCE

Process

Of four new, potentially relevant studies reviewed, all were excluded because they did not meet the inclusion criteria for this topic (see Appendix F). No new evidence was added for this edition; one Class 2 study from the 3rd Edition was included as evidence for this topic.⁸

Class 2 Study

The evidence from the Class 2 study of ventilation therapies is summarized in Table 5-2.

Table 5-2. Summary of Evidence (Ventilation Therapies)

| Reference Study Topic* | Study Design, N, and outcomes | Data Class | Results Conclusion |
|--|---|------------|---|
| Influence of hyperventilation on outcomes | | | |
| Muizelaar, 1991 ⁸ To compare normal ventilation (control: PaCO ₂ 35 ± 2 mm Hg) to prolonged hyperventilation (HV group: PaCa 25 ± 2 mm Hg with and without tromethamine | RCT N=113 Control=41 HV=36 HV & THAM=36 GOS 3, 6 and 12 months NOTE: The inclusion criteria included children (≥to 3 years old); the exact age distribution was not reported though the median age is 26 years old. | Class 2 | HV vs. control 3 months HV worse, p<0.03. 6 months HV worse, p<0.05. 12 months – Not statistically significant. Difference is due to patients with Motor score 4-5; no difference in patients with score 1-3. HV + tromethamine vs. control No significant difference. Patients with an initial GCS motor score of 4-5 that were hyperventilated to a PaCO ₂ of 25 mm Hg during the first 5 days after injury had significantly worse outcomes. |

Abbreviations: GCS=Glasgow Coma Scale, GOS=Glasgow Outcome Scale, HV=hyperventilation, N=total sample size, RCT=randomized controlled trial.

*No new studies were added to this edition.

The Level II B recommendation for this topic is based on one Class II RCT of 113 patients.⁸ The study used a stratified, randomized design to compare outcomes in severe TBI patients provided normal ventilation (PaCO₂ 35 ±2 mm Hg; n=41; control group), hyperventilation (PaCO₂ 25 ±2 mm Hg; n=36), or hyperventilation with tromethamine (THAM; n=36). One potential benefit of hyperventilation is considered to be minimization of cerebrospinal fluid (CSF) acidosis. However, the effect on CSF pH may not be sustained due to a loss of HCO₃⁻ buffer. THAM treatment was introduced to test the hypothesis that it would reverse the effects of the loss of buffer.

Patients were stratified based on the motor component of the Glasgow Coma Scale (GCS) (1-3 and 4-5). The GOS was used to assess patient outcomes at 3, 6, and 12 months. For patients with a motor GCS of 4-5, the 3- and 6-month GOS scores were significantly lower (worse) in the hyperventilated patients than in the control or THAM groups. However, the effect was not sustained at 12 months. Also, the effect was not observed in patients with the lower motor GCS, minimizing the sample size for the control, hyperventilation, and THAM groups to 21, 17, and 21, respectively. The absence of a power analysis resulted in uncertainty about the adequacy of

the sample size. For these reasons, the article was rated Class 2 and the recommendation that hyperventilation be avoided is Level II B.

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6. Anesthetics, Analgesics, and Sedatives

INTRODUCTION

Anesthetics, analgesics, and sedatives are important and commonly-used therapies in acute traumatic brain injury (TBI) for a variety of reasons, including prophylaxis or control of intracranial hypertension and seizures.¹⁻³ Barbiturates have a long history of being used to control intracranial pressure (ICP), presumably by preventing unnecessary movement, coughing, and straining against tubes as well as suppression of metabolism and alteration of cerebral vascular tone. Depressed cerebral metabolism and oxygen consumption is said to be neuro-protective in some patients.^{2,4} Anesthetics and sedatives, such as barbiturates, may also improve coupling of regional blood flow to metabolic demands resulting in higher brain oxygenation 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.^{2,5,6}

Side effects of anesthetics, analgesics, and sedatives include hypotension and decreased cardiac output, as well as increased intrapulmonary shunting, which may lead to hypoxia.² These may give rise to a paradoxical decrease in cerebral perfusion pressure, which may negate the benefits of decreased ICP.⁵ In addition, anesthetics such as propofol have been associated with hyperkalemia, metabolic acidosis, myocardial failure, rhabdomyolysis, and death.⁴ The administration of these medications may preclude the physical examination in following a patient's progress and may therefore necessitate more advanced therapeutic modalities such as continuous electroencephalographic (EEG) monitoring. Because of potential toxic side effects, duration and dose of administration also means that the monitoring of sedative doses needs to be diligently observed.

RECOMMENDATIONS

Level I and II A

- There was insufficient evidence to support a Level I or Level IIA recommendation for this topic.

Level II B

- Administration of barbiturates to induce burst suppression measured by EEG as prophylaxis against the development of intracranial hypertension is not recommended.
- High-dose barbiturate administration is recommended to control elevated ICP refractory to maximum standard medical and surgical treatment. Hemodynamic stability is essential before and during barbiturate therapy.
- Although propofol is recommended for the control of ICP, it is not recommended for improvement in mortality or 6-month outcomes. Caution is required as high-dose propofol can produce significant morbidity.^{7,8}

Changes from Prior Edition

There are no content changes from the 3rd Edition to the recommendations (although wording revisions were made). Newly identified Class 3 studies have been added to the evidence but did not change the recommendations.

EVALUATION OF THE EVIDENCE

Quality of the Body of Evidence

The research on this topic has focused on three questions: (1) Does the prophylactic use of barbiturates improve outcomes, (2) can barbiturates be used to reduce intracranial hypertension, and (3) does the use of sedatives improve outcomes? The Class 2 evidence is limited to a single, comparatively small study for each question. While there was one Class 3 study included in the 3rd Edition and four additional Class 3 studies were identified for this update, they all had serious flaws or null findings. For this reason, the body of evidence on which the recommendations are based remains the Class 2 studies. The quality of the body of evidence is considered low, as a new larger study could change the conclusions (Table 6-1). This evidence was used as the basis for the recommendations in the 3rd Edition, and these recommendations were retained in this 4th Edition.

Table 6-1. Quality of the Body of Evidence (Anesthetics, Analgesics, and Sedatives)

| Topic | COMPONENTS OF OVERALL QUALITY | | | | | | | |
|--|-------------------------------|---------------|--------------------|------------------|-----------------------------------|---------------------------------|---------------------------------|--|
| | Number of Studies | Meta-Analysis | Number of Subjects | Class of Studies | Consistency (High, Moderate, Low) | Directness (Direct or Indirect) | Precision (High, Moderate, Low) | Quality of Evidence (High, Moderate, Low, or Insufficient) |
| Prophylactic use of barbiturates ⁹ | 1 RCT | NA | 53 | 2 | NA | Direct | Low | Low |
| Barbiturates as a treatment for refractory ICP ¹⁰ | 1 RCT | NA | 73 | 2 | NA | Direct | Low | Low |
| Sedatives and analgesics ¹¹ | 1 RCT | NA | 42 | 2 | NA | Direct | Low | Low |

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

Applicability

The included Class 2 studies were conducted 15 to 30 years ago. The age of the studies may reduce their applicability to current practice.

SUMMARY OF THE EVIDENCE

Process

Of the nine new, potentially relevant studies reviewed, five were excluded because they did not meet inclusion criteria for this topic (see Appendix F), and the remaining four were rated Class 3.¹²⁻¹⁵ These are included in Table 6-3 with one Class 3 study from the 3rd Edition.¹⁶ Three Class 2 studies from the 3rd Edition remain the primary evidence for this topic.⁹⁻¹¹ The literature search also identified a recent update of a Cochrane Systematic review,² which also reported finding no new studies.

Class 2 Studies

The evidence from the Class 2 studies of anesthetics, analgesics, and sedatives is summarized in Table 6-2.

Table 6-2. Summary of Evidence: Class 2 Studies (Anesthetics, Analgesics, and Sedatives)

| Reference Study Topic* | Study Design, N, and Outcomes | Data Class | Results Conclusion |
|---|--|------------|---|
| Studies from 3rd Edition | | | |
| Prophylactic use of Barbiturates | | | |
| Ward et al., 1985 ⁹ To compare pentobarbital and standard treatment. | RCT N=53 Pentobarbital=27 Standard=26 Mortality Hypotension | Class 2 | No significant difference in mortality or GOS at 1 year between groups. Hypotension (SBP<80 mm Hg) occurred in 54% of pentobarbital-treated patients vs. 7% of controls, p<0.001. |
| Barbiturates for Refractory ICP | | | |
| Eisenberg et al., 1988 ¹⁰ To evaluate the influence of pentobarbital on patients with elevated ICP refractory to other treatment. | RCT N=73 Pentobarbital=37 Control=36 (crossover design allowed 32 of the 36 controls to receive pentobarbital Mortality | Class 2 | ICP is more likely to be controlled in treatment arm. Patients who responded to treatment with lower ICP had higher likelihood of survival (92% vs. 17% for non-responders.) In patients with hypotension prior to randomization, barbiturates provided no benefit. |
| Sedatives and Analgesics | | | |
| Kelly et al., 1999 ¹¹ To compare propofol and morphine sulfate | RCT N=42 Propofol=23 Morphine sulfate=19 Mortality ICP TIL GOS | Class 2 | Favorable outcome at 6 months Propofol 52.5% Morphine Sulfate 47.4% ICP and TIL were lower on day 3, p<0.05, in patients receiving propofol. There was no effect on mortality. In a post-hoc analysis of high vs. low-dose propofol patients, GOS favorable outcome was 70% vs. 38.5%, respectively, p<0.05. |

Abbreviations: GOS=Glasgow Outcome Scale, ICP=intracranial pressure, N=total sample size, RCT=randomized controlled trial, TIL=therapy intensity level.

***No new Class 2 studies were added to this edition.**

Barbiturates

In 1985, Ward et al. reported results of a randomized controlled trial (RCT) of pentobarbital in 53 consecutive TBI patients who had an acute intradural hematoma or whose best motor response was abnormal flexion or extension.⁹ There was no significant difference in 1-year GOS between treated patients and controls, while six in each group died from uncontrollable ICP. The undesirable side effect of hypotension (SBP<80 mm Hg) occurred in 54% of the barbiturate-treated patients compared with 7% in the control group (p<0.001).

Eisenberg et al., 1988 conducted a five-center RCT of high-dose barbiturate therapy for intractable ICP elevation in patients with a Glasgow Coma Scale (GCS) of 4-8.¹⁰ ICP control

was the primary outcome measure, although mortality was also assessed. The patients were randomly allocated to barbiturate treatment or control when standard conventional therapy failed. Patients in the control group were electively crossed over to barbiturate therapy at specific “ICP treatment failure” levels. There were 36 controls and 32 study patients, although 32 of the controls ultimately crossed over and received barbiturates. The odds of ICP control were two times greater with barbiturate treatment. The likelihood of survival for barbiturate responders was 92% at 1 month compared with 17% for non-responders. Of all deaths, 80% were due to refractory ICP. At 6 months, 36% of responders and 90% of non-responders were vegetative or had died. Due to the study design, the effects of barbiturate treatment on any outcome other than mortality cannot be conclusively determined. Additionally, when comparing the non-crossover control patients (n=10) with the patients initially randomized to barbiturates, the effect on mortality was lost (100% vs. 97.7% survival).

In 1999, The Cochrane Injuries Group undertook a systematic review of RCTs of barbiturates as part of the treatment for acute traumatic brain injury, and has been updating this review periodically.² Their update in 2012 (the latest report) did not identify any new studies. The group concluded that “There is no evidence that barbiturate therapy in patients with acute severe head injury improves outcome. Barbiturate therapy results in a fall in blood pressure in one of four patients. The hypotensive effect will offset any ICP lowering effect on cerebral perfusion pressure.” All studies included in this review were conducted prior to the initial search date for this edition except Perez-Barcena, 2008, which is included here.

Sedatives and Analgesics

Kelly et al., 1999 examined the use of propofol for treating severe TBI.¹¹ This double-blinded RCT compared multiple endpoints for patients who received either propofol or morphine sulfate. Propofol has become a widely used neuro-sedative, as its hypnotic anesthetic agent has a rapid onset and short duration of action. In addition, propofol has been shown to depress cerebral metabolism and oxygen consumption and thus has a putative neuroprotective effect. The primary end-point of the trial was drug safety, but they also evaluated clinically relevant end-points, including ICP control, cerebral perfusion pressure (CPP), therapeutic intensity level (TIL) for ICP/CPP control, 6-month neurologic outcome, and treatment-related adverse events. Daily

mean ICP and CPP were similar between the two groups; however, on day 3, ICP was lower in the propofol group ($p < 0.05$) and the TIL overall was higher in the morphine group.

There were no significant differences between groups in mortality or GOS. A favorable neurologic outcome based on the GOS occurred in 52.5% of patients treated with propofol compared with 47.4% of those receiving morphine, with mortality rates of 17.4% and 21.1% respectively. In a post hoc analysis authors compared outcomes for patients receiving “high dose” (total dose of >100 mg/kg for >48 hours) versus “low dose” propofol. While there were no significant differences in ICP/ CPP between these groups, there was a significant difference in neurologic outcome: high-dose favorable outcome 70% versus low-dose 38.5% ($p < 0.05$).

Significant concerns have subsequently arisen regarding the safety of high-dose propofol infusions. Propofol infusion syndrome was first identified in children but can occur in adults as well. Common clinical features include hyperkalemia, hepatomegaly, lipemia, metabolic acidosis, myocardial failure, rhabdomyolysis, and renal failure, resulting in death. Thus, extreme caution must be taken when using doses greater than 5 mg/kg/hour, or when usage of any dose exceeds 48 hours in critically ill adults.⁸

Class 3 Studies

The evidence from the Class 3 studies of anesthetics, analgesics, and sedatives is summarized in Table 6-3.

Table 6-3. Summary of Evidence: Class 3 Studies (Anesthetics, Analgesics, and Sedatives)

| Reference Study Topic | Study Design, N and Outcomes | Data Class | Results Conclusion |
|--|--|-------------------|--|
| New Studies | | | |
| Barbiturates | | | |
| Majdan 2013 ^{*12} Barbiturate use and its effects in patients with severe TBI | Observational studies in 13 centers in 5 European countries N=1172 High barbiturates=71 (6%) Low barbiturates=140 (13%) No barbiturate= 961 (81%) ICP | Class 3 | Few patients were given barbiturates. High barbiturates decreased ICP in 22 of 32 patients, but caused hemodynamic instability. After adjustment for baseline differences there were no significant differences in outcomes. |

| Reference Study Topic | Study Design, N and Outcomes | Data Class | Results Conclusion |
|---|--|------------|---|
| Perez-Barcelona 2008* ¹³ To assess the effectiveness of pentobarbital and thiopental in controlling refractory ICP | Prospective, randomized, cohort study. N=44 Pentobarbital=22 Thiopental=22 ICP Hypotension Respiratory infection Urinary infection Positive blood culture ICP catheter colonization CNS infection (CSF) SOFA pre and SOFA max | Class 3 | Uncontrollable intracranial pressure occurred in 11 patients (50%) in the thiopental treatment group and in 18 patients (82%) in the pentobarbital group, p=0.03. Thiopental was more effective than pentobarbital in terms of controlling intracranial pressure (OR 5.1, 95% CI 1.2 to 21.9), p=0.027, but CT characteristics and dosages were not similar across groups. The incidence of adverse effects was similar in both groups. |
| Sedatives and Analgesics | | | |
| Chiu 2006* ¹⁴ Propofol for head-injured patients | Retrospective Cohort N=104 Propofol=44 Non propofol=60 Survival rate Mean ICP Mean CPP Mean GCS Mean PaCO ₂ | Class 3 | Propofol vs. Non propofol Survival 81.2% vs. 46.47%, p<0.001. Mean ICP 3 days 17.23 vs. 33.19, p=0.017. Mean CPP 5 days 71.10 vs. 43.20, p<0.001. Mean PaCO ₂ 5 days 23.15 vs. 24.71, p=0.350. No significant adverse drug reactions. |
| Ghori 2007* ¹⁵ Propofol vs. midazolam | Prospective, double-blind, randomized trial. N=28 Treatment=15 Control=13 Serum S100B concentrations, concentration of nitric oxide then associated with neurological outcome at 3 months (indirect evidence). | Class 3 | Good neurological outcome 8/15 (53%) in the midazolam group and 7/13 (54%) in the propofol group. Patients with a poor outcome had higher serum S100β concentrations on ICU admission and on Days 1–4 in the ICU than those with a good outcome No significant difference on Day 5. Plasma nitric oxide concentrations were not associated with outcome. |
| Study from 3rd Edition | | | |
| Prophylactic use of Barbiturates | | | |
| Schwartz 1984* ¹⁶ Prophylactic pentobarbital vs. mannitol therapy for ICP elevations >25 mm Hg. | RCT of N=59 Prophylactic pentobarbital=28 Mannitol=31 Patients stratified based on presence/absence of intracranial hematoma. | Class 3 | Pentobarbital provided no benefits in mortality or ICP control for patients with intracranial mass lesions. In patients with diffuse injury, there was no benefit to ICP control, and significantly higher mortality in the pentobarbital group, p=0.03. |

Abbreviations: CT=computed tomography, GCS= Glasgow Coma Scale, ICP=intracranial pressure, ICU=intensive care unit.

*References new to the 4th Edition.

Barbiturates

The Class 3 studies of barbiturates provided no results that can be used to inform new or revised recommendations that would differ from those informed by the older Class 2 studies. A multi-site, multi-country retrospective study found low overall use of barbiturates, no difference in outcomes after adjustment for baseline differences, and that while ICP decreased, the treatment caused hemodynamic instability.¹² Likewise, the Class 3 study from the prior edition found no benefit and a higher mortality rate in patients treated with pentobarbital.¹⁶ A study that compared pentobarbital to thiopental reported that thiopental was more effective in controlling ICP but differences in the patient characteristics and the doses reduced confidence in the findings.¹³

Sedatives

The two Class 3 studies of sedatives new to this edition were not incorporated into the recommendations as higher-quality studies were available. Ghori, 2007 compared propofol and midazolam and found that the outcomes were similar.¹⁵ Chiu, 2006 reported a positive effect of treatment with sedatives but from a retrospective study that did not control for CT differences or collect complete data on adverse events.¹⁴

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7. Steroids

INTRODUCTION

Steroids were introduced in the early 1960s as a treatment for brain edema. Experimental evidence accumulated that steroids were useful in the restoration of altered vascular permeability in brain edema,¹ reduction of cerebrospinal fluid production,² attenuation of free radical production, and other beneficial effects in experimental models.^{1,3-7} Glucocorticoids were found to be beneficial to patients with brain tumors when administered in the perioperative period.^{8,9}

Based on this experience with patients with brain tumors, glucocorticoids became commonly administered to patients undergoing a variety of neurosurgical procedures and became commonplace in the treatment of severe traumatic brain injury (TBI). However, studies of severe TBI patients failed to find a benefit. After examining the existing evidence and conducting a systematic review, Alderson et al., 1997 reported that the data available at the time indicated no evidence for a beneficial effect of steroids to improve outcome in TBI patients.¹⁰ Analysis of the trials with the best blinding of groups revealed the summary odds ratio for death was 1.04 (0.83 to 1.30), and for death and disability was 0.97 (0.77 to 1.23). The authors stated that a lack of benefit from steroids remained uncertain, and recommended that a larger trial of greater than 20,000 patients be conducted to detect a possible beneficial effect of steroids. The Corticosteroid Randomization After Significant Head Injury Trial (CRASH) trial was designed to provide high-quality evidence on the impact of steroids on TBI patients.^{11,12}

RECOMMENDATIONS

Level I

- The use of steroids is not recommended for improving outcome or reducing ICP. In patients with severe TBI, high-dose methylprednisolone was associated with increased mortality and is contraindicated.

Changes from Prior Edition

The body of evidence was updated to include the 6-month outcomes of the CRASH trial.¹⁴ There were no changes to the recommendations for this topic.

EVALUATION OF THE EVIDENCE

Quality of the Body of Evidence

All the Class 1 and 2 studies included as evidence for the use of steroids to treat severe TBI were randomized controlled trials (RCTs) that compared steroids to a placebo (Table 7-1). The quality of the body of evidence was high because two smaller RCTs^{13,14} that found no effect were followed by a large, multi-site trial designed to address the potential lack of power in these smaller studies.^{11,12} This larger trial found a short-term negative effect (higher 2-week mortality) as well as worse outcomes at 6 months. No study demonstrated a benefit.

The Class 3 studies are reported in the Evidence Tables and Summary section below.¹⁵⁻¹⁹ They are not included in the assessment of the body of evidence and were not used to inform the recommendations given that higher-quality evidence was available that addressed the same question.

Table 7-1. Quality of the Body of Evidence (Steroids)

| COMPONENTS OF OVERALL QUALITY – Class 1 and 2 | | | | | | | | |
|---|-------------------|--|------------------------------------|------------------------|-----------------------------------|---------------------------------|---------------------------------|--|
| Topic | Number of Studies | Meta-Analysis | Number of Subjects | Class of Studies | Consistency (High, Moderate, Low) | Directness (Direct or indirect) | Precision (High, Moderate, Low) | Quality of Evidence (High, Moderate, Low, or Insufficient) |
| Steroid efficacy vs. placebo ¹¹⁻¹⁴ | 3 RCTs | NA Results would not differ given size of CRASH trial | 5,023 (Severe TBI in larger study) | 1 Class 1 2 Class 2 | High | Direct | High | High |

Abbreviations: CRASH=Corticosteroid Randomization After Significant Head Injury Trial, NA=not applicable, RCT=randomized controlled trial, TBI=traumatic brain injury.

Applicability

The included studies were large, and the CRASH study was conducted in multiple hospitals and countries.^{11,12}

SUMMARY OF THE EVIDENCE

Process

Of four new, potentially relevant studies reviewed, three were excluded because they did not meet the inclusion criteria for this topic (see Appendix F). The included Class 1 study reported 6-month outcomes from the CRASH trial.¹² Earlier results from CRASH, which were outcomes at 2 weeks, were included in the prior edition of these guidelines.¹¹ Additionally, two Class 2 studies^{13,14} and five Class 3 studies from the 3rd edition are included in the evidence tables below.¹⁵⁻¹⁹

Class 1 and 2 Studies

The evidence from the Class 1 and 2 studies of steroids is summarized in Table 7-2.

Table 7-2. Summary of Evidence: Class 1 and 2 Studies (Steroids)

| Reference Study Topic | Study Design, N, and outcomes | Data Class | Results Conclusion |
|--|--|---------------|--|
| Roberts 2004 ¹¹ Comparison of methylprednisolone vs. placebo | RCT CRASH Trial N=3,966/10,008 (severe TBI/total enrolled) Methylprednisolone=1985/5007 Placebo=1981/5001 | Class 1 | The study was halted after approximately 62 months, prior to reaching full enrollment, when the Data Monitoring Committee's interim analysis showed clear deleterious effect of treatment on survival. The deleterious effect of steroids was not different across groups stratified by injury severity. <u>Mortality at 2 weeks</u> Severe TBI Treatment: 39.8% vs. placebo 34.8% RR 1.14, 95% CI 1.05 to 1.23, p=0.0013. (calculated for this report based on counts provided by study authors) All Patients Treatment 21.1% vs. placebo 17.9% RR 1.18; 95% CI 1.09 to 1.27, p=0.0001. |

| Reference Study Topic | Study Design, N, and outcomes | Data Class | Results Conclusion |
|---|---|------------|--|
| Edwards 2005* ¹² Comparison of methylprednisolone vs. placebo | RCT CRASH Trial (Severe TBI /Total enrolled) N=9,673/3851 (96.7% of original enrollment) Methylprednisolone=912/4854 Placebo=808/4819 6-month results of MRC CRASH originally presented in 2004 | Class 1 | 6-month follow-up data (n=9673, 96, 7%). <u>Severe Only</u> (GCS 3-8) Mortality at 6 months: corticosteroid 47.1% vs. placebo 42.2% RR 1.12 (95% CI 1.04 to 1.20), p=0.0024. (calculated for this report based on counts provided by study authors) Unfavorable outcome (death and severe disability) corticosteroid 62.8% vs. placebo 62.1%. <u>All Severity Levels</u> Mortality at 6 months: Corticosteroid 25.7% vs. placebo 22.3% RR 1.15 (95% CI 1.07 to 1.24), p=0.0001. Unfavorable (death and severe disability) corticosteroid 38.1% vs. the favorable (moderate disability and good recovery) 36.3%, placebo, RR 1.05 (95% CI 0.99 to 1.10), p=0.079. |
| Marshall 1998 ¹³ Comparison of tirilazad vs. placebo | RCT N=957 (severely head injured) Tirilazad=482 Placebo=475 GOS and mortality at 6 months | Class 2 | Tirilazad vs. placebo Good recovery 39% vs. 42%, p=0.461. Death 26% vs. 25%, p=0.750. No overall benefit on outcome was detected, except in post hoc sub group analysis: men with traumatic subarachnoid hemorrhage had lower mortality. |
| Saul 1981 ¹⁴ Comparison of methylprednisolone vs. placebo | RCT N=100 Methylprednisolone=50 Placebo=50 GOS and mortality at 6 months | Class 2 | No significant difference in outcome at 6 months. In a subgroup analysis, in patients who improved during the first 3 days after TBI, the steroid-treated group had better outcomes than the placebo group. |

Abbreviations: CRASH=Corticosteroid Randomization After Significant Head Injury Trial, GOS=Glasgow Outcome Scale, GCS=Glasgow Coma Scale, MRC=Medical Research Council, N=total sample size, RCT=randomized controlled trial, RR=relative risk.

* Reference new to the 4th Edition.

The hypothesis that steroids would be beneficial in treating TBI was tested in two Class 2 RCTs conducted in 1981 and 1998. One comparatively small RCT included 100 patients.¹⁴ One group received methylprednisolone 5 mg/kg/day and the control group received no drug. There was no statistically significant difference in outcomes (mortality and GOS) between the treated and non-treated groups at 6 months. A subgroup analysis indicated that patients in the treatment group who improved during the first 3 days after TBI had better outcomes than patients who improved in the placebo group. In 1998, Marshall et al. conducted a larger RCT of the effect of the synthetic 21-amino steroid, tirilazad mesylate, on outcomes for patients with severe TBI.¹³ The trial enrolled 957 patients and found no overall benefit.

In 2004, investigators with the CRASH trial reported the results of an international RCT of methylprednisolone in patients with TBI that included 10,008 patients from 239 hospitals in 49 countries.¹¹ Participants were randomized to receive either 2 g intravenous methylprednisolone followed by 0.4 mg/hour for 48 hours, or placebo. Inclusion criteria were age 16 years or greater, Glasgow Coma Scale (GCS) 14 or less, and hospital admission within 8 hours of injury. Exclusion criteria included any patient with clear indications or contraindications for corticosteroids as interpreted by the referring or admitting physicians.

The data monitoring committee halted the study after approximately 5 years and 2 months of enrollment when interim analysis showed a deleterious effect of methylprednisolone. Two-week mortality in the steroid group was 21% versus 18% in controls, with a 1.18 relative risk of death in the steroid group (95% CI 1.09 to 1.27, $p=0.0001$). This increase persisted even when the results were adjusted for the presence of extracranial injuries. The authors stated that the cause of the increase in mortality was unclear, but was not due to infections or gastrointestinal bleeding. Edwards et al., 2005 reported the 6-month follow-up data ($n=9,673$, 96.7% of the original cohort) for the same trial.¹² These data also demonstrated a significant increase in mortality in the corticosteroid group (25.7%) compared with the placebo group (22.3%) (95% CI 1.07 to 1.24; $p=0.0001$). In addition, there were more corticosteroid-treated subjects in the unfavorable outcomes group (death and severe disability, 38.1%) compared with the favorable group (moderate disability and good recovery 36.3%; [RR 1.05; 95% CI 0.99 to 1.10; $p=0.079$]), supporting the initial conclusion that corticosteroids were harmful in the setting of severe TBI.

Both the 2-week and 6-month mortality results were reported for the subgroup of patients with severe TBI (GCS 3 to 8) and the results were similar (see Table 7-2).

Class 3 Studies

The evidence from the Class 3 studies of steroids is summarized in Table 7-3.

Table 7-3. Summary of Evidence: Class 3 Studies (Steroids)

| Reference Study Topic | Study Description | Data Class | Conclusion |
|---|---|------------|--|
| Studies from 3rd Edition | | | |
| Cooper 1979 ¹⁵ Comparison of dexamethasone vs. placebo | Prospective, double-blind study of 97 patients with severe TBI, stratified for severity, and treated with placebo 60 mg/day or 96 mg/day of dexamethasone; 76 patients available for follow-up at 6 months. | Class 3 | No significant difference was seen in 6-month outcome, serial neurological exams or ICP. |
| Faupel 1976 ¹⁶ Comparison of dexamethasone vs. placebo | Prospective, double-blind trial of dexamethasone vs. placebo in 95 patients with severe TBI. | Class 3 | Significant improvement in mortality in steroid-treated group; however, overall outcome was not improved. Of the active treatment groups, 25.4% were vegetative and 11.9% were severely disabled vs. 3.6% and 7.1% in the control group, respectively. |
| Gaab 1994 ¹⁷ Comparison of ultra-high dose dexamethasone vs. placebo | Randomized, double-blind, multicenter trial of ultra-high dose dexamethasone in 300 patients with moderate and severe TBI, randomized to placebo or dexamethasone: 500 mg within 3 hours of injury, followed by 200 mg after 3 hours, then 200 mg every 6 hours for 8 doses for a total dexamethasone dose of 2.3 g, given within 51 hours. | Class 3 | No significant difference in 12-month outcome or in time to improvement to GCS score \leq 8 in treatment group compared with placebo. |
| Giannotta 1984 ¹⁸ Comparison of high-dose methylprednisolone vs. low-dose vs. placebo | Prospective, double-blind study of 88 patients with severe TBI. Patients randomized to placebo, low-dose methylprednisolone (30 mg/kg/day) or high-dose methylprednisolone (100 mg/kg/day). | Class 3 | No significant difference in 6-month outcome in treatment groups compared with placebo. Subgroup analysis showed improved survival and speech function in patients under age 40 when high-dose group was compared with low-dose and placebo groups combined. |
| Watson 2004 ¹⁹ Glucocorticoids | Prospective cohort of 404 patients. Baseline differences between groups (more dural penetration by surgery and more nonreactive pupils in treatment group). | Class 3 | Patients who received glucocorticoids within 24 hrs had a 74% increase in risk of first late seizures, $p=0.04$. No difference in 2nd seizures or mortality. |

Abbreviations: ICP=intracranial pressure, GCS=Glasgow Coma Scale, TBI=traumatic brain injury.

Five studies conducted between 1976 and 2004 were rated Class 3. The earliest by Faupel et al. in 1976 reported that steroids had a favorable impact on mortality but not on overall outcome, as patients were surviving severely disabled.¹⁶ Similarly, none of the four other studies showed that patients experienced a substantial benefit from steroid treatment.^{15,17-19}

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8. Nutrition

INTRODUCTION

The complex interaction of the body with nutritional support is magnified during illness, particularly after severe traumatic brain injury (TBI). Seminal work from the 1980s demonstrated that severe TBI was associated with increased energy expenditure early after injury.¹ The presumption has been that the TBI itself causes an intrinsic increase in metabolism and requirement for caloric support—likely from a centrally mediated mechanism that is still unknown. More recent evidence suggests that contemporary neurocritical care may blunt this response,^{2,3} but these studies underscore the complex interactions that are in play simply in determining how many calories should be administered to patients with severe TBI. Similarly, it has long been known that an increase in serum glucose is observed after severe stress, including severe TBI.⁴ Studies from other critical illnesses have demonstrated that controlling this response with the use of insulin can lead to significant improvements in outcomes of critically ill patients.⁵ However, a similar approach in a population of adults with severe TBI demonstrated a worrisome pattern of metabolic responses within the brain interstitial fluid, implying that the practice of “tight glucose control” could have deleterious effects in patients with severe TBI.⁶

There are a number of questions that must be addressed for comprehensive guidance on nutritional support. How many calories are required for optimal recovery? What is the optimal method of administering these calories (enterally/parenterally/both)? When should this support start? What should the composition of such support include with regard to carbohydrates, proteins, and lipids? Are there nutritional supplements that might play a role in improved recovery? What is the role of insulin in controlling serum glucose concentrations in this vulnerable patient population? Can specialized diets play a role in the care of the patient with severe TBI? The literature summarized below does not address all of these questions, underscoring the need for more research on nutrition and severe TBI.

RECOMMENDATIONS

Level I

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

Level II A

- Feeding patients to attain basal caloric replacement at least by the fifth day and, at most, by the seventh day post-injury is recommended to decrease mortality.

Level II B

- Transgastric jejunal feeding is recommended to reduce the incidence of ventilator-associated pneumonia.

Changes from Prior Edition

Additional evidence was identified and incorporated into revised recommendations that emphasize early nutrition and address the method of feeding. The questions considered for nutrition did not change from the prior edition.

EVALUATION OF THE EVIDENCE

Quality of the Body of Evidence

The studies identified for this topic address four questions: (1) timing of feeding after injury,⁷⁻¹¹ (2) method of feeding,¹² (3) glycemic control,¹³⁻¹⁵ and (4) vitamins and supplements.¹⁶ The quality of the body of evidence for the questions of timing and method of feeding was sufficient to derive recommendations (Table 8-1). For glycemic control, the available evidence was inconsistent and insufficient to support a recommendation. The evidence for vitamins and supplements was insufficient, as only one small Class 2 study was identified in addition to the two Class 3 studies from the 3rd Edition, and these studied different vitamins and supplements.

Table 8-1. Quality of the Body of Evidence (Nutrition)

| Topic | COMPONENTS OF OVERALL QUALITY | | | | | | | Quality of Evidence (High, Moderate, Low, or Insufficient) |
|--|----------------------------------|------------------------|--------------------|------------------|-----------------------------------|---------------------------------|---------------------------------|--|
| | Number of Studies | Meta-Analysis | Number of Subjects | Class of Studies | Consistency (High, Moderate, Low) | Directness (Direct or Indirect) | Precision (High, Moderate, Low) | |
| Timing of feeding ⁷⁻¹¹ | 3 RCTs 2 Retrospective cohort | No: Different Outcomes | 1137 | 2 | Moderate | Direct | Moderate | Moderate |
| Method of feeding ¹² | 1 RCT | NA | 104 | 2 | NA | Direct | Moderate | Low |
| Glycemic control ¹³⁻¹⁵ | 3 RCTs | NA | 425 | 2 | Low | Direct | Low | Insufficient |
| Vitamins and supplements ¹⁶ | 1 RCT | NA | 38 | 2 | NA | Direct | Low | Insufficient |

Abbreviations: NA=not applicable, RCT=randomized controlled trial.

Applicability

The studies of nutrition were predominately single-site studies, but they were conducted in a variety of locations. One multi-center study was conducted in the United States,⁸ while two of the single-site studies were conducted in the United States,^{10,16} and one each in Greece,⁷ the United Kingdom,¹¹ France,⁹ Spain,¹² Italy,¹³ China,¹⁵ and Brazil.¹⁴

SUMMARY OF THE EVIDENCE

Process

Of the 21 new, potentially relevant studies reviewed, 11 were excluded because they did not meet the inclusion criteria for this topic (Appendix F). Of the remaining 10, seven were rated Class 2^{7-9,12-15} and are included with the three Class 2 studies from the 3rd Edition.^{10,11,16} Three were rated Class 3.¹⁷⁻¹⁹ These and 10 studies from the 3rd Edition^{4,20-28} were included as Class 3 evidence for this topic.

Class 2 Studies

The evidence from the Class 2 studies of nutrition is summarized in Table 8-2.

Table 8-2. Summary of Evidence: Class 2 Studies (Nutrition)

| Reference Study Topic | Study Design, N, and Outcomes | Data Class | Results Conclusion |
|--|---|------------|---|
| Timing of Feeding | | | |
| Chourdakis, 2012^{*7} Comparison of early enteral feeding (within 24-48 hours) vs. delayed enteral feeding (>48 hours but no later than 5 days after admission to ICU) | RCT N=59 EEF=34 DEF=25 Complications Hormonal profile | Class 2 | DEF vs. EEF N(%) vs. N(%), p-value VAP 12 (48.0) vs. 13 (38.2), p=0.637. Non VAP 8 (32.0) vs. 7(20.5), p=0.495. CNS infections 2 (8) vs. 2 (5.8), p=0.830. Hyperglycemia 4 (16.0) vs. 5 (14.7), p=0.805. Bacteremia, UTIs, diarrhea, constipation, feeding intolerance. All results not significant. There was no difference in infections, hyperglycemia, or other complications. Significant differences were found in intermediate outcomes with the EEF group receiving significantly more kcal/day at every time period and hormonal changes were significantly different suggesting early feeding may reduce inflammatory responses or reduce injury related changes. |
| Hartl, 2008^{*8} To determine the effect of nutrition given within 5 or 7 days on 2-week mortality | Retrospective Cohort N=797 Day Nutrition Reached Goal Day 1 to 3=43 Day 4 to 5=147 Day 6 to 7=113 Never reached within first 7 days=494 Mortality at 2 weeks | Class 2 | 2-week mortality Not fed within 7 days OR 4.10 (95% CI 1.80 to 9.32), p=0.0008. Never max nutrition in first 7 days OR 1.41 (95% CI 1.12 to 1.78), p=0.004. Never fed within 5 days OR 2.06 (95% CI 1.04 to 4.06), p=0.04. Never max nutrition in first 5 days OR 1.30 (95% CI 1.03 to 1.64), p=0.03. Nutritional support within 5 days was associated with a significant reduction in 2-week mortality. |
| Lepelletier, 2010^{*9} To determine the effect of early enteral feeding (initiated 24 hours after trauma) on early-onset Ventilator-acquired pneumonia | Retrospective Cohort N=161 EVAP=34 No VAP=96 Late VAP=31 Early onset VAP | Class 2 | Early enteral feeding has a protective effect on EVAP in logistic regression controlling for other factors OR 0.33 (95% CI 0.21 to 0.85), p=0.022. Univariate Analysis of Factors Associated with EVAP Early feeding in patients with EVAP 22 out of 34 (64.7%) No EVAP 107 out of 127 (84.3%), p=0.006. Findings suggest early feeding was protective, resulting in lower rates of EVAP. |
| Rapp, 1983¹⁰ To compare total parenteral nutrition with standard enteral nutrition | RCT N=38 TPN=20 SEN=18 Mortality | Class 2 | There were 8 deaths in the enteral nutrition group and none in the parenteral nutrition group in the first 18 days, p<0.001. Early feeding reduced mortality from TBI. |

| Reference Study Topic | Study Design, N, and Outcomes | Data Class | Results Conclusion |
|---|---|------------|--|
| Taylor, 1999 ¹¹ To compare early enhanced enteral feeding (full nutritional requirements from day 1) with standard feeding (gastric based on tolerance) | RCT N=82 Standard EN=41 Enhanced EN=41 GOS (3 months, 6 months) Infections | Class 2 | There was a trend toward better GOS at 3 months in the accelerated feeding cohort, but no difference at 6 months. Accelerated feeding met goals faster in the first week and there were fewer infections. |
| Method of Feeding | | | |
| Acosta-Escribano, 2010 * ¹² Comparison of transpyloric feeding route vs. gastric feeding route | RCT N=104 TPF=50 GF=54 Early pneumonia Late (ventilator-associated) pneumonia | Class 2 | TPF=lower incidence of all pneumonia OR 0.3 (95% CI 0.1 to 0.7), p=0.01. Early=no significant difference Late OR 0.2 (95% CI 0.1 to 0.9), p=0.02. Other nosocomial infections, no significant difference TPF enabled greater volume than GF (92% vs. 84%), p<0.01 due to lower rates of gastric residuals, OR 0.2 (95% CI 0.04 to 0.6), p=0.003. TPF results in less pneumonia than GF feeding; primarily due to differences in late pneumonia. |
| Glycemic Control | | | |
| Bilotta, 2008 * ¹³ Comparison of intensive (I) (4.44–6.66 mmol/l) vs. conventional (C) insulin therapy (12.22 mmol/l) | RCT N=97 I=48 C=49 Hypoglycemic episodes Duration of ICU stay Infection rate GOS | Class 2 | Conventional vs. Intensive Episodes of hypoglycemia for patients (<80 mg/dl or 4.44 mmol/l) median (min-max) 7 (0-11) vs. 15 (6-33), p<0.0001. At least one episode; N (%) 48 (98.0) vs. 48 (100.0), p=1.0. ICU stay (days, median) 10 vs. 7.7, p=0.05 Mortality at 6 months. (12.2) vs. 5 (10.4) GOS 5: 10 (20.4) vs. 11(22.9) GOS 4: 11 (22.5) vs. 12 (25.0) GOS 3: 12 (24.5) vs. 11(22.9) GOS 2: 10 (20.4) vs. 9 (18.8) No significant difference in mortality The number of glycemic measurements below the hypoglycemia threshold was significantly higher in the intensive insulin group. There was no relationship between hypoglycemia and worsened outcome. ICU days were higher in the conventional group. |

| Reference Study Topic | Study Design, N, and Outcomes | Data Class | Results Conclusion |
|--|--|------------|--|
| Coester, 2010* ¹⁴ Comparison of intensive (maintenance of blood glucose between 80 mg/dl and 110 mg/dl with continuous insulin infusion) vs. conventional (maintenance of blood glucose below 180 mg/dl with subcutaneous insulin and insulin infusion only if blood glucose levels exceeded 220 mg/dl) insulin therapy | RCT N=88 Intensive=42 Conventional=46 Mortality ICU days GOS | Class 2 | Intense vs. Conventional N (%) vs. N (%), p-value Favorable neuro outcome Intense vs. Conventional 16 (41) vs. 13 (32.5), p=0.27. Mortality at 6 months 11 (28.2) vs. 11 (27.5), p=1.0. ICU Days 18.2 vs. 12.9, p=0.59. No benefit of intensive insulin therapy in terms of neurologic outcome, mortality, infection rate, or duration of ICU stay. Intensive maintenance significantly increased the risk of hypoglycemic episodes. |
| Yang, 2009* ¹⁵ Comparison of intensive (received continuous insulin infusion to maintain glucose levels between 4.4 mmol/l (80 mg/dl) and 6.1 mmol/l (110 mg/dl) and conventional (not given insulin unless glucose levels were greater than 11.1 mmol/l (200 mg/dl) insulin therapy | RCT N=240 Mortality GOS Infection Days in NICU | Class 2 | Intense vs. Normal Overall mortality at 6 months 52.1% vs. 53.4%, p=0.8. In-hospital mortality 28.9% vs. 28.6%, p=0.85. Infection rate 31.4% vs. 46.2%, p<0.05. Days stay in NICU 4.2 vs. 5.6 days (medians), p<0.05. GOS at 6 months GOS 5 or 4: 29.1% vs. 2.4%, p<0.05 No significant difference in mortality but reduced infection, days in neurological ICU and better function with intense therapy. |
| Vitamins and Supplements | | | |
| Young, 1996 ¹⁶ To compare supplemental zinc vs. no zinc | RCT N=38 Treatment=12 Control=26 Mortality Albumin Pre-albumin RBP GCS | Class 2 | Nonsignificant trend toward higher mortality in control (n=26) vs. treatment (n=12), p=0.09. Albumin, prealbumin, RBP were significantly higher in treatment group, GCS did not differ significantly. |

Abbreviations: CNS=central nervous system, DEF=delayed enteral feeding, EEF=early enteral feeding, EN=enhanced enteral, EVAP=early-onset ventilator-acquired pneumonia, GF=gastric feeding, GCS=Glasgow Coma Scale, GOS=Glasgow Outcome Scale, ICU=intensive care unit, IIT=insulin infusion therapy, N=total sample size, NICU=neonatal intensive care unit, OR=odds ratio, RBP=retinol binding protein, RCT=randomized controlled trial, SEN=standard enteral nutrition, TPF=transpyloric feeding, TBI=traumatic brain injury, TPN=total parenteral nutrition, UTI=urinary tract infection, VAP=ventilator-acquired pneumonia.

* **Reference new to the 4th Edition.**

Timing of Feeding After Injury

Five studies were included that examined the influence of the timing of feeding on outcomes. Two Class 2 studies examined the influence of timing on mortality. Härtl et al., 2008 conducted a retrospective analysis of 797 patients from 22 trauma centers in the United States and found that early nutrition, defined as within the first 5 to 7 days post-injury, reduced 2-week mortality in patients with severe TBI, and that the amount of nutrition was inversely correlated with mortality.⁸ In a smaller randomized controlled trial (RCT) (n=38) Rapp et al., 1983 found that early feeding reduced mortality within 18 days after injury.¹⁰

Chourdakis et al., 2012 focused on the influence of early compared with delayed feeding by randomly assigning patients to one group that was fed within 24 to 48 hours (defined as early) versus 48 hours to 5 days (defined as delayed).⁷ Their analysis found no significant difference in rates of infection or complications. They demonstrated that early alimentation may improve endocrinologic factors after TBI such as thyroid stimulating hormone and thyroid hormone. Taylor, 1999 conducted an RCT comparing accelerated feeding (full caloric value on day 1) with standard feeding (nutrition as tolerated) and found a trend toward improvement at 3 months but no difference in outcome at 6 months as measured by the Glasgow Outcome Scale (GOS).¹¹

One Class 2 cohort study (n=161) concluded that early feeding had a protective effect based on lower rates of early-onset ventilator associated pneumonia in patients who received early enteral feeding.⁹

Method of Feeding

There are three options for the method of early feeding: gastric, jejunal (transpyloric), and parenteral. Percutaneous endoscopic gastrostomy is well tolerated in TBI patients, but there is the concern that early intragastric feeding may pose the risk of formation of residual, delayed gastric emptying, and aspiration pneumonia. Evidence from one Class 2 RCT of 104 severe TBI patients found that transpyloric feeding is superior to gastric feeding as it reduced gastric residual and patients had lower rates of ventilator-associated pneumonia.¹²

Glycemic Control

Three recent studies explored the influence of strict glucose control on neurological outcome, mortality, and/or hypoglycemia in patients with severe TBI. All three studies failed to demonstrate an improvement in mortality. Neurologic outcomes were not significantly different

in two studies^{13,14} while one study¹⁵ found some improvement in function at 6 months. Similarly, ICU days were lower for the strict control group in two studies,^{13,15} while one study found no significant difference.¹⁴ Increased incidence of hypoglycemic episodes occurred in the intensive management groups in two of the studies.^{14, 15} Given the lack of consistency in these findings, it is not clear whether aggressive therapy is better than conventional glucose control. For this reason, the evidence was rated as insufficient and no recommendation about glucose control can be made at this time.

Vitamins and Supplements

One pilot RCT¹⁶ published in 1996 (38 patients) found no significant effects of supplemental zinc, although it is likely the study did not have sufficient power to detect changes in mortality or function. Therefore, there is insufficient evidence about the influence of vitamins and supplements to inform recommendations.

Class 3 Studies

The evidence from the Class 3 studies of nutrition is summarized in Table 8-3.

Table 8-3. Summary of Evidence: Class 3 Studies (Nutrition)

| Reference Study Topic | Study Design, N, and Outcomes | Data Class | Results Conclusion |
|---|--|------------|--|
| New Studies | | | |
| Timing of Feeding | | | |
| Dhandapani 2012*¹⁷ Comparison of timing of feeding | Prospective Observational N=67 Mortality GOS Clinical Features of Malnutrition | Class 3 | Mortality Timing of feeding: # (%) ≤3 days: 2/12 (17%) 4-7 days: 8/52 (15%) >7 days: 15/31 (48%). 80% of those fed before 3 days had favorable outcome at 3 months vs. 43% among those fed later. OR 5.29 (95% CI 1.03 to 27.03) p=0.04. The difference at 6 months was not significant. Clinical features of malnutrition: ≤3 days: 4/7 (57%) 4-7 days: 23/34 (68%) >7 days: 24/26 (92%) |

| Reference Study Topic | Study Design, N, and Outcomes | Data Class | Results Conclusion |
|---|--|------------|---|
| Vitamins and Supplements | | | |
| Razmkon 2011* ¹⁸ Comparison of vitamin C, vitamin E, or placebo | RCT N=100 Group A Low Dose Vitamin C=26 Group B High Dose Vitamin C=23 Group C Vitamin E=24 Group D Placebo=27 Mortality | Class 3 | Mortality at 6 months Group A - 9 (34.6%) Group B - 7 (30.4%) Group C - 6 (25.0%) Placebo - 8 (29.7%) The vitamin E group showed a significantly lower rate of mortality than the control and other treatment groups (p=0.04, Table 2). The GOS scores at discharge and follow-up were also significantly better for the vitamin E group patients, p=0.04. |
| Stippler 2007* ¹⁹ Effect of magnesium level and correction of low levels | Retrospective Cohort Analysis Magnesium Replacement N=216 GOS at 6 months | Class 3 | Low initial serum magnesium: 56.67% An initial serum magnesium of <1.3 mEq/L was 2.37 times more likely to have a poor outcome (CI 1.18 to 4.78, p=0.016). Depressed serum magnesium remained a predictor of poor outcomes, even in patients whose serum magnesium levels were corrected within 24 h (OR 11.03, CI 1.87 to 68.14), p<0.008. Patients with an initial high CSF magnesium were 7.63 more likely to have a poor outcome, p=0.05. Elevated CSF magnesium correlated with depressed serum magnesium only in patients with poor outcome, p=0.013. Patients with low serum magnesium and high cerebrospinal fluid magnesium are most likely to have poor outcome after severe TBI. Rapid correction of serum magnesium levels does not reverse the prognostic value of these markers. |
| Studies from 3rd Edition | | | |
| Timing of Feeding | | | |
| Rhoney, 2002 ²⁰ Bolus vs. continuous gastric feeding | Retrospective Cohort of 152 severe TBI subjects comparing bolus vs. continuous gastric feeding. | Class 3 | Feeding intolerance was greater in bolus group. Continuous group reached 75% goals earlier, trend towards less infection in continuous feeding. No difference in outcome (hospital/ICU stay, GOS, death) |
| Method of Feeding | | | |
| Borzotta' 1994 ²¹ Parenteral vs. jejunal nutrition | Energy expenditure (MREE) and nitrogen excretion (UNN) measured in patients with severe TBI randomized to early parenteral (TPN, n=21) or jejunal (ENT, n=17) feeding with identical formulations. | Class 3 | Either TPN or ENT support is equally effective when prescribed according to individual measurements of MREE and nitrogen excretion. MREE rose to 2400 ±531 kcal/day in both groups & remained at 135% to 146% of predicted energy expenditure over 4 weeks. Nitrogen excretion peaked the second week at 33.4 (TPN) and 31.2 (ENT) g N/day. Equal effectiveness in meeting nutritional goals. Infection rates and hospital costs similar. |

| Reference Study Topic | Study Design, N, and Outcomes | Data Class | Results Conclusion |
|---|--|-------------------|--|
| Graham, 1989 ²² Nasojejunal vs. gastric nutrition | Thirty-two TBI patients were randomized to nasojejunal or gastric feeding. Nitrogen balance in the nasojejunal group was -4.3 g/day vs. -11.8 g/day in the gastric feeding group. | Class 3 | Nasojejunal feeding permitted increased caloric intake and improved nitrogen balance. |
| Hadley, 1986 ²³ Parenteral vs. enteral nutrition | Forty-five acute TBI patients were randomized into 2 groups comparing the efficacy of TPN and enteral nutrition. | Class 3 | TPN patients had significantly higher mean daily N intakes ($p < 0.01$) and mean daily N losses ($p < 0.001$) than nasogastric-fed patients; however, nitrogen balance was not improved. Patients with TBI who are fed larger nitrogen loads have exaggerated nitrogen losses. |
| Kirby, 1991 ²⁴ Effectiveness of enteral nutrition | Twenty-seven patients with severe TBI underwent feeding with percutaneous endoscopic gastrojejunostomy. | Class 3 | Average nitrogen balance was -5.7 g/day. The reduction in N loss by this technique appeared equal or superior to gastric or TPN. |
| Klodell, 2000 ²⁵ Percutaneous endoscopic gastrostomy vs. intragastric feeding | Prospective observational study of 118 moderate to severe TBI patients provided percutaneous endoscopic gastrostomy and intragastric feeding. | Class 3 | Intragastric feeding was tolerated in 111 of 114 patients. Five patients aspirated. |
| Young, 1987 ²⁶ Total parenteral nutrition vs. enteral nutrition | Fifty-one TBI patients with admission GCS 4-10 were randomized to receive TPN or enteral nutrition. The TPN group received higher cumulative intake of protein than the enteral nutrition group (8.75 vs. 5.7 g/day of N). | Class 3 | Nitrogen balance was higher in the TPN group in the first week after injury. Caloric balance was higher in the TPN group (75% vs. 59%). Infections, lymphocyte counts, albumin levels were the same in both groups as was outcome. At 3 months the TPN group had a significantly more favorable outcome but at 6 months and 1 year the differences were not significant. |
| Young, 1987 ²⁷ Total parenteral nutrition vs. enteral nutrition | Ninety-six patients with severe TBI were randomly assigned to TPN or enteral nutrition. The incidence of increased ICP was measured in both groups for a period of 18 days. | Class 3 | There was no difference in peak daily ICP, responses to therapies. |
| Glycemic Control | | | |
| Lam, 1991 ²⁸ Hyperglycemia and neurological outcome | The clinical course of 169 patients with moderate or severe TBI was retrospectively reviewed and outcome correlated with serum glucose. | Class 3 | Among the more severely injured patients (GCS < 8), a serum glucose level greater than 200 mg/dl postoperatively was associated with a significantly worse outcome. |

| Reference Study Topic | Study Design, N, and Outcomes | Data Class | Results Conclusion |
|--|---|------------|--|
| Young, 1989 ⁴ Hyperglycemia and neurologic outcome | Serum glucose levels were followed in 59 consecutive TBI patients for up to 18 days after injury and correlated with outcome. | Class 3 | The patients with the highest peak admission 24-hour glucose levels had the worst 18-day neurologic outcome. |

Abbreviations: C=conventional, CNS=central nervous system, DEF=delayed enteral feeding, EEF=early enteral feeding, EN=enhanced enteral, ENT=jejunal nutrition, EVAP=early-onset ventilator-acquired pneumonia, GF=gastric feeding, GCS=Glasgow Coma Scale, GOS=Glasgow Outcome Scale, I=intensive, ICU=intensive care unit, IIT=insulin infusion therapy, N=total sample size, NICU=neonatal intensive care unit, N=total sample size, NR=not reported, NS=not significant, OR=odds ratio, RBP=retinol binding protein, RCT=randomized controlled trial, SEN=standard enteral nutrition, TBI=traumatic brain injury, TPF=transpyloric feeding, TPN=total parenteral nutrition, UTI=urinary tract infection.

* **Reference new to the 4th Edition.**

Timing of Feeding After Injury

Two Class 3 studies compared timing of feeding. One, new to this edition, reported that earlier feeding was associated with better outcomes at 3 months, although there was no significant difference at 6 months.¹⁷ The other from the 3rd Edition compared intermittent feeding to continuous feeding and found no differences in outcomes, although continuous feeding patients were able to reach caloric goals sooner.²⁰

Method of Feeding

Seven Class 3 studies included in the 3rd Edition concerned the method of feeding. Of these, three reported patient outcomes (e.g., mortality and morbidity) but none found sustained positive effect.^{21,26,27} The remaining four studies reported only on intermediate outcomes, caloric intake, and/or nitrogen balance,^{20,22-24} and while they reported differences, these were not used to develop recommendations, as Class 2 evidence was available about patient outcomes.

Glycemic Control

Glycemic control was the subject of two Class 3 studies from the 3rd Edition.^{4,28} These studies described the association of high glucose with poor outcomes, but they predate the focus on intensive control which is the subject of more recent studies. They are included in Table 3 for the sake of continuity.

Vitamins and Supplements

Two Class 3 studies that evaluated the impact of vitamins and supplements were added to this edition. In one, patients given Vitamin E had lower mortality rates and better GOS scores, but the sample size (N=100, 24 patients in the vitamin E group) and methodological concerns made it insufficient to support a recommendation.¹⁸ The other study retrospectively examined serum and CSF magnesium levels as well as whether low serum levels were corrected. Correction of serum levels did not change the fact that low serum levels and elevated CSF level seem to be associated with poor outcomes.¹⁹ This finding needs to be confirmed in additional studies.

Concordance With Other Systematic Reviews

In conducting the literature searches for this section, we identified two systematic reviews of studies of nutrition and severe TBI. We included some of the studies in these reviews and excluded others. We also included studies that were not in these reviews. Given this overlap and the fact that our evidence synthesis and these reviews reached similar conclusions, we decided to describe the systematic reviews here in the text rather than include their results in the evidence table.

Perel et al., 2008 conducted a review designed to quantify the effect of nutritional support strategies on mortality and morbidity. They identified 11 trials: seven are included in our review above; two were excluded for sample sizes under our requirement; and two did not include any of our required clinical or intermediate outcomes. This review was limited to RCTs, so they did not include observational studies that we included. The review authors concluded, as we did, that early feeding is associated with better outcomes. Additionally, the review authors pooled the trial results in order to compare parenteral to enteral routes and found no significant difference, with a slight trend toward better outcomes with parenteral nutrition. However, the precision of the estimates was low.²⁹

Wang et al., 2013 also conducted a review of the research on the timing and route of feeding. They included observational studies as well as RCTs and pooled the results of 16 studies (13 RCTs and 3 observational studies). Nine of these are included in our review: one is pediatric only and is in the pediatric guideline; three had mixed ages, pathologies, or severity; and three had small sample sizes. Combining the studies to include those we excluded for sample size did

not lead to a different conclusion. As such, we did not use the result of the meta-analysis. This review also found that early feeding was associated with better outcomes, and that parenteral nutrition is associated with slightly better outcomes than enteral routes, but the difference is not significant.³⁰

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9. Infection Prophylaxis

INTRODUCTION

There has been a strong movement to reduce hospital-acquired infections and minimize their potentially devastating effects on hospital morbidity, mortality, and length of stay. Severe traumatic brain injury can increase a patient's susceptibility to infection because of necessary mechanical ventilation to prevent airway obstruction, aspiration, and consequential hypoxia, in addition to invasive monitoring. Infection risks such as ventilator associated pneumonias (VAP) and central line-associated bacteremias are increased in all critically ill patients. Patients undergoing intracranial pressure (ICP) monitoring are reported to have related infection rates as high as 27%.¹ For external ventricular drains (EVDs), the historic focus of routine catheter exchanges has been replaced by attention to proper care during insertion, cerebrospinal fluid (CSF) sampling techniques, and the question of whether prophylactic intravenous (IV) antibiotics reduces infection rates or increases the risk for emergence of drug-resistant organisms.²

While a larger volume of literature across the spectrum of critically ill patients has identified techniques to reduce VAP, a small number of studies have addressed the severe traumatic brain injury (TBI) population specifically. Definitions for use in the surveillance and prevention of VAP were revised in 2011 and updated in 2015.³ In this Centers for Disease Control and Prevention (CDC) definition, possible VAP requires a positive culture, purulent respiratory secretions, or positive results on one of several tests. Data prior to the 2011 CDC definitions show that VAP in patients with TBI may be as high as 40%, and it is strongly associated with longer exposure to mechanical ventilation.⁴ The occurrence of VAP represents a significant morbidity and is associated with factors such as hypoxia, fevers, hypotension, and increased ICP, known to worsen the TBI patient's hospital course. Similarly, the risk of infection associated with EVDs is of particular concern for TBI patients. In this topic we focus on literature about VAP and EVD infection.

RECOMMENDATIONS

Level I

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

Level II A

- Early tracheostomy is recommended to reduce mechanical ventilation days when the overall benefit is felt to outweigh the complications associated with such a procedure. However, there is no evidence that early tracheostomy reduces mortality or the rate of nosocomial pneumonia.
- The use of povidone-iodine (PI) oral care is not recommended to reduce ventilator-associated pneumonia and may cause an increased risk of acute respiratory distress syndrome.

Level III

- Antimicrobial-impregnated catheters may be considered to prevent catheter-related infections during EVD.

Changes from Prior Edition

The Level II recommendation from the 3rd Edition of these guidelines that stated “Periprocedural antibiotics for intubation should be administered to reduce the incidence of pneumonia” has not been carried forward. This was based on one Class 2 study (still listed in the evidence table) that reported reductions in pneumonia but no improvement in mortality or function. The recommendation was not carried forward, as the evidence of benefit is not strong and general critical care practice has established protocols to prevent VAP, while infectious disease policies do not endorse this use of antibiotics.

Two questions are addressed in the 4th Edition of these guidelines for this topic. The question of prevention of VAP was maintained from the 3rd Edition because the rates of VAP are higher in TBI patients than non-TBI patients. Also, the question of prevention of infection associated with EVD was maintained. The recommendations from the 3rd Edition were revised due to new evidence.

EVALUATION OF THE EVIDENCE

Quality of the Body of Evidence

The studies identified for this topic (Table 9-1) address two questions: (1) prevention of VAP and (2) prevention of infection associated with EVD. For the question about VAP, the available evidence addressed three approaches to preventing VAP in TBI patients. Three randomized controlled trials (RCTs) assessed the influence of the timing of tracheostomy on pneumonia and mortality.⁵⁻⁷ These studies provided moderate-quality evidence that timing does not influence these outcomes. The second approach is oral care with PI. This was tested in two RCTs.^{8,9} However, the second, designed to address limitations of the first, failed to replicate the positive findings, and included non-TBI as well as TBI patients. These factors contribute to the rating of low quality of the body of evidence. The third approach, prophylactic antibiotics, was the subject of one RCT that was included in the last edition of these guidelines.¹⁰ As a single study in one site, this was considered insufficient evidence.

For the question about prevention of infection associated with EVD, two systematic review/meta-analyses^{11,12} and two Class 3 studies^{13,14} about the use of antimicrobial-impregnated catheters were included. These meta-analyses and studies were conducted with samples that included any pathology requiring EVD. As such, the evidence could only support a Level III recommendation.

Table 9-1. Quality of the Body of Evidence (Infection Prophylaxis)

| Topic | Number of Studies | Meta-Analysis | Number of Subjects | Class of Studies | Consistency (High, Moderate, Low) | Directness (Direct or Indirect) | Precision (High, Moderate, Low) | Quality of Evidence (High, Moderate, Low, or Insufficient) |
|--|-------------------|--|--------------------|--------------------------|-----------------------------------|---------------------------------|---------------------------------|--|
| COMPONENTS OF OVERALL QUALITY | | | | | | | | |
| Timing of tracheostomy ^{5,6} | 2 RCTs | No Different definitions of early intervention | 129 | 2 | Moderate | Direct | Low | Moderate |
| Povidone-iodine oral care ^{8,9} | 2 RCTs | No Differences in study design | 277 | Class 1: 1 Class 2: 1 | Low | One Direct, One Indirect | Moderate | Moderate |
| Prophylactic antibiotics ¹⁰ | 1 RCT | NA | 100 | 2 | NA | Direct | Low | Insufficient |

| Topic | Number of Studies | Meta-Analysis | Number of Subjects | Class of Studies | Consistency (High, Moderate, Low) | Directness (Direct or Indirect) | Precision (High, Moderate, Low) | Quality of Evidence (High, Moderate, Low, or Insufficient) |
|--|-------------------|---------------|--------------------|--------------------------------|-----------------------------------|---------------------------------|---------------------------------|--|
| Antimicrobial-impregnated catheters ^{12,15} | 2 Meta-analyses | Yes | 4,722 | Moderate Quality Meta-analyses | Moderate | Indirect | Moderate | Low |

Abbreviations: NA=not applicable, RCT=randomized controlled trial.

Applicability

For the question about VAP, two of the three studies of timing of tracheostomy were at single sites, one in Morocco⁵ and one in the United States.⁷ The third was conducted in six sites in the United States.⁶ The studies of povidone-iodine (PI) oral care included one single-site study and one study conducted in six sites that were both in France.^{8,9} The single study of antibiotics was conducted in Spain and published in 1997. It may not be relevant to current practice, as many hospital infection control policies may limit antibiotic use in order to prevent antibiotic-resistant infections.¹⁰

For the question about EVD, two studies were moderate-quality meta-analyses that pooled data from RCTs and non-randomized prospective studies comparing antimicrobial-impregnated catheters to standard catheters.^{12,15} We also included two Class 3 studies.^{13,14} Because the samples mixed pathologies, the applicability to TBI patients is uncertain.

SUMMARY OF THE EVIDENCE

Process

Of 18 new, potentially relevant studies reviewed, nine were excluded because they did not meet the inclusion criteria for this topic (Appendix F). Of the remaining nine, one was rated Class 1,⁹ one Class 2,⁸ five Class 3,^{7,13,14,16,17} and two were rated moderate-quality meta-analyses,^{12,15} which were included as evidence for this topic. Additionally, two Class 2 studies^{5,6} and two Class 3 studies^{18,19} from the 3rd Edition were included as evidence.

Class 1 and 2 Studies and Meta-Analyses

The evidence from the Class 1 and 2 studies and meta-analyses on infection prophylaxis is summarized in Table 9-2.

Table 9-2. Summary of Evidence: Class 2 Studies and Meta-Analyses (Infection Prophylaxis)

| Reference, Study Topic | Study Design, N, and Outcomes | Data Class | Results Conclusion |
|---|---|------------|---|
| VAP – Timing of Tracheostomy | | | |
| Bouderka, 2004 ⁵ Early tracheostomy (5 or 6 days) vs. prolonged endotracheal intubation | RCT N=62 Early tracheostomies=31 Prolonged intubation=31 Pneumonia; mortality; Mechanical ventilation days; ICU days | Class 2 | Early vs. Intubation Pneumonia 58% vs. 61.3%, p=0.79. Death 38.7% vs. 22.5%, p=0.27. Recovery 61.3% vs. 74.2%, p=0.41. There was no difference in the rate of mortality or pneumonia between the groups. Early tracheostomy group showed a decrease in the number of overall mechanical ventilation days, and mechanical ventilation days after the diagnosis of pneumonia. ICU days were not reduced. |
| Sugerman, 1997 ⁶ Early (3-5 days) vs. late (10-14 days) tracheostomy | RCT N=67 had severe TBI Early tracheostomy=35 Late tracheostomy=25 Continued tracheostomy=7 Pneumonia; mortality; ICU stay | Class 2 | There was no significant difference in rate of pneumonia or death in TBI patients undergoing early tracheostomy vs. later tracheostomy. |
| VAP – Oral Care | | | |
| Seguin, 2006* ⁸ Comparison of PI, saline, and control (standard care) | RCT N=98 PI=36 Saline=31 Control=31 VAP | Class 2 | % VAP (p value vs. PI) PI=8% Saline=39% p=0.003. Control 42%, p=0.001. Oral care with PI reduces VAP vs. standard care. |

| Reference, Study Topic | Study Design, N, and Outcomes | Data Class | Results Conclusion |
|--|---|------------------|---|
| Seguin, 2014* ⁹ Comparison of oral care with PI vs. a placebo | RCT N=179 PI=91 Placebo=88 VAP Tracheobronchitis Acute respiratory distress syndrome ICU and hospital length of stay ICU and 90-day mortality | Class 1 | VAP-PI vs. Placebo 31% vs. 28% RR 1.11 (95% CI 0.67 to 1.82), p=0.69. TBI Only 32% vs. 25%, p=0.346. Acute Respiratory Distress Syndrome PI=5, Placebo=0, p=0.06. No significant difference in other outcomes. No evidence to recommend PI oral care (no benefit) and increase risk of acute respiratory distress syndrome. |
| VAP – Prophylactic Antibiotics | | | |
| Sirvent, 1997 ¹⁰ | RCT N=100 (86 with TBI) Antibiotics=50 (43 with TBI) No treatment=50 (43 with TBI) Pneumonia Mortality | Class 2 | The overall incidence of pneumonia was 37%, 24% in Group 1, and 50% in the control group. The difference was statistically significant. There was no difference in mortality. A short course of prophylactic cefuroxime was effective in decreasing the incidence of nosocomial pneumonia in mechanically ventilated patients. |
| Catheter-related Infections During EVD | | | |
| Ratilal 2008* ¹⁵ Compared AIS to placebo or no antibiotic to prevent shunt infections | Meta-analysis 17 studies included in review 10 RCTs 7 Non-randomized prospective studies N=2,134 15 included in meta-analysis | Moderate Quality | Pooled results showed a significant effect of antibiotics on rate of shunt infections (OR 0.51, 95% CI 0.36 to 0.73). For the included trials that had adequate allocation concealment, there was no significant effect of antibiotics on rate of shunt infections (OR 0.78, 95% CI 0.44 to 1.38). For included trials that did not report allocation conceal or that had inadequate allocation concealment, there was a significant effect of antibiotics on rate of shunt infections (OR 0.40, 95% CI 0.25 to 0.63). For placebo-controlled trials, there was a significant effect of antibiotics on rate of shunt infections (OR 0.46, 95% CI 0.30 to 0.71). For standard care-controlled trials, there was no significant effect of antibiotics on rate of shunt infections (OR 0.66, 95% CI 0.34 to 1.26). |

| Reference, Study Topic | Study Design, N, and Outcomes | Data Class | Results Conclusion |
|--|--|------------------|---|
| Wang 2013* ¹² Comparison of AIC to SC to prevent CFI | Meta-analysis 4 RCTs 4 Non-randomized prospective studies N=3,038 | Moderate Quality | Overall rate of CFI: AIC group 3.6%, SC group 13.7% (OR, 0.25, 95% CI 0.12 to 0.52, p<0.05). Significant reduction in 20-Day infection rate for AIC group (HR 0.52, 95% CI 0.29 to 0.95, p<0.05). Significant decrease in rate of catheter bacterial colonization for AIC group (OR 0.37, 95% CI 0.21 to 0.64, p<0.05). |

Abbreviations: AIC=antimicrobial-impregnated catheters, AIS=antibiotic-impregnated shunts, CFI=cerebrospinal fluid, CI=confidence interval, GOS=Glasgow Outcome Scale, GCS=Glasgow Coma Scale, HR=hazard ratio, ICU=intensive care unit, IIT=insulin infusion therapy, N=total sample size, OR=odds ratio, PI=povidone-iodine, RCT=randomized controlled trial, RR=relative risk, S=saline, SC=standard catheters, TBI=traumatic brain injury, VAP=ventilator-associated pneumonia

* Reference new to the 4th Edition.

Ventilator Associated Pneumonia

Included Class 1 and 2 studies addressed three approaches to preventing pneumonia in TBI patients. Two tested early tracheostomy,^{5,6} two tested oral care with povidone-iodine,^{8,9} and one tested a short course of prophylactic antibiotics.¹⁰

Timing of Tracheostomy

Early tracheostomy has been proposed to decrease the incidence of pneumonia in critically ill patients. Two randomized trials, with small numbers of subjects (n=62 and n=67) and different definitions of early (3-5 days and 5-6 days), found no differences in pneumonia rates or mortality in severe TBI patients undergoing early tracheostomy compared with patients with later tracheostomy.^{5,6}

Oral Care with Povidone-Iodine

Seguin et al. conducted two RCTs of the use of PI as an oral antiseptic.^{8,9} The first trial, conducted in 2006, had three arms and compared PI to saline and usual care and found a significant reduction in VAP with PI compared with standard care. This study was conducted at one site and was not blinded. To address these limitations, a second study was conducted in 2014 in six ICUs to compare PI to a placebo mixture, and in which VAP assessment was blinded. This study did not replicate the positive findings of the earlier study; it found no difference in VAP rates and it reported significantly more cases of respiratory distress syndrome in the treatment groups.

Prophylactic Antibiotics

Sirvent et al. conducted an RCT of 100 critically ill patients, 86% of whom had severe TBI, evenly divided into a treatment group of cefuroxime 1.5 g for two doses within 6 hours after intubation and a control group not given antibiotics after endotracheal intubation.¹⁰ There was a statistically significant decrease in the incidence of pneumonia in the treated group but no difference in mortality. This was the basis for the recommendation included in the 3rd Edition that has not been carried forward, as the benefits of this use of prophylactic antibiotics may not outweigh the harms of developing resistant organisms.

External Ventricular Drain

Ratilal et al. conducted a moderate-quality systematic review and meta-analysis comparing shunt infection rates between patients managed with antibiotic-impregnated shunts (AIS) versus placebo and standard care.¹⁵ Seventeen studies were reviewed (10 RCTs and 7 non-randomized prospective studies; N=2,134) and 15 were included in the meta-analysis. While the pooled results indicated a significant decrease in shunt infection for the AIS group, secondary analysis showed no significant effect for the subset of studies with adequate allocation concealment, and no significant effect for the subset of studies that compared AIS to standard care (vs. those that compared AIS to placebo).

Similarly, Wang et al. conducted a moderate-quality systematic review and meta-analysis comparing cerebrospinal fluid infection (CFI) rates between patients managed with antimicrobial-impregnated catheters (AICs) versus standard catheters (SCs).¹² Four RCTs and four non-randomized prospective studies were included (total N=3,038). Patients managed with AICs had significantly lower overall rate of CFIs, 20-day infection rate, and rate of catheter bacterial colonization.

Because the samples for these studies included multiple pathologies, the evidence is indirect and was used to support a Level III recommendation.

Class 3 Studies

The evidence from the Class 3 studies of infection prophylaxis is summarized in Table 9-3.

Table 9-3. Summary of Evidence: Class 3 Studies (Infection Prophylaxis)

| Reference Study Topic | Study Design, N and Outcomes | Data Class | Results Conclusion |
|---|--|------------|---|
| New Studies | | | |
| VAP – Timing of Tracheostomy | | | |
| Ahmed 2007* ¹⁶ Early vs. late tracheostomy | Retrospective Cohort N=55 Early: 27 Late: 28 Ventilator Days ICU Days Pneumonia Hospital Stay Mortality | Class 3 | Early – On or before day 7. Late – After day 7. Average time of the tracheostomy 5.5 + 1.8 days in the early group 11.0 + 4.3 days in the late group. Early group had significantly fewer ICU days than the late group (19.0 + 7.7 vs. 25.8 + 11.8), p=0.000. No decrease in the incidence of pneumonia or ventilator days were observed with early tracheostomy. Overall mortality, total length of stay, discharge or discharge to rehabilitation All no significant difference. Pneumonia Early Tracheostomy 41% Late Tracheostomy 50%, p=0.59. |
| Dunham 2014* ⁷ Early vs. late tracheostomy | RCT N=24 Early: 15 Late: 9 Pneumonia, Ventilator/ICU Days, Mortality | Class 3 | No significant difference in VAP rates, ventilator/ICU days, or hospital mortality. |
| Wang 2012* ¹⁷ Early vs. late tracheostomy | Retrospective Cohort N=66 Early: 16 Late: 50 ICU Length of Stay Hospital Length of Stay Pneumonia Mortality | Class 3 | Early – On or before day 10. Late – After day 10. ICU LOS was significantly shorter in the ET group, p<0.001. The incidence of nosocomial pneumonia was lower in the ET group (p=0.04) and the duration of antibiotic use was significantly shorter in the ET group (p<0.001). The patients in the ET group had a lower incidence of pneumonia caused by gram-negative microorganisms. |
| Catheter-related Infections during EVD | | | |
| Muttaiyah 2010* ¹³ AI EVDs vs. control group | Prospective vs. historical controls N=120 AI: 60 Controls: 60 Rate of cerebrospinal fluid infections | Class 3 | Significant decrease in rate of infection in AI group than controls, p<0.0001. |

| Reference Study Topic | Study Design, N and Outcomes | Data Class | Results Conclusion |
|---|---|------------|---|
| Wright 2013* ¹⁴ ac-EVDs compared in three phases: (1) before ac-EVDs, (2) mixed phase, and (3) ac-EVDs only. | Retrospective chart review N=141 Phase 1: 51 Phase 2: 43 Phase 3: 47 Rate of VRIs | Class 3 | Significant decrease in VRIs from period 1 to 3, p=0.03. |
| Studies from 3rd Edition | | | |
| VAP – Timing of Tracheostomy | | | |
| Hsieh, 1992 ¹⁸ Extubation and pneumonia | Retrospective review of 109 severe TBI patients on mechanical ventilation for >24 hours. Extubation was performed when patients met respiratory criteria for extubation and possessed an intact cough and gag reflex. | Class 3 | Forty-one percent of the patients developed pneumonia, which increased the duration of intubation and ventilation, and hospital/ICU length of stay, but not mortality. Extubation was not significantly associated with an increased risk of pneumonia. |
| VAP – Prophylactic Antibiotics | | | |
| Goodpasture, 1977 ¹⁹ Antibiotics and infection rate | Prospective study of 28 patients with severe TBI; 16 (Group 1) were given prophylactic antibiotics for endotracheal intubation. A subsequent cohort of 12 TBI patients (Group 2) were not given prophylactic antibiotics. | Class 3 | An increased respiratory tract infection rate was noted in Group 2, but usually with Gram positive organisms. Antibiotic prophylaxis did not alter the rate of bacterial colonization and was associated with an earlier appearance of Gram negative organisms, the infections of which were more severe. |

Abbreviations: ac-EVD=antibiotic-coated extraventricular, AI=antibiotic-impregnated, ET=early tracheostomy, EVD=external ventricular drain, ICU=intensive care unit, LOS=length of stay, TBI=traumatic brain injury, VAP=ventilator-associated pneumonia, VRI=ventriculostomy-related infection

***References new to the 4th Edition.**

Ventilator-Associated Pneumonia

Timing of Tracheostomy. One of the Class 3 studies that address the timing of tracheostomy was an RCT,⁷ and three are retrospective. Dunham et al. conducted a small RCT comparing outcomes for 15 patients whose tracheostomies were performed at days 3-5 post-injury with 9 patients whose tracheostomies were performed at days 10-14. No difference was observed in VAP rates, ventilator/ICU days, or in-hospital mortality. Based on methodologic issues and sample size, this study is rated Class 3. Ahmed et al., 2007¹⁶ compared 27 people with tracheostomies classified as early (mean 5.5 days) and 28 as late (11.0 days). They found no significant differences in pneumonia or mortality. The early group had significantly fewer ICU days. Similarly, Wang et al., 2012¹⁷ found that early tracheostomy reduced ICU days. This study also found that the incidence of pneumonia was lower in the 16 patients classified as early, but

the result was not replicated in any other study. Hsieh et al. reported that extubation was not associated with an increased risk of pneumonia.¹⁸

Prophylactic Antibiotics. One Class 3 study addressed this topic in a small prospective study and found that antibiotics did not reduce bacterial colonization and were associated with more severe infections.¹⁹

External Ventricular Drain

Two Class 3 studies contributed uncontrolled information indicating a positive effect of antibiotic-impregnated EVDs in minimizing infection.^{13,14} They are summarized in the table but not used to support a recommendation.

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10. Deep Vein Thrombosis Prophylaxis

INTRODUCTION

Patients with traumatic brain injury (TBI) are at significant risk for developing venous thromboembolism (VTE).¹ Knudson et al. found that head injury with an Abbreviated Injury Score of ≥ 3 , among other factors, was an independent predictor of VTE in trauma patients.² TBI has been associated with up to 54% incidence of deep venous thrombosis without prophylactic treatment³ and a 25% incidence in patients with isolated TBI treated with sequential compression devices.⁴ Ekeh found that deep vein thrombosis (DVT) occurred in one-third of moderate and severe TBI patients with isolated head injuries, having a lower incidence than those patients with concomitant extracranial injuries. Age, subarachnoid hemorrhage, Injury Severity Score >15 , and extremity injury were predictors of DVT.⁵ Reiff et al. demonstrated a three-to-four-fold increase in the DVT risk in TBI despite use of mechanical and chemoprophylaxis.⁶ VTE risk increases with TBI severity.⁷

Severe TBI patients can be at significant risk for VTE due to hypercoagulability resulting from the primary brain injury, prolonged periods of immobilization, and focal motor deficits. If untreated, DVT can result in potentially debilitating or fatal pulmonary embolism. Of particular concern is the initiation of pharmacological VTE prophylaxis, which, in conjunction with mechanical compression boots, has increased effectiveness over mechanical prophylaxis alone.⁸ Problematically, such drugs constitute low dose anticoagulation, which has the potential to result in clinically significant intracranial hemorrhage expansion.

RECOMMENDATIONS

Level I and II

- There was insufficient evidence to support a Level I or II recommendation for treatment of deep vein thrombosis (DVT) in severe TBI patients.

Level III

- Low molecular weight heparin (LMWH) or low-dose unfractionated heparin may be used in combination with mechanical prophylaxis. However, there is an increased risk for expansion of intracranial hemorrhage.

In addition to compression stockings, pharmacologic prophylaxis may be considered if the brain injury is stable and the benefit is considered to outweigh the risk of increased intracranial hemorrhage. There is insufficient evidence to support recommendations regarding the preferred agent, dose, or timing of pharmacologic prophylaxis for deep vein thrombosis.

Changes from Prior Edition

The Level 3 recommendation supporting use of compression stockings has been incorporated in the recommendation about pharmacologic prophylaxis, as mechanical treatments such as stockings are the general standard of care and there is not a body of evidence or issues that are TBI-specific. DVT pharmacologic prophylaxis is both a topic in general trauma and ICU care and a topic with issues specific to TBI, so the issues specific to TBI are the focus of the recommendations. Five descriptive, non-comparative studies from the 3rd Edition are not included in the evidence tables for this edition as they do not meet the inclusion criteria.⁹⁻¹²

EVALUATION OF THE EVIDENCE

Quality of the Body of Evidence

The included studies addressed three questions related to VTE prophylaxis (Table 10-1). The quality of the body of evidence for the first question was low, and it was insufficient for the other two. Three studies addressed whether outcomes are better with or without prophylaxis and reported inconsistent findings and imprecise estimates of effect, providing low-quality evidence.¹³⁻¹⁵ Two studies^{16,17} compared outcomes for periods before and after protocols were implemented for anticoagulation, and the single study from the 3rd Edition compared prophylactic anticoagulation in the 72 hours post-injury with later administration.¹⁸ These three studies provided insufficient evidence to support recommendations.

Table 10-1. Quality of Body of Evidence (Deep Vein Thrombosis Prophylaxis)

| COMPONENTS OF OVERALL QUALITY-Class 3 | | | | | | | | |
|---|----------------------------------|---|--------------------|------------------|-----------------------------------|---------------------------------|---------------------------------|---|
| Topic | Number of Studies | Meta-Analysis | Number of Subjects | Class of Studies | Consistency (High, Moderate, Low) | Directness (Direct or Indirect) | Precision (High, Moderate, Low) | Quality of Evidence (High, Moderate, Low, Very Low or Insufficient) |
| DVT prophylaxis vs. no prophylaxis ¹³⁻¹⁵ | 0 RCT 4 Retrospective Studies | No: different interventions and populations | 1486 | 3 | Low | Indirect | Low | Low |
| Prophylaxis protocol vs. no protocol ^{16,17} | 0 RCT 2 Pre Post | No different interventions | 371 | 3 | Low | Indirect | Low | Insufficient |
| Early vs. late prophylaxis administration ¹⁸ | 0 RCT 1 Retrospective cohort | NA | 64 | 3 | NA | Direct | Low | Insufficient |

Abbreviations: DVT=deep vein thrombosis, NA=not applicable, RCT=randomized controlled trial.

Applicability

Most of these studies reported results in patients with a wide range of severities. There is sufficient uncertainty about differences in the relevant physiology across pathologies to warrant caution when considering studies of patients with mixed pathologies as indirect evidence. Reviewing studies of mixed severity levels raised issues as well, such as whether the risk of further bleeding is related to the Glasgow Coma Scale (GCS) score. Nevertheless, we decided using studies with mixed severity was the better option, in part because it is unclear whether initial post-resuscitation GCS should be used as the inclusion criteria for this topic, as the treatment decision may occur hours or days after the initial assessment that defined the severity of the TBI.

SUMMARY OF THE EVIDENCE

Process

Of 22 potentially relevant studies reviewed, none met the inclusion criteria for direct evidence for this review. We then re-examined the excluded studies in order to identify potential indirect evidence. Six studies that included mixed levels of severity were included as indirect

evidence. The studies were all rated Class 3.^{13-17,19} One Class 3 study from the 3rd Edition was included.¹⁸

Class 3 Studies

The evidence from the Class 3 studies of deep vein thrombosis prophylaxis is summarized in Table 10-2.

Table 10-2. Summary of Evidence – Class 3 Studies (Deep Vein Thrombosis Prophylaxis)

| Reference Study Topic | Study Design, N and Outcomes | Data Class | Results Conclusion |
|---|--|------------|--|
| New Studies | | | |
| Prophylactic Anticoagulation vs. No Anticoagulation | | | |
| Daley 2015 * ¹⁹ Compared VTE rates for enoxaparin vs. no enoxaparin for craniotomy patients. | Retrospective Cohort N=271 Enoxaparin=45 No enoxaparin=226 In-hospital VTE, mechanical ventilation days, ICU and hospital LOS, in-hospital mortality | Class 3 | No significant difference in rates of VTE, mechanical ventilation days, or LOS. Significantly higher rate of mortality for no- treatment group. |
| Kwiatt, 2012 * ¹³ Comparison of LMWH for VTE prophylaxis vs. no prophylaxis | Retrospective Cohort N=1,215 LMWH=220 (mean GCS=8) No LMWH=995 (mean GCS=11.4) Hemorrhage progression VTE | Class 3 | LMWH vs. No LMWH Progression of bleed 42% (93) vs. 24% (239), p<0.0001. Progression after LMWH 14.5% (32). Neurosurgical intervention for bleed 14.5% (32) vs. 4.9% (49), p<0.001. VTE 9.1% (20) vs. 3.1% (31), p<0.001 Note: More LMWH patients (42% vs. 11%) had lower-extremity duplex ultra sounds. Given higher risk of hemorrhage, risk may exceed benefit. |

| Reference Study Topic | Study Design, N and Outcomes | Data Class | Results Conclusion |
|--|--|------------|--|
| Mohseni, 2012* ¹⁴ Comparison of patients treated prophylactically with anticoagulants vs. no anticoagulants | Retrospective Case-control N=78 Treatment=41 Control=37 Mortality VTE SICU HLOS, adverse effects of anticoagulation | Class 3 | Treatment vs. Control Mortality 5% vs. 19%, p=0.001. Only 1 case due to PE. VTE 11% vs. 30%; OR of VTE in control 3.5, 95% CI 1.0 to 12.1, p=0.002. There was no significant difference in SICU length of stay. No adverse outcomes or complications. Reduced risk of VTE. |
| Scudday, 2011* ¹⁵ Early chemical thromboprophylaxis (subcutaneous or intravenous unfractionated heparin or low molecular weight heparin before VTE diagnosis) vs. controls with no thromboprophylaxis | Retrospective Cohort N=812 (300 GCS≤9, GCS not available for all patients.) Treatment: Chemical thromboprophylaxis N=402(49.5%) Within 48 hours=169 Within 72 hours=242 VTE Injury Progression | Class 3 | Prophylaxis vs. None VTE 1% (3) vs. 3% (11); p=0.019. Risk ratio of no prophylaxis to treated 0.194 (95% CI 0.049 to 0.760). Injury progression, 6% (25) vs. 3% (11) vs. p=0.055. Risk ratio of no prophylaxis to treated 0.474 (95% CI 0.221 to 1.015). Reduced VTE and no significant increase in bleed. |
| Protocol for Prophylactic Anticoagulation vs. No Protocol | | | |
| Farooqui, 2013* ¹⁶ Evaluation of a protocol (30 mg of Lovenox 2 times per day or 5000 U of heparin 3 times a day 24 hours after intracranial hemorrhage was stable on CT) | Retrospective Cohort N=236 Protocol=107 No routine administration=129 (groups are different time periods) DVT PE Increase in ICH | Class 3 | Protocol vs. no routine administration DVT 0% vs. 5.6% (6), p=0.0080. PE 0.78% (1) vs. 3.74% (4), p=0.18 NS. ICH 0.7% (1) vs. 2.8% (3), p=0.3 NS. |
| Nickele, 2013* ¹⁷ Assess PTP protocol | Retrospective Cohort Quality Improvement Study N=87 patients during 1-year protocol period N=48 patients during 6-month pre-protocol period DVT and PE % receiving prophylaxis | Class 3 | Protocol vs. pre protocol DVTs 6.9% (6) vs. 4.2% (2) p=0.20 PE 5.75% (5) vs. 4.2% (2) p=0.45 Received PTP 72.4% (63) vs. 45.8% (22) p<0.00001 Average time from admission to first dose 3.4 days vs. 4.9 days |

| Reference Study Topic | Study Design, N and Outcomes | Data Class | Results Conclusion |
|--|--|------------|---|
| Study from 3rd Edition | | | |
| Kim, 2002 ¹⁸ Early vs. late administration | Retrospective study N=64 patients with severe TBI Level I trauma center. Early: prophylaxis with 5000 units of subcutaneous heparin was begun less than 72 hours Late: 72 hours or more after admission. (late administration group includes those who received no drug). | Class 3 | Early vs. Late Mortality (4% vs. 1% p=1.0) Rates of DVT were 4% vs. 6% (Study was underpowered to detect efficacy of intervention) Did not find increase in bleeding complications |

Abbreviations: CT=computed tomography, DVT=deep venous thrombosis, HLOS=hospital length of stay, ICH=intracranial hemorrhage, GCS= Glasgow Coma Scale, LMWH=low molecular weight heparin, NS=not significant, PE=pulmonary embolism, PTP=pharmacologic thromboembolism prophylaxis, SICU=surgical intensive care unit, TBI=traumatic brain injury, VTE=Venous thromboembolism.

***References new to the 4th Edition.**

Prophylactic Anticoagulation Versus No Anticoagulation

The four studies comparing patients who received prophylaxis anticoagulants to those who did not reported conflicting results and provided a low-quality body of evidence.^{13-15,19} Kwaitt et al. conducted a retrospective cohort study using data from seven Level 1 trauma centers in the United States.¹³ Adults with intracranial hemorrhage caused by blunt trauma were identified through each center’s trauma registry and divided into those who received LMWH and those who did not. Patients who received LMWH were more severely injured on admission (mean GCS of 8 vs. 11.4, p<0.0001). Based on findings that 14.5% had hemorrhage progression after receiving LMWH with 4.1% requiring neurosurgical intervention, and that later prophylaxis (after 48 hours) did not decrease the rate of bleeding, the researchers concluded that they could not demonstrate the safety of LMWH for TBI patients.¹³ In a smaller study at one urban trauma center, researchers used propensity matching to create 34 pairs of patients with similar demographic and clinical characteristics, except that one received prophylactic anticoagulation and one did not. Patients in the controls had higher rates of VTE (30% vs. 11%), and there were no adverse outcomes reported in the treated group, leading these authors to conclude that prophylactic anticoagulation decreases the risk of VTE.¹⁴ A third retrospective cohort study of 812 patients included 300 patients with severe injuries (GCS ≤9); however, they did not report the results by severity. In all these patients, VTE was significantly lower in the treated group (1% vs. 3%, p=0.019), and injury progression was not statistically significantly different (6% vs. 3%,

p=0.055).¹⁵ Finally, a fourth retrospective cohort study of 271 patients who received craniotomies compared VTE rates and outcomes for patients who were treated with enoxaparin (n=45) with those not treated for prevention of VTE (n=226). Identification of patients for VTE prophylaxis was at the discretion of the treating neurosurgeon. There were no significant differences between groups in VTE rates, mechanical ventilation days, or LOS. There was significantly higher in-hospital mortality for the untreated group.

Protocol for Prophylactic Anticoagulation Versus No Protocol

Three additional studies were considered separately, as they addressed different questions and did not provide sufficient evidence for recommendations. Two of these studies compared DVT rates in a single institution before and after the initiation of a protocol for the use of chemoprophylaxis for TBI patients. In one study, the protocol called for administration of either enoxaparin or heparin 24 hours after an intracranial hemorrhage was demonstrated as stable on brain CT. DVT rates were significantly lower in the treated group, while PE and the increase in the size of the hemorrhage were not statistically significantly different.¹⁶ Another study described the results of a quality improvement initiative designed to implement a drug treatment protocol to prevent VTE. The authors reported that physicians increased the use of anticoagulants, but that the differences in DVT and PE were not significantly different and required further study.¹⁷ The final included study followed patients who received heparin within 72 hours of injury and those who received heparin after 72 hours. VTE rates were not different and no patients in the early group experienced an adverse event defined as increased bleeding or deterioration.¹⁸

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11. Seizure Prophylaxis

INTRODUCTION

Acute symptomatic seizures may occur as a result of severe traumatic brain injury (TBI). Such post-traumatic seizures (PTS) are classified as *early* when they occur within 7 days of injury or *late* when they occur after 7 days following injury. Post-traumatic epilepsy (PTE) is defined as recurrent seizures more than 7 days following injury. In patients with severe TBI, the rate of clinical PTS may be as high as 12%, while that of subclinical seizures detected on electroencephalography may be as high as 20% to 25%. The risk factors for early PTS include: Glasgow Coma Scale (GCS) score of ≤ 10 ; immediate seizures; post-traumatic amnesia lasting longer than 30 minutes; linear or depressed skull fracture; penetrating head injury; subdural, epidural, or intracerebral hematoma; cortical contusion; age ≤ 65 years; or chronic alcoholism.¹ A 2010 population-based study² showed that rates of PTE are substantially higher than the risk of developing epilepsy in the general population.³ Those most at risk for PTE are individuals who have suffered the following: severe TBI and early PTS prior to discharge; acute intracerebral hematoma or cortical contusion; posttraumatic amnesia lasting longer than 24 hours; age >65 years; or premorbid history of depression.¹

Seizure prophylaxis for PTS refers to the practice of administering anticonvulsants to patients following TBI in order to prevent the occurrence of seizures. The rationale for routine seizure prophylaxis is that there is a relatively high incidence of PTS in severe TBI patients, and there are potential benefits to preventing seizures following TBI (e.g., limiting derangement in acute physiology, preventing the development of chronic epilepsy, and preventing herniation and death). However, it is also desirable to avoid the neurobehavioral and other side effects of these medications, particularly if they are ineffective in preventing seizures. It is, therefore, important to evaluate the efficacy and overall benefit, as well as potential harms, of anticonvulsants used for the prevention of PTS.

Levetiracetam (known by the brand name Keppra) appears to be increasing in use for seizure prophylaxis for various pathologies, including TBI. The available comparative studies are insufficient to support a recommendation for or against the use of levetiracetam over another

agent. Future studies are necessary to better understand the potential benefits or harms of levetiracetam in treating patients with TBI.

RECOMMENDATIONS

Level I

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

Level II A

- Prophylactic use of phenytoin or valproate is not recommended for preventing late PTS.
- Phenytoin is recommended to decrease the incidence of early PTS (within 7 days of injury), when the overall benefit is felt to outweigh the complications associated with such treatment. However, early PTS have not been associated with worse outcomes.

At the present time there is insufficient evidence to recommend levetiracetam over phenytoin regarding efficacy in preventing early post-traumatic seizures and toxicity.

Changes from Prior Edition

The recommendations have not changed for this update from the 3rd Edition. Two new Class 2 studies and four new Class 3 studies were added as evidence, but these and the Class 3 studies included from the 3rd Edition did not provide sufficient evidence to inform new recommendations.

EVALUATION OF THE EVIDENCE

Quality of the Body of Evidence

The 11 studies identified for this topic (1) addressed the effectiveness of seizure prophylaxis in preventing early and late seizures following TBI, (2) assessed potential adverse effects, and (3) compared one agent to another or compared an agent to a placebo in seizure prevention and neuropsychological function (Table 11-1). Two new Class 2 studies^{4,5} and four new Class 3 studies⁶⁻⁹ were identified. Three Class 2 studies¹⁰⁻¹² and two Class 3 studies^{13,14} from the 3rd Edition of these guidelines were included.

All studies except one¹² reported results for samples with mixed pathologies and/or TBI severities. Thus, the body of evidence is primarily indirect. As such, the overall quality of the

body of evidence that supports the recommendations is moderate despite the consistent results and high precision.

Table 11-1. Quality of Body of Evidence (Seizure Prophylaxis)

| COMPONENTS OF OVERALL QUALITY – Class 2 | | | | | | | | |
|--|-----------------------------|-------------------------|---|------------------|-----------------------------------|---|---------------------------------|--|
| Topic | Number of Studies | Meta-Analysis | Number of Subjects | Class of Studies | Consistency (High, Moderate, Low) | Directness (Direct or Indirect) | Precision (High, Moderate, Low) | Quality of Evidence (High, Moderate, Low, or Insufficient) |
| Prevention of early PTS ^{10,11} | 2 RCTs | No different treatments | 783 | 2 | High | Indirect | High | Moderate |
| Prevention of late PTS ^{10,11} | 2 RCTs | No different treatments | 783 | 2 | High | Indirect | High | Moderate |
| Prevention of harms (negative cognitive effects) ¹² | 1 RCT | NA | 244 (analysis of same subjects included in above) | 2 | NA | Direct (results are reported by GCS sub groups) | Low | Insufficient |
| Comparative effectiveness of levetiracetam vs. phenytoin for early seizures ⁴ | 1 Prospective observational | NA | 813 | 2 | NA | Indirect | High | Insufficient |
| Comparative effectiveness of valproate vs. phenytoin for neuro-psychological function ⁵ | 1 RCT | NA | 279 | 2 | NA | Indirect | Low | Insufficient |

Abbreviations: GCS=Glasgow Coma Scale, NA=not applicable, PTS=post-traumatic seizure, RCT=randomized controlled trial.

Applicability

Three of the five Class 2 studies and two of the six Class 3 studies were conducted in the 1980s and 1990s. Two Class 2 and the four Class 3 studies were conducted more recently.

SUMMARY OF THE EVIDENCE

Process

Of nine new, potentially relevant studies reviewed, three were excluded because they did not meet the inclusion criteria for this topic (see Appendix F). Of the remaining six, two were rated Class 2^{4,5} and four were rated Class 3.⁶⁻⁹ Three Class 2 studies¹⁰⁻¹² and two Class 3^{13,14} from the 3rd Edition were included as evidence for this topic.

Class 2 Studies

The evidence from the Class 2 studies of seizure prophylaxis is summarized in Table 11-2.

Table 11-2. Summary of Evidence – Class 2 Studies (Seizure Prophylaxis)

| Reference Study Topic | Study Design, N, and Outcomes | Data Class | Results Conclusion |
|--|---|------------|--|
| Prevention of Early and Late PTS | | | |
| New Studies | | | |
| Inaba 2013* ⁴ LEV vs. PHE | Prospective Observational N=813 LEV=406 PHE=407 18.8% GCS ≤8 Prevention of early PTS | Class 2 | No difference in seizure rate (1.5% vs.1.5%, p=0.997), adverse drug reactions (7.9% vs. 10.3%, p=0.227), or mortality (5.4% vs. 3.7%, p=0.236). |
| Dikmen 2000* ⁵ To compare 1 week of PHT, 1 month of valproate, or 6 months of valproate | RCT N=279** (PHT=94; 1 month valproate=94; 6 months valproate=91) Neuropsychological function at 1, 6, and 12 months post-injury. | Class 2 | <u>PHT vs. Valproate</u> <u>Neuropsychological function:</u> No significant beneficial or adverse neuropsychological effects of valproate. |

| Reference Study Topic | Study Design, N, and Outcomes | Data Class | Results Conclusion |
|--|---|------------|---|
| Studies from 3rd Edition | | | |
| Temkin, 1990 ¹⁰ To compare PHT and placebo | RCT N=404 PHT=208 (60% GCS≤10) Placebo=196 (67% GCS≤10) Early and late PTS | Class 2 | Phenytoin vs. Placebo Early PTS (first week) Risk Ratio 0.27 (0.12 to 0.62), p<0.001. Cumulative (+-SE) Seizure Rate PHT Group 3.6+-1.3; Placebo 14.2+-2.6. Day 8 to 1 year 21.5% vs. 15.7%, p>0.2. at 2 years 27.5% vs. 21.1%, p>0.2. Early PTS: Significant reduction by phenytoin. Late PTS: no significant effect. |
| Temkin, 1999 ¹¹ To compare 1 week of PHT, 1 month of valproate, or 6 months of valproate | RCT N=379 (phenytoin: 132; 1 month valproate: 120; 6 months valproate:127) Early and Late PTS Adverse Events | Class 2 | PHT vs. Valproate <u>Early PTS: 1.5% vs. 4.5%</u> <u>Late PTS: No significant difference</u> 15% PHT for 1 week 16% valproate 1 month 24% valproate 6 months. <u>Serious adverse events: no difference</u> Non-significant trend toward higher mortality in valproate groups. No benefit suggests valproate should not be routinely used. |
| Negative Cognitive Effects | | | |
| Dikmen, 1991 ¹² To compare PHT and placebo | RCT N=244** PHT=128 Placebo=126 Subgroup GCS≤8 N=71 PHT=37 Placebo=34 Neurobehavioral Measures | Class 2 | 1 month PHT group performed significantly more poorly 12 months No significant effect More improvement in month 24 in those who stopped taking PHT at month 12 then in placebo group. PHT has negative side effects in people with severe TBI |

Abbreviations: GCS=Glasgow Coma Scale, LEV=levetiracetam, N=total sample size, PHT=phenytoin, PTS=post-traumatic seizure, RCT=randomized controlled trial, TBI=traumatic brain injury.

***References new to the 4th Edition.**

**Subgroup of patients included in Temkin, 1990

Temkin et al., 1990 reported the results of a large, randomized, double-blinded, placebo-controlled trial of 404 patients evaluating the effect of phenytoin on early and late PTS. This trial was unique in that serum levels were independently monitored and dosages were adjusted so that therapeutic levels were maintained in at least 70% of the patients. Moreover, three-quarters of

the patients who had levels monitored on the day of their first late seizure had therapeutic levels. There was a significant reduction in the incidence of early PTS in the treated group from 14.2% to 3.6% ($p < 0.001$) but no significant reduction in the incidence of late PTS. The survival curves for the placebo and active treatment groups showed no significant difference in mortality.¹⁰

A secondary analysis was performed on the data from this trial to determine if treatment for early PTS was associated with significant drug-related adverse side effects. The occurrence of adverse drug effects during the first 2 weeks of treatment was low and not significantly different between the treated and placebo groups. The study conclusion was that incidence of early PTS can be effectively reduced by prophylactic administration of phenytoin for 1 or 2 weeks without a significant increase in serious drug-related side effects.

In another secondary analysis of the same trial, Dikmen et al. found significantly impaired performance on neuropsychological tests at 1 month after injury in severe TBI patients maintained on phenytoin. However, the difference was not apparent at 1 year following injury.¹²

A second randomized, double-blinded study was designed to evaluate the effect of valproate to reduce the incidence of early and late PTS. The trial compared phenytoin to valproate for the prevention of early PTS, and valproate to placebo for the prevention of late PTS. The incidence of early PTS was similar in patients treated with either valproate or phenytoin. The incidence of late PTS was similar in patients treated with phenytoin for 1 week and then placebo, or patients treated with valproate for either 1 month then placebo, or with valproate for 6 months. There was a trend toward higher mortality in patients treated with valproate.¹¹ Dikmen conducted a secondary analysis of 279 patients from this trial and tested them for neuropsychological function at 1, 6, and 12 months post-injury. No beneficial or adverse effects of valproate were found compared with phenytoin or placebo.⁵

Inaba et al., 2013 conducted a prospective, observational study in two Level I trauma centers comparing levetiracetam (LEV) to phenytoin (PHE) for the prevention of early seizures after TBI. The selection of medication was made by the medical staff. However, one of the two institutions preferred LEV, and the other PHE. Patients were included with a GCS ≤ 8 , or > 8 with positive CT findings; only 18.8% had a GCS ≤ 8 , rendering the evidence as indirect for this study. Groups were comparable on age, gender, Injury Severity Score, intubation rates, GCS of ≤ 8 , Head Abbreviated Injury Score of ≥ 3 , and Marshall scores. No significant differences were

found in seizure rates, adverse drug reactions, complications, or mortality. The results of this study suggest no benefit of one drug over the other, but because it is a single study consisting of indirect evidence, it cannot be used to support a recommendation.⁴

Class 3 Studies

The evidence from the Class 3 studies of seizure prophylaxis is summarized in Table 11-3.

Table 11-3. Summary of Evidence – Class 3 Studies (Seizure Prophylaxis)

| Reference Study Topic | Study Design, N and Outcomes | Data Class | Results Conclusion |
|--|---|------------|---|
| New Studies | | | |
| Bhullar 2013* ⁸ Compared PHT to no AED for prevention of early seizures | Retrospective Cohort N=93 Treatment=50 Control=43 Seizures within 7 days following TBI. | Class 3 | No significant difference in early seizure rates, ICU LOS, ventilator days, or TBI-caused mortality. Treatment group had significantly longer hospital stay and worse functional outcome at discharge (GOS 3.4 +/- 1.1 vs. 2.9 +/- 1.0, p=0.01). |
| Jones 2008* ⁹ Equivalence study of LEV and PHT for seizure prophylaxis. | Prospective cohort vs. historical controls. N=73 LEV=32 PHT=41 Only patients with EEG included in analysis. N=27 LEV=15 PHT=12 Early seizures and dichotomized GOS at 3 and 6 months post-injury. | Class 3 | Seizure activity equivalent between groups. Higher incidence of seizure activity in levetiracetam group (p=0.003). No difference in GOS at 3 and 6 months post-injury. |
| Ma 2010* ⁶ Assessment of sodium valproate for prevention of early PTS | Retrospective Cohort N=159 Treatment=35 Control=124 Early posttraumatic seizures defined as seizures within the first week following TBI. | Class 3 | The incidence of early PTS Sodium valproate treatment vs. control 0 vs. 4.4%, $\chi^2=0.5529$, p>0.05. There were fewer early PTS with sodium valproate but the difference between the treatment and control group was not statistically significant. |

| Reference Study Topic | Study Design, N and Outcomes | Data Class | Results Conclusion |
|--|---|------------|---|
| Szaflarski 2010* ⁷ LEV vs. PHT for seizure prophylaxis | Prospective, randomized, single-blinded comparative trial N=52 89% with TBI LEV=34 PHT=18 Clinical adverse events including Seizures, fever, neurological changes, cardiovascular, hematologic and dermatologic abnormalities, liver failure, renal failure, LOS in hospital and death. Secondary endpoints were seizure frequency and long-term outcomes (seizures, GOSE, DRS). | Class 3 | LEV vs. PHT Seizure during cEEG:5/34 vs. 3/18, p=1.0 Seizure at 6 months: 1/20 vs. 0/14, p=1.0 Mortality 14/34 vs. 4/18, p=0.227. Average GOS at 6 months 5 vs. 3 p=0.016* (higher score is better functional outcome). *surviving patients only No difference in side effects except Worse neuro status 6/34 vs. 9/18, p=0.024 Gastrointestinal problems: 1/34 vs. 4/18, p=0.043. Patients treated with PHT or LEV have the same outcomes with respect to death or seizures. LEV results in less undesirable side effects and better long-term outcomes for surviving patients. |
| Studies from 3rd Edition | | | |
| Manaka 1992 ¹³ Phenobarbital vs. placebo for late PTS | Randomized, double-blind study of 126 patients receiving placebo or phenobarbital for effect on late PTS. Treatment was started 1 month following TBI. | Class 3 | No significant effect of phenobarbital on late PTS. |
| Young 1983 ¹⁴ PHT vs. placebo for early and late PTS | Randomized, double-blind study of 244 patients receiving placebo vs. phenytoin for the prevention of early and late PTS. | Class 3 | No significant effect of phenytoin on early or late PTS |

Abbreviations: AED=anti-epileptic drug, DRS=Disability Rating Scale, EEG=electroencephalography, ICU=intensive care unit, GOSE=Glasgow Outcome Scale Extended, LEV=levetiracetam, LOS=length of stay, PHT=phenytoin, PTS=post-traumatic seizure, TBI=traumatic brain injury.

***References new to the 4th Edition.**

Of the four Class 3 studies included since the 3rd Edition of these guidelines, two were retrospective,^{6,8} one was a prospective cohort compared with historical controls,⁹ and one was an RCT.⁷ Both Class 3 studies maintained from the 3rd Edition were RCTs.^{13,14}

Three of these studies reported no consistent positive impact on primary outcomes such as seizures, mortality, or neurological function when comparing different anti-seizure medications and placebos.^{6,13,14} As seizures are a relatively rare event, these studies may not have been large enough to detect a difference. Bhullar et al. found no difference between phenytoin and no anti-

epileptic drug treatment in early seizure rates, ICU length of stay, ventilator days, or TBI-related mortality (N=93). However, the treatment group had significantly longer hospital length of stays and worse functional outcomes at discharge (GOS 3.4 +/- 1.1 vs. 2.9 +/- 1.0, p=0.01).

Szaflarski et al. found that patients who survived had a higher score on the Extended Glasgow Outcome Scale (GOS-E) at 6 months post-injury if they were treated with levetiracetam instead of phenytoin.⁷ This study also reported that some side effects (2 out of 12 studied) were less frequent with levetiracetam. Although an RCT, issues with random assignment, allocation concealment, sample size, and maintenance of comparable groups render this a Class 3 study. In a sample of 73, 27 of which were used in the analysis, Jones et al. found equivalence with levetiracetam and phenytoin for rate of early seizures, and no difference in the dichotomized GOS at 3 and 6 months post-trauma. This study was under-powered to determine equivalence or outcomes.

Additionally, Young et al. reported results suggesting that higher levels of the medications may be more effective in preventing late PTS.¹⁴ No patient with a phenytoin plasma concentration of 12 mcg/ml or higher had a seizure.

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Evidence Synthesis and Recommendations, Part II: Monitoring

It is not monitoring per se that affects outcomes; rather, it is using the information from monitoring to direct treatment. Treatment informed by data from monitoring may result in better outcomes than treatment informed solely by data from clinical assessment. This section of the guidelines includes the evidence and recommendations related to the influence on patient outcomes of three types of monitoring: intracranial pressure (ICP), cerebral perfusion pressure monitoring (CPP), and advanced cerebral monitoring (ACM).

While we reviewed and report on these monitoring modalities separately, it is important to acknowledge that clinical practice in most high-income countries incorporates multiple monitoring approaches as well as ongoing clinical assessment. As such, treatment decisions are not made using one source of information in isolation. Conversely, limited resources in low-and-middle-income countries often do not allow for monitoring, and medical decisions may be driven by clinical assessment alone. Therefore, the application of these guidelines will vary depending upon the medical environment in which they are used.

Changes from the 3rd Edition

In the 3rd Edition of the guidelines, there were three sections about ICP monitoring: Indications, Technology, and Thresholds. *Indications for ICP Monitoring* was organized around the sub-questions of who to monitor, the utility of information from the monitor, and the influence of the information on outcomes for patients. For the first and second sub-questions, the studies in the 3rd Edition do not meet the inclusion criteria for this update, and therefore have been dropped. For the third sub-question, four Class 3 studies have been maintained.¹⁻⁴ Two studies that had been rated Class 2 in the 3rd Edition have been excluded.^{5,6} Eisenberg, 1988 was an RCT of barbiturates.⁵ It was not designed to test ICP-directed management (it remains in the section about barbiturates). The second study, Palmer 2001, was a pre/post natural experiment.⁶ It compared a patient cohort treated before implementation of the guidelines to a different cohort treated after implementation of the guidelines. All patients had ICP monitors; the study did not have a non-monitored comparison group, and thus was excluded in this edition as it was not designed to assess the impact of using a monitor to guide treatment on outcomes.

As is indicated below, no new studies were identified to address the sub-questions from the 3rd Edition about who to monitor and about the utility of the ICP monitor. The third sub-question about the influence of information from the ICP monitor on outcomes was maintained and addressed in this 4th Edition.

The *ICP Monitoring Technology* topic in the 3rd Edition included a description and ranking of the technologies available for ICP. Assessing technology utilizes different methods and standards than conducting a systematic review of evidence or developing treatment guidelines. For this reason, the technology topic is no longer included in the guidelines.

The *Intracranial Pressure Thresholds* topic from the 3rd Edition was expanded for the 4th Edition and was moved into a section on thresholds that includes thresholds for blood pressure, CPP, and ACM, as well as ICP.

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12. Intracranial Pressure Monitoring

INTRODUCTION

A mainstay of the care of the patients with the most severe brain injuries has been the monitoring of—and treatment of—intracranial pressure (ICP). Decades ago, it was recognized that cerebral swelling after traumatic injury to the brain can lead to brain herniation syndromes, with the brain being forced under pressure into abnormal anatomical spaces, which leads first to death of those areas of the brain and ultimately of the brain itself. At the advent of contemporary critical care, technological advances to measure intracranial pressure by placement of devices within the brain became available, which allowed clinicians to titrate therapies based on objective information from ICP monitors.¹

Because of its fundamental place in the care of patients with severe traumatic brain injury (TBI) and its relationship to overall outcomes, ICP monitoring has been included in every guideline for severe TBI published by the Brain Trauma Foundation. In the developed world, ICP monitoring is routinely used, leading to a lack of equipoise for assigning patients to a “non-monitored” arm of potential interventional trials. Therefore, in many studies, the evidence supporting the utility of ICP monitoring was observational in nature and largely found that ICP crises led to poorer outcomes.²⁻⁵ A recent study has challenged this paradigm by randomizing patients to protocols to treat intracranial hypertension therapies based on either an invasive ICP monitor or a clinical/radiological examination.⁶ This study, performed in a region of the world where equipoise existed for a non-monitored group of patients, failed to find differences between the groups. Summaries of the studies are outlined below. What is clear from the literature is that intracranial hypertension is an important secondary insult after severe TBI, and its alleviation plays a pivotal role in providing good patient care to achieve optimal outcomes.

RECOMMENDATIONS

Level I and II A

- There was insufficient evidence to support a Level I or II A recommendation for this topic.

Level II B

- Management of severe TBI patients using information from ICP monitoring is recommended to reduce in-hospital and 2-week post-injury mortality.

As noted above in the introduction to this “Part II. Monitoring” section, the Level II and III recommendations from the 3rd Edition of these guidelines were not carried forward because they were derived from descriptive studies, or from studies that do not meet the current inclusion criteria for this topic. While no evidence is available from comparative studies to support a formal recommendation, the Committee chose to re-state here the 3rd Edition recommendations. The rationale for doing so is to maintain sufficient recognition of the patient characteristics associated with risk of increased intracranial pressure. (Refer to the 3rd Edition for summary of supporting studies.)

Recommendations from the Prior (3rd) Edition Not Supported by Evidence Meeting Current Standards

- Intracranial pressure (ICP) should be monitored in all salvageable patients with a severe traumatic brain injury (TBI) (GCS 3-8 after resuscitation) and an abnormal computed tomography (CT) scan. An abnormal CT scan of the head is one that reveals hematomas, contusions, swelling, herniation, or compressed basal cisterns.
- 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 over 40 years, unilateral or bilateral motor posturing, or systolic blood pressure (BP) <90 mm Hg.

Changes from Prior Edition

New Class 2 studies provide evidence for recommendations that replace those of the 3rd Edition of these guidelines. See the introduction to this “Part II. Monitoring” section (above) for details about changes from the 3rd Edition.

EVALUATION OF THE EVIDENCE

Quality of the Body of Evidence

The five Class 1 and 2 studies included for this topic addressed the question of the influence on outcomes of information from the ICP monitor to direct management of patients with severe

TBI.²⁻⁶ The overall quality of the body of evidence was moderate; however, the consistency across studies was low (Table 12-1).

There was high-quality evidence from a multi-center, Class 1 RCT (N=324) that outcomes for patients managed with information from clinical assessment *do not differ* from those for patients managed with information from the ICP monitor.⁶ *As such, the findings do not constitute the basis for a recommendation to use either method preferentially.* There was moderate-quality evidence from four Class 2 observational studies (N=13,164) that treatment guided by information from the ICP monitor results in decreased in-hospital and 2-week post-injury mortality.²⁻⁵ Taking into consideration the applicability of the individual studies (discussed below), the results of the randomized controlled trial (RCT) temper, but do not negate, the results of the observational studies.

Five new Class 3 studies⁷⁻¹¹ and four from the 3rd Edition of these guidelines¹²⁻¹⁵ are reported in the Evidence Table and Summary section below; however, given that higher-quality evidence was available, they were not included in the assessment of the body of evidence and were not used to inform the recommendations.

Table 12-1. Quality of the Body of Evidence (Intracranial Pressure Monitoring)

| COMPONENTS OF OVERALL QUALITY – Class 1 and 2 | | | | | | | | |
|---|-------------------|--|--------------------|------------------------------------|-----------------------------------|---------------------------------|---------------------------------|--|
| Topic | Number of Studies | Meta-Analysis | Number of Subjects | Class of Studies (1or 2) | Consistency (High, Moderate, Low) | Directness (Direct or Indirect) | Precision (High, Moderate, Low) | Quality of Evidence (High, Moderate, Low, or Insufficient) |
| Use of information from the ICP monitor to guide treatment ²⁻⁶ | 4 Cohort 1 RCT | No: different study designs, outcomes, and populations | 13,488 | Class 1: 1 Class 2: 4 | Low | Direct | Moderate | Low |

Abbreviations: ICP=intracranial pressure, RCT=randomized controlled trial.

Applicability

Two of the studies used the same database.^{3,4} Their strengths are large sample size, multiple sites, and study duration over almost 10 years. However, all sites were in New York State, and the practice environment and patient populations may differ from those of other geographic regions. Alali 2013 reported on a very large sample taken from multiple centers across the

United States and Canada,² while Talving 2013 analyzed data from a single Level I trauma center in California.⁵

The Class 1 RCT was conducted in countries with very limited pre-hospital care, and where monitors are not common. This has raised concerns about applicability for some researchers and clinicians. Detailed discussions of these concerns are available in publications by the studies' authors as well as others.¹⁶⁻³⁴

SUMMARY OF THE EVIDENCE

Process

Of 40 new, potentially relevant studies reviewed, 30 were excluded because they did not meet the inclusion criteria for this topic (see Appendix F). Of the remaining 10, one new Class 1 study,⁶ four new Class 2 studies,²⁻⁵ and five new Class 3 studies were included as evidence,⁷⁻¹¹ along with four Class 3 studies from the 3rd Edition.¹²⁻¹⁵

Class 1 and 2 Studies

The evidence from Class 1 and 2 studies of intracranial pressure monitoring is summarized in Table 12-2.

Table 12-2. Summary of Evidence: Class 1 and 2 Studies (Intracranial Pressure Monitoring)

| Reference Study Topic | Study Design, N, Setting and Outcomes | Data Class | Results Conclusion |
|---|--|------------|---|
| Influence on outcomes of information from ICP monitor to guide treatment | | | |
| Alali, 2013² Assessed relationships between ICP monitoring and mortality | Retrospective Cohort N=10,628 patients ICP monitored=1,874 (17.6%) 155 level I and II Trauma Centers in the United States and Canada In-hospital mortality | Class 2 | ICP monitoring was associated with significantly lower odds of death (adjusted odds ratio 0.44; 95% CI 0.31 to 0.63, p<0.0001, patient-level analysis). The association between ICP monitoring and lower mortality was more pronounced in patients under 65. At the hospital level, hospitals with higher levels of ICP monitoring had lower mortality. However the variability in ICP monitoring explained only a small portion of the variability in mortality. |

| Reference Study Topic | Study Design, N, Setting and Outcomes | Data Class | Results Conclusion | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
|--|---|------------|---|-------|---|-------|-------|-------|-------|-------|-------|-------|-------------|-----|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-----------|----------|-------|-------|-------|-------|-------|-------|-------|-------|-------|
| Chesnut, 2012* ⁶ Comparison of outcomes for patients whose treatment was informed by ICP monitoring with those whose treatment was informed by imaging and clinical exam. | RCT N=324 ICP monitored=157 Imaging=167 6 hospitals in Bolivia and Ecuador with ICUs with intensivists, 24-hour CT, neurosurgery, and high volume of trauma. Mortality and GOS-E at 6 months. Composite of 21 measures of function and cognitive status. | Class 1 | <u>6-month mortality</u> ICP - 39% Imaging - 41%, p=0.6. <u>GOS- E 6 months</u> Unfavorable Outcome ICP=24 (17%) Imaging=26 (17%) Favorable Outcome ICP=63 (44%) Imaging=60 (39%), p=0.4. <u>Composite of 21 measures</u> ICP=56, Imaging=53, p=0.4. Results did not support the hypothesized superiority of ICP monitoring over clinical assessment in this environment. | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Farahvar, 2012* ³ Comparison of patients with ICP monitors vs. those who did not receive monitors; all patients received at least 1 of 5 intracranial hypertension-targeting treatments | Retrospective Cohort N=1,307 ICP Monitored=1,084 No Monitor=223 20 New York State Level I and II Trauma Centers Mortality at 2 weeks | Class 2 | <u>Adjusted OR for 2-week mortality</u> <u>Adults</u> OR 0.64; 95% CI 0.41-1.00; p=0.05. <u>All ages</u> (N=1446; includes 139 patients under 16 years old) OR 0.63; 95% CI 0.41-0.94; p=0.02. | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Gerber, 2013* ⁴ Comparison of trends over time in mortality with guideline adherence | Retrospective Cohort Study N=2,320 ICP Monitored: 1,966 New York State Trauma Centers: Level I (20) and Level II (2) 2-week mortality | Class 2 | <u>Age adjusted mortality 2001-2009</u> <table border="1"> <thead> <tr> <th>Years</th> <th>%</th> </tr> </thead> <tbody> <tr> <td>01-03</td> <td>22.4%</td> </tr> <tr> <td>04-06</td> <td>19.7%</td> </tr> <tr> <td>07-09</td> <td>13.3%</td> </tr> </tbody> </table> <u>Compliance with Guidelines</u> <table border="1"> <thead> <tr> <th>Years</th> <th>ICP Monitor</th> <th>CPP</th> </tr> </thead> <tbody> <tr> <td>01-03</td> <td>55.6%</td> <td>14.6%</td> </tr> <tr> <td>04-06</td> <td>72.3%</td> <td>34.2%</td> </tr> <tr> <td>07-09</td> <td>75.2%</td> <td>48.2%</td> </tr> </tbody> </table> <table border="1"> <thead> <tr> <th>Years</th> <th>Nutrition</th> <th>Steroids</th> </tr> </thead> <tbody> <tr> <td>01-03</td> <td>41.0%</td> <td>97.7%</td> </tr> <tr> <td>04-06</td> <td>46.4%</td> <td>96.4%</td> </tr> <tr> <td>07-09</td> <td>50.1%</td> <td>98.6%</td> </tr> </tbody> </table> Significant decrease in mortality appears to be associated with increase in adherence to guidelines, particularly ICP and CPP management. | Years | % | 01-03 | 22.4% | 04-06 | 19.7% | 07-09 | 13.3% | Years | ICP Monitor | CPP | 01-03 | 55.6% | 14.6% | 04-06 | 72.3% | 34.2% | 07-09 | 75.2% | 48.2% | Years | Nutrition | Steroids | 01-03 | 41.0% | 97.7% | 04-06 | 46.4% | 96.4% | 07-09 | 50.1% | 98.6% |
| Years | % | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 01-03 | 22.4% | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 04-06 | 19.7% | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 07-09 | 13.3% | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Years | ICP Monitor | CPP | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 01-03 | 55.6% | 14.6% | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 04-06 | 72.3% | 34.2% | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 07-09 | 75.2% | 48.2% | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Years | Nutrition | Steroids | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 01-03 | 41.0% | 97.7% | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 04-06 | 46.4% | 96.4% | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 07-09 | 50.1% | 98.6% | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |

| Reference Study Topic | Study Design, N, Setting and Outcomes | Data Class | Results Conclusion |
|--|--|------------|---|
| Talving, 2013* ⁵ Comparison of patients with and without ICP monitoring | Prospective Cohort N=216 ICP Monitored=101 No Monitor=115 Single Level I Trauma Center in California In hospital Mortality Mortality due to brain herniation ICU and Hospital LOS | Class 2 | <u>Adjusted OR Mortality</u> (no ICP is referenced). OR 0.15; 95% CI -0.03 to 0.74, p=0.019. due to Brain Herniation OR 0.34; 95% CI 0.10 to 0.87, p=0.046. <u>ICU and Hospital LOS</u> Longer in ICP group even before and after excluding deaths. |

Abbreviations: CPP=cerebral perfusion pressure, CT=computed tomography, GOS=Glasgow Outcome Scale, ICP=intracranial pressure monitoring, ICU=intensive care units, LOS=length of stay, N=total sample size, OR=odds ratio, RCT=randomized controlled trial.

***References new to the 4th Edition.**

Chesnut et al., 2012 conducted a multi-center RCT in Bolivia and Ecuador that compared management guided by ICP monitoring to management guided by imaging and clinical assessment, and found no difference in 6-month mortality.⁶ This was a tightly controlled trial in which patients were successfully randomized, the management for both the ICP group and the imaging group was standardized, and fidelity to the protocols was tracked. As a result, the internal validity of this study is high and it was rated as Class 1.

This study also found reduced treatment time in the ICP monitor group and reduced incidence of pressure ulcers in the clinical assessment group. In addition, it suggested that titration of treatment to manage ICP could be influenced by CT findings and exam, and that these two forms of assessment may be able to contribute additional insight into the management of brain swelling after TBI, even in patients who have ICP monitors. Although the evidence from this study was not used to contribute to a recommendation in these guidelines (outcomes for treatment and control groups did not differ, therefore neither approach is recommended over the other), the study may contribute an empirically-based algorithm—based on its CT and clinical examination protocol—for the treatment of increased ICP in low technology settings.

The other included studies that address this question used observational study designs and were rated Class 2, indicating that the internal validity of these studies is not as strong as that of the RCT.

Gerber et al., 2013 conducted a Class 2 retrospective cohort study that analyzed trends in adherence to specific guideline recommendations and 2-week mortality between 2001 and 2009.⁴ The analysis documented a significant decrease in mortality at the same time as an increase in compliance with the selected guideline recommendations. Guideline adherence for ICP monitoring varied across participating hospitals, and the rate of change in adherence to other elements of the guidelines (e.g., nutrition and steroids) was less than the rate of changes in ICP and cerebral perfusion pressure (CPP) monitoring during the study period. However, while the change in practice and the decrease in mortality occurred at the same time, it is difficult to establish causality using this study design. These findings suggest the need for future research about the patterns and determinants of guidelines adherence, and the possible inclusion of such a topic in future guidelines.

Alali 2013² and Talving 2013⁵ both identified groups of patients who, according to the Brain Trauma Foundation guidelines should have received ICP monitoring, and they compared outcomes for patients who were monitored to those who were not. They found that those who were monitored had lower odds of mortality. The study by Alali retrospectively identified 10,628 patients treated at 155 Level I and II trauma centers in the United States and Canada. Data were obtained from hospital records about whether or not patients were monitored and patients' in-hospital survival status. Treatments were not controlled, and details about treatment were not reported. The study's hospital-level analysis suggests that care likely varied across hospitals. This restricts the ability to attribute the cause of the lower mortality to the ICP monitor-driven treatment alone. However, the large number of hospitals and their geographic distribution increases the likelihood, but does not guarantee, that similar results would be obtained in other time periods or settings.

Talving 2013 prospectively followed a group of 216 patients who met the criteria for monitoring and who were admitted to a single Level I medical center in California.⁵ They found that in-hospital mortality (both all-cause and mortality due to brain herniation) was significantly lower for monitored patients. The treatments were not controlled or documented, though the authors speculate that some of the patients who were not monitored may have been treated less intensely. The prospective design allowed data to be collected from the treating physicians about why an ICP monitor was not placed. The most common reason was physician discretion. No

further detail was provided. The prospective design increases confidence that all eligible patients were included and minimizes the likelihood of missing data. However, as it was conducted in one medical center, the applicability may be more limited than studies conducted at multiple sites.

In another observational study, Farahvar et al. defined the population as patients with severe TBI who received at least one of five specific ICP-lowering therapies.³ Defining the population this way limited inclusion to only patients considered at high risk for intracranial hypertension or who had documented intracranial hypertension, either through monitoring or clinical assessment. Thus, the population was more specific than those in the Alali or Talving studies.^{2,5} While the Brain Trauma Foundation criteria were designed to identify patients at risk for intracranial hypertension (ICH), there may be patients who meet these criteria for whom monitoring is not appropriate. Using the subset of the population treated for ICH increases the likelihood that the patients who were monitored and those who were not monitored were similar, thereby contributing to the internal validity. Therefore, the interpretation of the results can also be more specific; the conclusion is that treatment directed by ICP monitoring results in better outcomes for patients with or at high risk for intracranial hypertension. However, using treatment to identify the comparison group may make it difficult to replicate the results, as there are no standards for using ICP-lowering therapy when a patient's ICP is not monitored. Whether this is a serious threat to the generalizability of results cannot be known until attempts are made to replicate the results.

The approach taken by Farahvar et al. is problematic in terms of application to clinical practice. It is possible to use treatment to identify a population to study retrospectively, but a clinician needs to decide whether to monitor a patient before and during, not after, treatment. Thus, while this study offers a stronger conclusion about the benefit of monitoring, it does not offer a practical application for how to implement more targeted monitoring that could replicate these gains in patient survival.

Class 3 Studies

The evidence from the Class 3 studies of intracranial pressure monitoring is summarized in Table 12-3.

Table 12-3. Summary of Evidence – Class 3 Studies (Intracranial Pressure Monitoring)

| Reference Study Topic | Study Description | Data Class | Results Conclusion |
|---|--|------------|---|
| Influence on outcomes of information from ICP monitor to guide treatment | | | |
| New Studies | | | |
| Haddad 2011*⁷ Assessed relationship between ICP monitoring and outcomes | Retrospective Cohort N=477 ICP monitored=52 (10.9%) Single Tertiary Care Teaching Hospital in Riyadh, Saudi Arabia In-hospital Mortality ICU mortality Mechanical Ventilation Days Tracheostomy ICU and Hospital LOS | Class 3 | ICP monitoring vs. None Hospital Mortality OR 1.71, 95% CI 0.79 to 3.70, p=0.17. ICU mortality OR 1.01, 95% CI 0.41 to 2.45, p=0.99, (respectively). Need for tracheostomy OR 2.02, 95% CI 1.02 to 4.03, p=0.04. Hospital LOS OR 8.32, 95% CI -82.6 to 99.25, p=0.86. Mechanical ventilation duration OR 5.66, 95% CI 3.45 to 7.88, p<0.0001. ICU LOS OR 5.62, 95% CI 3.27 to 7.98, p<0.0001. |
| Kostic 2011*⁸ Compared ICP with no ICP for mortality | RCT N=61 ICP monitored: 32 (52.5%) Single Center in Serbia | Class 3 | ICP vs. no ICP Survival rate $\chi^2=2.11$; p=0.15; p>0.05. No significant difference. |
| Liew 2009*⁹ Compared 3 groups (ICP/ CPP monitored, ventilated, or intubated) on mortality and discharge, 3-month, and 6-month GOS | Prospective Cohort N=72 ICP/ CPP: 15 Ventilated: 16 Intubated: 41 Single Center in Johor Bahru, Malaysia. Mortality and GOS | Class 3 | ICP vs. Ventilation Group Higher risk of mortality (p<0.001), Worse GCS improvement upon discharge (p<0.001) Longer ICU LOS (p=0.016). There were no significant differences in GOS at 3 and 6 months post-injury between across all three groups. |
| Mauritz 2008*¹⁰ Identified reasons why patients did or did not receive ICP monitoring; identify factors influencing hospital mortality | Prospective Cohort N=1,856 ICP monitored=1031 (55.5%) 32 Centers in Austria Mortality | Class 3 | ICP vs. No ICP Hospital Mortality 39% vs. 38% p=NS ICU Mortality 35% vs. 34% p=NS Results addressing characteristics associated with whether a patient was monitored or not are reported in the article but not repeated here as the guideline focuses on the impact of monitoring on outcomes. |

| Reference Study Topic | Study Description | Data Class | Results Conclusion |
|---------------------------------|---|------------|---|
| Shafi 2008* ¹¹ | Retrospective Cohort N=1646 ICP monitored: 708 (43%) Centers participating in the National Trauma Data Bank Mortality | Class 3 | ICP monitoring was associated with a 45% reduction in survival (OR 0.55; 95% CI 0.39 to 0.76; p<0.001). |
| Studies from 3rd Edition | | | |
| Cremer 2005 ¹² | Retrospective study with prospective outcome data collection comparing mortality and 12-month GOS in severe TBI patients treated in 2 hospitals, one with ICP monitoring (n=211) and the other without (n=122). | Class 3 | No significant difference in mortality or GOS at 12 months. Baseline differences between groups in hypotension on admission and number of patients transferred from other hospitals. |
| Fakhry 2004 ¹³ | Retrospective comparison of mortality and outcomes for severe TBI patients in three groups: 1) before the use of guidelines-based protocol (1991 to 1994, n=219) 2) after initiation of the protocol with low compliance (1995 to 1996, n=188) 3) after initiation of the protocol with high compliance (1997 to 2000, n=423). | Class 3 | Significant decrease in mortality between patients from 1991-1996 and those from 1997-2000 (4.5%, p=0.047). Significantly more patients with GOS scores of 4 or 5 in the 1997-2000 cohort (61.5%) than in the 1995-1996 (50.3%) or 1991-1994 (43.3%) cohorts (p<0.001). |
| Lane 2000 ¹⁴ | Retrospective review of the Ontario Trauma Registry evaluating 5,507 severe TBI patients, 541 with ICP monitoring. | Class 3 | When severity of injury was controlled for, ICP monitoring was associated with improved survival. |
| Patel 2002 ¹⁵ | Comparative retrospective review of severe TBI patients from two time periods, pre (1991 to 1993, n=53) and post (1994 to 1997, n=129) establishment of a dedicated NCCU. | Class 3 | Patients treated in the pre-establishment group (n=53) had 59% ICP monitoring. Patients in the post-establishment group (n=129) had 96% ICP monitoring. Significantly better 6-month GOS scores in the post-establishment group. |

Abbreviations: CPP=cerebral perfusion pressure, CT=computed tomography, GCS=Glasgow Coma Scale, GOS=Glasgow Outcome Scale, ICP=intracranial pressure monitoring ICU=intensive care unit, LOS=length of stay, N=total sample size, NCCU=Neurosciences Critical Care Unit, NS=not significant, OR=odds ratio, RCT=randomized controlled trial.

***References new to the 4th Edition.**

Of the five new Class 3 studies included since the 3rd Edition of these guidelines, one was an RCT in which patients were randomized to ICP monitoring or no ICP monitoring.⁸ Due to concerns about randomization, allocation concealment, sample size, and potential selection bias, the findings from this study cannot be used to support a Level I or II recommendation.

Two retrospective studies^{7,11} and two prospective cohort studies^{9,10} compared outcomes for patients who received ICP monitoring with those who did not. Of 4,112 total patients observed,

1,838 were monitored (44.7%). There was no association between monitoring and (a) mortality in three studies, (b) hospital length of stay (LOS) in one study, and (c) Glasgow Outcome Scale (GOS) at 3 and 6 months in one study. There was a significant association between monitoring and (a) increased mechanical ventilation time in one study, (b) need for tracheostomy in one study, and (c) ICU length of stay in two studies.

The four Class 3 studies maintained from the 3rd Edition were retrospective.¹²⁻¹⁵ One compared outcomes for patients from two hospitals (one used ICP monitors and the other did not); one compared monitored versus non-monitored patients; one compared cohorts of patients from pre-guidelines protocols versus post-guidelines protocols; and one compared cohorts of patients from time periods with low ICP monitoring compliance versus high ICP monitoring compliance. A total of 1,886 patients were observed. Two studies found decreased mortality and two improved outcomes in the monitored groups; one found no difference in mortality.

Due to the observational nature of these studies, the reasons for selecting patients for monitoring could be determinants of the observed outcomes, independent of the influence of the information from ICP monitoring. As such, they were rated Class 3.

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13. Cerebral Perfusion Pressure Monitoring

INTRODUCTION

Cerebral perfusion pressure (CPP) is defined as the pressure gradient across the cerebral vascular bed, between blood inflow and outflow. Inflow pressure is taken as mean arterial pressure (MAP), which by convention is calibrated to the level of the right atrium of the heart. In normal physiology the outflow or downstream pressure is the jugular venous pressure (JVP), which is also calibrated to the level of the right atrium. Traumatic brain injury (TBI) is a special pathological state in which pressure surrounding cerebral vessels—intracranial pressure (ICP)—is elevated and higher than the JVP. In this circumstance CPP will be proportional to the gradient between MAP and mean ICP, and changes in CPP can occur with alterations in either MAP or ICP.¹

Cerebral autoregulation is defined as the maintenance of cerebral blood flow (CBF) over a wide range of CPPs, brought about by homeostatic change in cerebral vascular resistance.² Thus, assuming that CPP provides the stimulus for cerebral autoregulation, no change in flow would be anticipated as long as the CPP remained within the upper and lower limits of autoregulation. TBI management includes CPP monitoring in the “bundle” of care. However, the question remains as to whether CPP can, itself, influence outcome, separate from MAP and ICP monitoring.

RECOMMENDATIONS

Level I

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

Level II B

- Management of severe TBI patients using guidelines-based recommendations for CPP monitoring is recommended to decrease 2-week mortality.

Changes from Prior Edition

In the 3rd Edition of these guidelines, CPP monitoring and thresholds were combined into one section. In this edition they are reported separately with new evidence added. Of the 11 publications included in the section about CPP in the 3rd Edition, seven provided information about thresholds and are addressed in that topic, and one was eliminated because it is not

comparative and thus does not meet the criteria for this review. Four are summarized in this topic (one was used for both CPP topics). The recommendations from the 3rd Edition were about thresholds and are addressed in that topic in this 4th Edition. One study rated Class 2 in the 3rd Edition³ was reevaluated and rated Class 3.

EVALUATION OF THE EVIDENCE

Quality of the Body of Evidence

The quality of the body of evidence on CPP monitoring appears in Table 13-1. Three new studies were identified relevant to the use of CPP monitoring to manage hospitalized patients with severe TBI.⁴⁻⁶ One that was rated Class 2⁴ assessed the influence on outcomes of guidelines-based protocols (which require ICP and CPP monitoring). This study provided moderate-quality evidence that management guided by information from CPP monitoring leads to decreased mortality at 2 weeks post-injury. The new Class 3 studies^{5,6} and four from the 3rd Edition of these guidelines^{3,7-9} are summarized in Table 13-3 and the text below, but are not used for recommendations and are not included in the overall body of evidence.

Table 13-1. Quality of the Body of Evidence (Cerebral Perfusion Pressure Monitoring)

| Topic | Number of Studies | Meta-Analysis | Number of Subjects | Class of Studies | Consistency (High, Moderate, Low) | Directness (Direct or Indirect) | Precision (High, Moderate, Low) | Quality of Evidence (High, Moderate, Low, or Insufficient) |
|--|---|---------------|--------------------|------------------|-----------------------------------|---------------------------------|---------------------------------|--|
| COMPONENTS OF OVERALL QUALITY – Class 2 | | | | | | | | |
| Use of guidelines based protocols that include CPP monitoring ⁴ | 1 Cohort 0 RCT | NA | 2,320 | 2 | NA | Direct | Low | Low |
| COMPONENTS OF OVERALL QUALITY – Class 3 | | | | | | | | |
| Evaluation of CPP-driven management ^{3, 7-9} | 1 RCT 4 Pro-spective 1 Retro-spective | NA | 944 | 3 | Low | Direct | Low | Insufficient |

Abbreviations: CPP=cerebral perfusion pressure, NA=not applicable, RCT=randomized controlled trial.

Applicability

The study included 22 hospitals; however, they were all in one state (New York), suggesting the possibility of some limits to applicability if practice patterns in New York State differ significantly from those in other geographic areas.

SUMMARY OF THE EVIDENCE

Process

Of eight new, potentially relevant studies reviewed, five were excluded because they did not meet the inclusion criteria for this topic (see Appendix F). Of the remaining three, one was rated Class 2,⁴ and two were rated Class 3.^{5,6} These and four Class 3 studies from the 3rd Edition are included for this topic.^{3,7-9}

Class 2 Study

The evidence from the Class 2 study of CPP monitoring is summarized in Table 13-2.

Table 13-2. Summary of Evidence – Class 2 Study (Cerebral Perfusion Pressure Monitoring)

| Reference Study Topic | Study Design, N, Setting, and Outcomes | Data Class | Results Conclusion |
|--|---|------------|---|
| Influence on outcomes of adherence to guidelines-based protocols that require ICP monitoring | | | |
| Gerber, 2013*⁴ Comparison of trends over time in mortality with guideline adherence | Retrospective Cohort N=2,320 ICP Monitored (and thus CPP available for adherence to treatment thresholds): 1,966 out of 2,347 Monitored on Day 1 or 2: 1,506 New York State Trauma Centers: Level I (20) and Level II (2) 2-week mortality | Class 2 | <u>Age adjusted 2-week mortality</u> <u>Years</u> <u>%</u> 01-03 22.4% 04-06 19.7% 07-09 13.3% <u>Compliance with Guidelines</u> <u>ICP Monitor</u> <u>CPP</u> 01-03 55.6% 14.6% 04-06 72.3% 34.2% 07-09 75.2% 48.2% <u>Nutrition</u> <u>Steroids</u> 01-03 41.0% 97.7% 04-06 46.4% 96.4% 07-09 50.1% 98.6% Significant decrease in mortality appears to be associated with increase in adherence to guidelines, particularly management guided ICP and CPP monitoring. |

Abbreviations: CPP=cerebral perfusion pressure, ICP=intracranial pressure, N=total sample size.

***References new to the 4th Edition.**

Gerber et al., 2013 conducted a retrospective cohort study between 2001 and 2009 that analyzed trends in adherence to guidelines and 2-week mortality.⁴ They documented a significant

decrease in mortality at the same time as an increase in guidelines compliance, including CPP monitoring. The rate of increase in CPP monitoring was the highest of the guidelines components analyzed in the study. The applicability of this study is moderate. Its strengths are large sample size, multiple sites, and study duration over almost 10 years. However, all sites were in New York State, and the practice environment and patient populations may have differed from those of other geographic regions.

Class 3 Studies

The evidence from the Class 3 studies of CPP monitoring is summarized in Table 13-3.

Table 13-3. Summary of Evidence – Class 3 Studies (Cerebral Perfusion Pressure Monitoring)

| Reference Study Topic | Study Design, N, Setting, and Outcomes | Data Class | Results Conclusion |
|--|---|-------------------|--|
| New Studies | | | |
| Huang 2006* ⁵ Compared ICP-targeted to CPP-targeted therapy | Retrospective Cohort N=213 ICP-targeted: 84 CPP-targeted > 70 mm Hg: 77 mCPP-targeted > 60 mm Hg: 52 University Hospital in Taiwan Mortality Dichotomized GOS at 6 months post-injury | Class 3 | Mortality rate in ICP-targeted therapy group was significantly higher than that in the CPP and mCPP groups (p=0.02 and p=0.03, respectively) Favorable outcome in the ICP group was lower than in the CPP and mCPP groups (p=0.04 and p=0.01, respectively). No difference in mortality or outcomes between CPP and mCPP groups. |
| Johnson 2011* ⁶ Compared outcomes for patients with high/low CPA and high/low CPP | Prospective Cohort N=58 Group 1: Active CPA/low CPP: 10 Group 2: Active CPA/high CPP: 8 Group 3: Passive CPA/low CPP: 15 Group 4: Passive CPA/high CPP: 6 University Hospital in Sweden Dichotomized GOS-E | Class 3 | Favorable outcomes significantly higher in Group 3 (passive CPA/low CPP) than Group 4 (passive CPA/high CPP) (p=0.0067). No significant difference in outcomes between Group 2 (active CPA/high CPP) and Group 1 (active CPA/low CPP). |
| Studies from 3rd Edition | | | |
| Cruz 1998 ⁷ | Prospective observational study of 6-month outcomes in adults with severe TBI characterized by brain swelling where 178 were treated according to cerebral oxygen extraction and CPP and 175 were treated with management of CPP alone at values >70 mm Hg. | Class 3 | Mortality in the cohort managed according to jugular venous saturation was 9% vs. 30% in the CPP group. |

| Reference Study Topic | Study Design, N, Setting, and Outcomes | Data Class | Results Conclusion |
|-----------------------------|---|------------|---|
| Howells 2005 ⁸ | Prospective observation of 6-month outcome for 131 severe TBI adults who received either ICP (Lund) or CPP targeted acute care. | Class 3 | Patients with intact autoregulation had better outcomes with CPP elevation. Patients with defective autoregulation had better outcomes with ICP targeted acute care and lower CPPs of 50-60 mm Hg. |
| Robertson 1999 ³ | RCT comparing the influence of CPP- vs. ICP-targeted management on 6-month outcome in 189 adults with severe TBI. | Class 3 | No difference in outcome. ICP group had more jugular desaturations but these were rapidly managed. CPP group had more systemic complications. ARDS was 5 times greater in the CBF-targeted group (p=0.007). |
| Rosner 1990 ⁹ | Prospective study of outcomes in 34 TBI patients who were managed by actively keeping CPP above 70 mm Hg. | Class 3 | The mortality rate was 21%, and good recovery rate was 68%. |

Abbreviations: ARDS=acute respiratory distress syndrome, CBF= cerebral blood flow, CPA=cerebral perfusion autoregulation, CPP=cerebral perfusion pressure, ICP=intracranial pressure, GOS=Glasgow Outcome Scale, GOS-E=Extended Glasgow Outcome Scale, RCT=randomized controlled trial, TBI=traumatic brain injury.

Two new Class 3 studies^{5,6} and four from the 3rd Edition of these guidelines^{3,7-9} provided information about CPP monitoring. Four were prospective, one retrospective, and one was an RCT. All were from single centers. Outcomes included mortality and function measured by the Glasgow Outcome Scale, the Extended Glasgow Outcome Scale, and the Disability Rating Scale. A total of 944 patients were observed across studies, with sample sizes ranging from 58 to 353. Inconsistency in findings, as well as the low quality of the studies, does not allow for a Level III recommendation from these studies.

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14. Advanced Cerebral Monitoring

INTRODUCTION

Multiple pathophysiologic pathways that include local and systemic influences contribute to evolving brain damage after traumatic brain injury (TBI). When oxygen or glucose delivery to tissue is limited to the point that tissue needs are not met, metabolism fails and cells die. Advanced cerebral monitoring techniques for blood flow and oxygen include: transcranial Doppler (TCD)/duplex sonography, differences between arterial and arterio-jugular venous oxygen (AVDO₂), and measurements of local tissue oxygen. Arterio-jugular AVDO₂ globally measures cerebral oxygen extraction. However, the measured AVDO₂ can potentially differ from the other unmeasured hemisphere in TBI patients.¹ Tissue monitors are placed in the cerebral cortex and directly measure tissue oxygen in the immediate area. The relationship between brain tissue oxygen, oxygen delivery, and diffusion of dissolved oxygen across the blood brain barrier is not simple, and most studies using tissue oxygen monitors treat initial desaturation episodes with 100% inspired oxygen rather than a transfusion of red blood cells or vasopressor administration to improve cerebral perfusion pressure (CPP).²

Additional monitoring methods include microdialysis to measure brain metabolism (glucose, lactate, pyruvate, and glutamate) and electrocorticography to determine cortical spreading depression; however, use of these last two monitoring techniques is not common outside of research settings.

Theoretically, use of advanced monitoring in tandem with intracranial pressure (ICP) and CPP monitoring adds to the assessment of brain metabolic needs and the effects of therapies to meet them. However, all techniques have limitations and potential risks. This topic provides a systematic review of the literature pertaining to such monitoring in severe TBI.

RECOMMENDATIONS

Level I and II

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

(Although patients with desaturations identified with advanced cerebral monitoring have poorer outcomes, Level II evidence showed no improvement in outcomes for monitored patients.)

Level III

- Jugular bulb monitoring of arteriovenous oxygen content difference (AVDO₂), as a source of information for management decisions, may be considered to reduce mortality and improve outcomes at 3 and 6 months post-injury.

Changes from Prior Edition

In the 3rd Edition of these guidelines, monitoring and thresholds were combined into one section. In this 4th Edition they are reported separately, and this topic has been renamed Advanced Cerebral Monitoring (ACM). The Level III recommendation about monitoring AVDO₂ from the 3rd Edition was articulated as a statement, not a recommendation, and thus has been revised. The Level III recommendation about brain tissue oxygen monitoring has been removed because of higher-quality, contradictory evidence acquired since the 3rd Edition of these guidelines.

EVALUATION OF THE EVIDENCE

Quality of the Body of Evidence

The literature for this topic addresses four cerebral monitoring approaches: brain tissue oxygen (PbrO₂) monitoring, jugular bulb monitoring of arteriovenous oxygen content difference (AVDO₂), cerebral autoregulation monitoring with TCD, and microdialysis monitoring of extracellular glutamate.

Brain Tissue Oxygen (PbrO₂) Monitoring. One Class 2 study³ (Table 14-2) provided information showing that hypoxia detected by monitors is associated with worse outcomes but does not link treatment in response to PbrO₂ monitoring to outcomes. This rendered the overall quality of the body of evidence insufficient to support a Level II recommendation, particularly given the findings from this study were null. Six Class 3 studies⁴⁻⁹ addressed PbrO₂ monitoring, three of which found an effect, and three of which did not. The inconsistency across this body of evidence prevents its use to support a Level III recommendation. These studies are included in Table 14-3 and the summary section below.

Arteriovenous Oxygen Content Difference (AVDO₂). Four Class 3 studies¹⁰⁻¹³ constituted a low quality of the body of evidence about AVDO₂ monitoring and support a Level III recommendation.

Transcranial Doppler and Microdialysis. Two Class 3 studies were found, one each addressing the two remaining monitoring approaches, TCD¹⁴ and microdialysis.¹⁵ Given they were single-center Class III studies, and there was only one study for each of the approaches, the body of evidence is insufficient to support a Level III recommendation. The studies are included in Table 14-3 and the summary section below.

Table 14-1. Quality of the Body of Evidence (Advanced Cerebral Monitoring)

| Topic | Number of Studies | Meta-Analysis | Number of Subjects | Class of Studies | Consistency (High, Moderate, Low) | Directness (Direct or Indirect) | Precision (High, Moderate, Low) | Quality of Evidence (High, Moderate, Low, or Insufficient) |
|--|-------------------------|---------------|--------------------|------------------|-----------------------------------|---------------------------------|---------------------------------|--|
| COMPONENTS OF OVERALL QUALITY – Class 2 | | | | | | | | |
| PbrO ₂ monitoring ³ | 1 Cohort 0 RCT | NA | 629 | 2 | NA | Direct | Low | Insufficient |
| COMPONENTS OF OVERALL QUALITY – Class 3 | | | | | | | | |
| AVDO ₂ monitoring ¹⁰⁻¹³ | 4 Prospective cohort | NA | 678 | 3 | High | Direct | Low | Low |

Abbreviations: NA=not applicable, RCT=randomized controlled trial.

Note: Different abbreviations such as pBtO₂/PbtO₂ and P_{ti}O₂ are used to mean brain tissue oxygen monitoring and brain tissue oxygen tension; we use PbrO₂ for consistency, which may differ from what the study authors used.

Applicability

All patients in these studies were from single centers, which limited their applicability.

SUMMARY OF THE EVIDENCE

Process

Of 51 new, potentially relevant studies reviewed, 42 were excluded because they did not meet the inclusion criteria for this topic (Appendix F). Of the remaining nine, one was rated Class 2 and was included as evidence for this topic.³ The remaining eight were rated Class 3. These studies, along with five studies from the 3rd Edition, were included as Class 3 evidence for this topic.⁴⁻¹⁵

Class 2 Study

The evidence from the Class 2 study of advanced cerebral monitoring is summarized in Table 14.2

Table 14-2. Summary of Evidence: Class 2 Study (Advanced Cerebral Monitoring)

| Reference Study Topic | Study Design, N, and Outcomes | Data Class | Results Conclusion |
|--|---|------------|--|
| Brain Tissue Oxygen Monitoring | | | |
| Martini, 2009 * ³ Comparison of both PbrO ₂ and ICP monitoring vs. ICP monitoring only | Retrospective Cohort - N=629 PbO ₂ and ICP=123 ICP only=506 In-hospital mortality FIM LOS Hospital cost Duration of mechanical ventilation | Class 2 | Mortality ICP and PbrO ₂ =36 (29.3%) ICP=114 (22.5%), p=0.12. No difference in hospital mortality rate in patients who were managed with ICP and PbrO ₂ monitoring compared with those who were managed with ICP monitoring only. Mean FIM scores in survivors were significantly lower and hospital costs were higher for the PbrO ₂ group (p<0.01). |

Abbreviations: ACM=advanced cerebral monitoring, ICP=intracranial pressure monitoring, FIM=Functional Independence Measure, LOS=length of stay, N=total sample size, PbrO₂=brain tissue oxygen, RCT=randomized controlled trial.

Note: Different abbreviations such as pBtO₂/PbtO₂ and P_iO₂ are used to mean brain tissue oxygen monitoring and brain tissue oxygen tension; we use PbrO₂ for consistency, which may differ from what the study authors used.

***Reference new to the 4th Edition.**

Brain Tissue Oxygen (PbrO₂) Monitoring. Martini et al., 2009 conducted a retrospective study of all 629 patients admitted to one Level I trauma center with severe TBI between July 1, 2004, and October 15, 2007.³ All patients had ICP monitors while some were also monitored using the Licox Brain Tissue Oxygenation Probe. Decision to use the Licox was at the discretion of the attending neurosurgeon. This observational study was retrospective and had unequal groups (123 with both brain tissue oxygen monitors and ICP monitors, and 503 with ICP monitors alone). While the analysis accounted for the potential influence of unequal numbers across groups, the patients with the additional monitor had more severe injuries and were treated more intensively. The researchers attempted to control for confounding variables (AIS Score, admission Glasgow Coma Scale [GCS], and Marshall classification of head CT) but acknowledged that the groups may have had important differences in prognosis. Given this

uncertainty and the null findings, this was considered insufficient evidence to support a recommendation.

Class 3 Studies

The evidence from the Class 3 studies of advanced cerebral monitoring is summarized in Table 14-3.

Table 14-3. Summary of Evidence – Class 3 Studies (Advanced Cerebral Monitoring)

| Reference Study Topic | Study Description | Data Class | Results Conclusion |
|--|---|------------|---|
| New Studies | | | |
| Brain Tissue Oxygen Monitoring | | | |
| Green 2013* ⁴ Assessed goal-directed PbrO ₂ monitoring vs. ICP/ CPP monitoring | Retrospective Cohort N=74 Single Level I Trauma Center in the United States Mortality, discharge GCS, GOS, and FIMS | Class 3 | No significant difference in mortality, GCS, GOS, or FIMS. PbrO ₂ group had significantly lower ISS (26 [25–30] vs. 30 [26–36], p=0.03) and AIS Chest (0 [0–0] vs. 2 [0–3], p=0.02). |
| Lee 2010* ⁵ Assessed PbrO ₂ monitoring-guided management | RCT N=45 Single University Hospital in Taichung, Taiwan Compared outcomes for <u>Group A</u> (ICP/ CPP management) N=16, <u>Group B</u> (ICP/ CPP management with hypothermia) N=15, and <u>Group C</u> (brain tissue oxygen monitoring P _t O ₂ and CPP management with hypothermia) N=14 Mortality and GOS at 6 months post-injury | Class 3 | Mortality 12.5% in <u>Group A</u> , 6.7% in <u>Group B</u> 8.5% in <u>Group C</u> (no significant difference). Favorable neurologic outcome 50% in <u>Group A</u> , 60% in <u>Group B</u> , 71.4% in <u>Group C</u> (p=0.0426). <u>Mean GOS</u> Group A 3.3 ± 1.3 Group B 3.5 ± 1.2 Group C 3.9 ± 1.2. |

| Reference Study Topic | Study Description | Data Class | Results Conclusion |
|---|---|------------|--|
| McCarthy 2009* ⁶ Assessed cerebral oxygen monitoring-guided management | Prospective Cohort N=145 Single Level I Trauma Center in the United States Compared outcomes for patients monitored for cerebral oxygen/pressure in addition to ICP and CPP (n=81) vs. ICP and CPP (n=64) Mortality, Hospital LOS, ICU LOS, GOS at 3 and 6-months post-injury | Class 3 | PbrO ₂ with ICP and CPP vs. no PbrO ₂ Mortality, 31% vs. 36%, p=0.52 Hospital LOS (mean days) 22.7 vs. 21.2, p=0.64 ICU LOS 12.4 vs. 12.8, p=0.79 GOS at 3,6, and 12 months: no difference. GOS 24 months Moderate disability or recovered 2% vs. 13% , p=0.04. |
| Meixensberger 2003* ¹⁶ Assessed PbrO ₂ guided treatment | Prospective Cohort Before/After Single University Hospital in Germany N=93 ICP/ CPP Group (1993 to 1996) N=40 PbrO ₂ Group (1997 to 2000) N=53 Dichotomized GOS at 6 months post-injury | Class 3 | PbrO ₂ vs. CPP/ICP GOS at 6-months post-injury GOS 1-3 35% vs. 46% GOS 4-5 65% vs. 54% p=0.27. |
| Narotam 2009* ⁷ Assessed brain tissue oxygen monitoring-directed therapy | Prospective Cohort vs. Historical Data Prospective for subgroup analysis of severe TBI=96 Historical controls from Traumatic Coma Data Bank=25 Single University Medical Center in the United States Compared outcomes for patients managed based on information from PbrO ₂ monitoring with those from a ICP/ CPP-managed historical controls Mortality, and GOS at discharge and 6 months post-injury | Class 3 | Mean GOS at 6 months post-injury significantly higher in PbrO ₂ group than historical controls (3.55 +-1.75 vs. 2.71 +- 1.65, p<0.01). OR for good outcome for PbrO ₂ group 2.09 (95% CI 1.031 to 4.24). RR reduction in mortality of 37% for PbrO ₂ group (25.9% vs. 41.5%). |

| Reference Study Topic | Study Description | Data Class | Results Conclusion |
|---|--|------------|--|
| Spiotta 2010* ⁸ Assessed brain tissue oxygen-based therapy vs. ICP/ CPP-based therapy | Prospective Cohort vs. Historical Data N=123 Prospective (n=70) Historical Controls (n=53) Single Level I Trauma Center in the United States Compared outcomes for patients managed based on information from PbrO ₂ monitoring with those from a ICP/ CPP-managed historical controls Mortality and dichotomized GOS at 3 months post-injury | Class 3 | Significantly lower mortality at 3 months post-injury for patients who received PbrO ₂ -directed care than those who received ICP and CPP-based therapy (25.7% vs. 45.3%, p<0.05). Significantly more favorable outcome at 3 months post-injury (64.3% vs. 39.6%, p=0.01). |
| Cerebral Autoregulation Monitoring with Transcranial Doppler | | | |
| Budohoski 2012* ¹⁴ Assessed cerebral autoregulation using transcranial Doppler systolic, mean, and diastolic flow velocity | Retrospective Cohort N=300 Single Critical Care Center in Cambridge, UK Dichotomized GOS at 6 months post-injury | Class 3 | For favorable/unfavorable and death/survival outcomes, systolic flow velocity showed the strongest association when correlated with CPP (F=20.11; p=0.00001 and F=13.10; p=0.0003, respectively); and when correlated with ABP (F=12.49; p=0.0005 and F=5.32; p=0.02, respectively). |
| Microdialysis Monitoring of Extracellular Glutamate | | | |
| Chamoun 2010* ¹⁵ Assessed extracellular glutamate measured by cerebral microdialysis | Prospective Cohort N=165 Single Level I Trauma Center in United States Mortality and GOS at 6 months post-injury | Class 3 | <u>Pattern 1</u> – glutamate levels tended to normalize over 120-hour monitoring period. <u>Pattern 2</u> – glutamate levels tended to increase with time or remain elevated. Patients showing Pattern 1 had a lower mortality rate (17.1 vs. 39.6%) and a better 6-month functional outcome among survivors (41.2 vs. 20.7%). |

| Reference Study Topic | Study Description | Data Class | Results Conclusion |
|---|--|------------|---|
| Studies from 3rd Edition | | | |
| Brain Tissue Oxygen Monitoring | | | |
| Stiefel 2005 ⁹ | Prospective study of 53 severe TBI patients from before PbrO ₂ monitoring=25 and after=28 Mortality | Class 3 | Significantly higher mortality in control (44%) vs. treatment group (25%), p<0.05. Mortality related to brain O ₂ : O ₂ > 25 mm Hg: 30%, O ₂ <20 mm Hg: 43% O ₂ <15 mm Hg: 50% O ₂ <20 mm Hg and not improved by resuscitation: 60%. A total of 9 patients (36%) died. |
| Jugular Bulb Monitoring of Arteriovenous Oxygen Content Difference | | | |
| Cruz, 1998 ¹⁰ | Prospective, controlled but non-randomized and non-blinded study of 353 TBI patients undergoing continuous jugular bulb saturation and cerebral extraction of oxygen (AVDO ₂) monitoring, in which GOS at 6 months was compared between patients who underwent monitoring and those who did not. | Class 3 | Outcome at 6 months by GOS improved in patients who underwent SjO ₂ and AVDO ₂ monitoring. Monitoring SjO ₂ may improve outcome in severe TBI. However, caution must be utilized in interpreting the results of this study as the non-randomized, non-blinded nature of the study may introduce treatment bias. |
| Le Roux 1997 ¹¹ | Prospective, observational study of 32 TBI patients with GCS ≤8 who underwent jugular bulb oxygen and AVDO ₂ monitoring, in which the incidence of delayed cerebral infarction and GOS at 6 months post-injury was assessed. | Class 3 | A limited improvement in elevated AVDO ₂ after treatment (craniotomy or mannitol administration) was significantly associated with delayed cerebral infarction and unfavorable outcome. Lack of response of SjO ₂ to treatment measures may be associated with poor outcome in severe TBI. |
| Robertson 1993 ¹² | Prospective, observational study of SjO ₂ monitoring in 116 TBI patients (100 with closed head injury and 16 with penetrating head injury) in which desaturation episodes (SjO ₂ <50%) were monitored and correlated to GOS at 3 months post-injury. | Class 3 | The number of episodes of desaturation were found to be associated with mortality as follows: no desaturation episodes: mortality 18% one desaturation episode: mortality 46% multiple desaturation episodes: mortality 71%. Episodes of desaturation are related to mortality and GOS at 3 months. |

| Reference Study Topic | Study Description | Data Class | Results Conclusion |
|------------------------------|--|------------|--|
| Robertson 1995 ¹³ | Prospective, observational study of continuous SjO ₂ monitoring during first 5-10 days after injury in 177 TBI patients with GCS ≤8 in which episodes of desaturation (SjO ₂ <50%) were correlated with GOS at 3 months post-injury. | Class 3 | <p>Causes of desaturation are about equally divided between systemic and cerebral causes. 39% of patients had at least one episode of desaturation (112 episodes in 69 patients) Systemic causes (hypotension, hypoxia, hypocarbia, anemia) were responsible for 51 episodes, while cerebral causes (elevated ICP, vasospasm) were responsible for 54 episodes. The number of desaturation episodes were related to outcome as follows:</p> <p>Good recovery/moderate disability No episodes: 44% One episode: 30% Multiple episodes: 15%</p> <p>Severe disability/vegetative state No episodes: 35% One episode: 33% Multiple episodes: 15%</p> <p>Death No episodes: 21% One episode: 37% Multiple episodes: 69%</p> <p>Episodes of desaturation are common and are related to mortality and GOS at 3 months.</p> |

Abbreviations: AVDO₂=arteriovenous difference of oxygen content, CT=computed tomography, CPP=cerebral perfusion pressure, FIMS=Functional Independence Measure Score, GCS= Glasgow Coma Scale, GOS=Glasgow Outcome Scale, ICP=intracranial pressure monitoring, ICU=intensive care units, ISS=Injury Severity Score, LOS=length of stay. N=total sample size, OR=odds ratio, PbrO₂=brain tissue oxygen, RCT=randomized controlled trial, TBI=traumatic brain injury, TCD=transcranial Doppler.

Note: Different abbreviations such as AJDO₂, and ajDO₂ are used to mean arteriovenous difference of oxygen content; we use AVDO₂ for consistency, which may differ from what the study authors used. Different abbreviations such as pBtO₂/PbtO₂ and P_iO₂ are used to mean brain tissue oxygen monitoring and brain tissue oxygen tension; we use PbrO₂ for consistency, which may differ from what the study authors used.

***References new to the 4th Edition.**

Brain Tissue Oxygen (PbrO₂) Monitoring. Of the six Class 3 studies that addressed PbrO₂ monitoring, one was an RCT,⁵ two were prospective cohorts compared with historical data,^{7,8} one was a prospective before/after study,¹⁶ one was a prospective cohort,⁶ and one was retrospective.⁴ All were from single centers. Outcomes included mortality, Glasgow Outcome Scale (GOS), and Functional Independence Measure (FIM) at various time points; intensive care unit and hospital length of stay; and discharge GCS. A total of 5676 patients were observed across these six studies, with sample sizes ranging from 45 to 145. Lower mortality was reported in the PbrO₂ group in two studies, and better outcomes in three studies. No significant difference

was found in mortality in two studies, and in outcomes in three studies. The inconsistency across these Class 3 studies prevents their use for a recommendation.

Nangunoori et al.¹⁷ conducted a systematic review that included four of the Class 3 studies evaluated above.^{6-8,16} They calculated odds ratios, pooled the data, and reported an overall odds ratio for favorable outcome of 2.1 (95% CI 1.4 to 3.1) for the PbrO₂ group. Authors qualitatively assessed the studies to determine if the data could be pooled, but they did not conduct a quantitative test of homogeneity. As with the individual studies, the results of this review cannot be used to support a recommendation.

Jugular Bulb Monitoring of Arteriovenous Oxygen Content Difference (AVDO₂). All of the four Class 3 studies that addressed AVDO₂ monitoring were prospective.¹⁰⁻¹³ All were from single centers. A total of 678 patients were observed, with sample sizes ranging from 32 to 353. Outcomes included mortality and GOS at 3 and 6 months post-injury. All four studies reported improved outcomes in patients who received AVDO₂ monitoring and management of desaturation episodes. Thus they support the Level III recommendation.

Cerebral Autoregulation Monitoring with TCD. One Class 3 study addressed use of information from TCD monitoring to manage patients.¹⁴ It was a single center retrospective study (N=300). The study provided information suggesting a strong relationship between the acute state of autoregulation and outcomes measured by a dichotomized GOS at 6 months post-injury. This single Class III study is insufficient to support a recommendation.

Microdialysis Monitoring of Extracellular Glutamate. One Class 3 study addressed use of information from microdialysis monitoring to manage patients.¹⁵ It was a single center prospective study (N=165). Patients whose glutamate levels tended to normalize within 120 hours of monitoring had lower mortality and better outcomes measured by the GOS at 6 months post-injury. This single Class III study is insufficient to support a recommendation.

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Evidence Synthesis and Recommendations, Part III: Thresholds

This section of the guidelines includes the evidence and recommendations related to threshold values for parameters that are monitored during the in-hospital management of patients with severe traumatic brain injury (TBI). Many physiologic functions may be monitored and considered during the management of a critically injured patient. This section is limited to those parameters that are specific to TBI, either because they are only measured in TBI or because the value may be different in TBI patients than in other trauma patients. We also focus on measures for which it is assumed or demonstrated that response to treatment improves outcomes.

In this 4th Edition we include thresholds for blood pressure (BP), intracranial pressure (ICP), cerebral perfusion pressure monitoring (CPP), and advanced cerebral monitoring (ACM). The threshold can be a value to avoid in order to decrease the probability of negative outcomes or a value to aim for in order to increase the probability of positive outcomes, and it can be a value that triggers a change in treatment.

15. Blood Pressure Thresholds

INTRODUCTION

The level of systolic blood pressure (SBP) has long been felt to play a critical role in the secondary injury cascade after severe traumatic brain injury (TBI). As early as 1989, Klauber et al. reported a mortality of 35% in patients admitted with a SBP <85 mm Hg, compared with only 6% in patients with a higher SBP.¹ Additionally, hypotension has been shown to correlate with diffuse brain swelling.²

There are several underlying pathophysiologic mechanisms. If autoregulation remains intact, a drop in SBP triggers an autoregulatory vasodilation in an attempt to maintain adequate brain perfusion. This results in increased cerebral blood volume, which in turn elevates intracranial pressure. If autoregulation is not intact, there is dependency on SBP to prevent cerebral ischemia, which has been ascribed to be the single most important secondary insult.³

The traditional definition of hypotension has been a SBP <90 mm Hg, and this was the target recommended in the first iterations of these guidelines. As will be noted, the literature now supports a higher level that may vary by age. The interrelationship between SBP, mean arterial pressure (MAP), and cerebral perfusion pressure (CPP) should be kept in mind as one considers threshold recommendations in these guidelines.

RECOMMENDATIONS

Level I and II

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

Level III

- Maintaining SBP at ≥ 100 mm Hg for patients 50 to 69 years old or at ≥ 110 mm Hg or above for patients 15 to 49 or over 70 years old may be considered to decrease mortality and improve outcomes.

Changes from Prior Edition

Recommendations from prior editions have been revised due to new evidence. The focus in this topic has been narrowed to concerns specific and different for TBI patients. Monitoring blood pressure and avoiding hypotension is considered general good trauma and ICU care and

are not included. Brain tissue oxygenation is included in the Advanced Cerebral Monitoring section.

EVALUATION OF THE EVIDENCE

Quality of the Body of Evidence

This topic addresses the question about what level of SBP should be achieved and maintained in severe TBI patients in order to improve outcomes. One large, retrospective, Class 2 study⁴ and two Class 3 studies are included as evidence^{5,6} (Table 15-1).

The Class 2 study is being used to support a Level III recommendation because it is a single study that provides indirect evidence; the study includes patients with both moderate and severe TBI, and the outcomes are not reported separately by severity levels. The indirect evidence combined with direct, low-quality evidence from the Class 3 studies support the Level III recommendation.

Table 15-1. Quality of the Body of Evidence (Blood Pressure Thresholds)

| Topic | Number of Studies | Meta-Analysis | Number of Subjects | Class of Studies (1 or 2) | Consistency (High, Moderate, Low) | Directness (Direct or Indirect) | Precision (High, Moderate, Low) | Quality of Evidence (High, Moderate, Low, or Insufficient) |
|--|-----------------------------|---------------|------------------------------|---------------------------|-----------------------------------|---------------------------------|---------------------------------|--|
| COMPONENTS OF OVERALL QUALITY – Class 2 | | | | | | | | |
| Hypotension: Threshold ⁴ | 1 Cohort 0 RCT | NA | 15,733 (26.9% Severe TBI) | 2 | NA | Indirect | High | Low |
| COMPONENTS OF OVERALL QUALITY – Class 3 | | | | | | | | |
| Hypotension Threshold ^{5,6} | 1 Cohort 1 Retrospective | NA | 6,861 | 3 | Moderate | Direct | Moderate | Low |

Abbreviations: NA=not applicable, RCT=randomized controlled trial, TBI=traumatic brain injury.

Applicability

The indirect evidence is not as directly applicable as it would be if the study had included only patients with severe TBI or if the results had been separated by severity. Due to study design concerns, the applicability of the direct evidence from the Class 3 studies is difficult to assess.

SUMMARY OF THE EVIDENCE

Process

Of eight new, potentially relevant studies reviewed, five were excluded because they did not meet the inclusion criteria for this topic (see Appendix F). One was rated Class 2,⁴ and two were rated as Class 3.^{5,6} These and 16 Class 3 studies from the 3rd Edition were included as evidence for this topic.

Class 2 Study

The evidence from the Class 2 study of blood pressure thresholds is summarized in Table 15-2.

Table 15-2. Summary of Evidence – Class 2 Study (Blood Pressure Thresholds)

| Reference Study Topic | Study Design, N, and Outcomes | Data Class | Results Conclusion |
|---|---|------------|---|
| Berry, 2012* ⁴ To determine if a higher hypotension threshold is needed for patients with moderate to severe TBI | Retrospective Cohort N=15,733 (26.9% GCS ≤8) Mortality | Class 2 | Optimal threshold of hypotension (to minimize probability of death). 110 mm Hg for patients 15 to 49 years of age (AOR 1.98, 95% CI 1.65 to 2.39), p<0.0001. 100 mm Hg for patients 50–69 years (AOR 2.20, 95% CI 1.46 to 3.31), p=0.0002. 110 mm Hg for patients 70 years and older (AOR 1.92, 95% CI 1.35 to 2.74), p=0.0003. The results suggest the threshold for hypotension in moderate to severe TBI patients should be systolic blood pressure less than 110 mm Hg. |

Abbreviations: AOR=adjusted odds ratio, CI=confidence interval, GCS= Glasgow Coma Scale, N=total sample size, TBI=traumatic brain injury.

***Reference new to the 4th Edition.**

Berry et al., 2012 analyzed data on all adult trauma patients admitted to any one of 13 trauma centers in Los Angeles County between January 1998 and December 2005.⁴ They predefined three age categories (15 to 49, 50 to 69, and 70 or older), and for each age category estimated the probability of death using multiple logistic regression for systolic blood pressure cut-offs from 60 to 150 mm Hg in increments of 10. They identified the optimal level for hypotension by finding the level for which the model balanced the best statistical fit with the best discriminatory power. They concluded that the current definition of hypotension as systolic blood pressure

below 90 mm Hg should be reconsidered based on their identification of 100 mm Hg and 110 mm Hg as the thresholds associated with lower mortality, although they state that more studies are needed to confirm the optimal BP threshold for TBI patients of different ages.

Class 3 Studies

The evidence from the Class 3 studies of blood pressure thresholds is summarized in Table 15-3.

Table 15-3. Summary of Evidence – Class 3 Studies (Blood Pressure Thresholds)

| Reference Study Topic | Study Description | Data Class | Results Conclusion |
|--|--|------------|--|
| New Studies | | | |
| Brenner 2012* ⁵ Correlated SBP thresholds with outcome | Prospective Cohort N=60 Single Level 1 Trauma Center in the United States In-hospital Mortality GOS-E at 12 months post-injury | Class 3 | SBP <110 mm Hg and <120 mm Hg within the first 48 hours are thresholds to avoid to minimize mortality and improve outcomes 12 months post-injury. |
| Butcher 2007* ⁶ Examined relationship of thresholds for SBP and MABP with outcome | Retrospective Cohort N=6,801 SBP N=6,647 MABP IMPACT Database of individual patient data from 3 observational studies and 8 RCTs GOS at 6 months post-injury | Class 3 | SBP ranges from 120 mm Hg and 150 mm Hg, and MABP ranges from 85 mm Hg and 110 mm Hg are thresholds to target to improve outcomes. |
| Studies from 3rd Edition | | | |
| Chesnut 1993 ⁷ | A prospective study of 717 consecutive severe TBI patients admitted to four centers investigated the effect on outcome of hypotension (SBP <90 mm Hg) occurring from injury through resuscitation. | Class 3 | Hypotension was a statistically independent predictor of outcome. A single episode of hypotension during this period doubled mortality and also increased morbidity. Patients whose hypotension was not corrected in the field had a worse outcome than those whose hypotension was corrected by time of ED arrival. |
| Fearnside 1993 ⁸ | A prospective study of prehospital and in-hospital predictors of outcome in 315 consecutive severe TBI patients admitted to a single trauma center. | Class 3 | Hypotension (SBP <90 mm Hg) was an independent predictor of increased morbidity and mortality. |

| Reference Study Topic | Study Description | Data Class | Results Conclusion |
|--------------------------------|---|------------|---|
| Gentleman 1992 ⁹ | A retrospective study of 600 severe TBI patients in three cohorts evaluating the influence of hypotension on outcome and the effect of improved pre-hospital care in decreasing its incidence and negative impact. | Class 3 | Management strategies that prevent or minimize hypotension in the prehospital phase improve outcome from severe TBI. |
| Hill 1993 ¹⁰ | A retrospective study of prehospital and ED resuscitative management of 40 consecutive, multi-trauma patients. | Class 3 | Hypotension (SBP \leq 80 mm Hg) correlated strongly with mortality. |
| Jeffreys 1981 ¹¹ | A retrospective review of hospital records in 190 TBI patients who died after admission. | Class 3 | Hypotension was one of the four most common avoidable factors correlated with death. |
| Kohi 1984 ¹² | A retrospective evaluation of 67 severe TBI patients seen over a 6-month period were correlated with 6-month outcome. | Class 3 | Early hypotension increases the mortality and worsens the prognosis of survivors in severe TBI. |
| Marmarou 1991 ¹³ | From a prospectively collected database of 1,030 severe TBI patients; all 428 patients who met ICU monitoring criteria were analyzed for monitoring parameters that determined outcome and their threshold values. | Class 3 | The two most critical values were the proportion of hourly ICP readings greater than 20 mm Hg and the proportion of hourly SBP readings less than 80 mm Hg. The incidence of morbidity and mortality resulting from severe TBI is strongly related to ICP and hypotension measured during the course of ICP management. |
| Miller 1982 ¹⁴ | A prospective study of 225 severely head-injured patients regarding the influence of secondary insults on outcome. | Class 3 | Hypotension (SBP $<$ 95 mm Hg) was significantly associated with increased morbidity and mortality. |
| Miller 1978 ¹⁵ | One hundred consecutive severe TBI patients were prospectively studied regarding the influence of secondary insults on outcome. Seminal report relating early hypotension to increased morbidity and mortality. Influence of hypotension on outcome not analyzed independently from other associated factors. | Class 3 | Hypotension (SBP $<$ 95 mm Hg) associated with a non-significant trend toward worse outcome in entire cohort. This trend met statistical significance for patients without mass lesions. Hypotension is a predictor of increased morbidity and mortality from severe TBI. |
| Pietropaoli 1992 ¹⁶ | A retrospective review of the impact of hypotension (SBP $<$ 90 mm Hg) on 53 otherwise normotensive severe TBI patients who received early surgery (within 72 hours of injury). | Class 3 | Early surgery with intraoperative hypotension was significantly correlated with increased mortality from severe TBI in a duration-dependent fashion. The mortality rate was 82% in the group with hypotension and 25% in the normotensive group ($p < 0.001$). The duration of intraoperative hypotension was inversely correlated with Glasgow Outcome Scale score using linear regression ($R = -0.30$, $p = 0.02$). |

| Reference Study Topic | Study Description | Data Class | Results Conclusion |
|-------------------------------|---|------------|---|
| Rose 1977 ¹⁷ | A retrospective review of hospital and necropsy records of 116 TBI patients who were known to have talked before dying. | Class 3 | Hypotension is a major avoidable cause of increased mortality in patients with moderate TBI. |
| Seelig 1986 ¹⁸ | A study of all patients (n=160) with an ICP of 30 mm Hg during the first 72 hours after injury from a prospectively collected database of severe TBI patients (n=348). | Class 3 | Early hypotension was significantly correlated with increased incidence and severity of intracranial hypertension and increased mortality. |
| Stocchetti 1996 ¹⁹ | A cohort study of 50 trauma patients transported from the scene by helicopter, which evaluated the incidence and effect of hypoxemia and hypotension on outcome. | Class 3 | Fifty-five percent of patients were hypoxic (SaO ₂ <90%) and 24% were hypotensive. Both hypoxemia and hypotension negatively affected outcome, however, the degree to which each independently affected the outcome was not studied. |
| Jones 1994 ²⁰ | Prospective analysis of 124 patients ≥14 years old admitted to single center with a GCS ≤12, or >12 and Injury Severity Score ≥16, with clinical indications for monitoring. Subgroup analysis performed on 71 patients for whom data existed for 8 potential secondary insults (ICP, hypotension, hypertension, CPP, hypoxemia, pyrexia, bradycardia, tachycardia) to identify predictors of morbidity/ mortality. | Class 3 | Mortality is best predicted by durations of hypotensive (p=0.0064), hypoxemic (p=0.0244), and pyrexia (p=0.0137) insults. Morbidity (“Good” vs. “Bad” outcome) was predicted by hypotensive insults (p=0.0118), and papillary response on admission (p=0.0226). |
| Manley 2001 ²¹ | Prospective cohort of 107 patients with GCS <13 admitted to a single center; primarily evaluating impact of hypoxic and hypotensive episodes during initial resuscitation on mortality. Impact of multiple episodes of hypoxia or hypotension analyzed. | Class 3 | Early in-hospital hypotension but not hypoxia is associated with increased mortality. Odds ratio for mortality increases from 2.1 to 8.1 with repeated episodes of hypotension. |
| Struchen 2001 ²² | Cohort of 184 patients with severe TBI admitted to a single level I trauma center neurosurgical ICU who received continuous monitoring of ICP, MAP, CPP, and SjO ₂ . Primary outcomes were GOS and DRS. Analysis included multiple regression model evaluating effect of physiologic variables on outcome. | Class 3 | Adjusting for age and emergency room GCS, ICP >25 mm Hg, MAP <80 mm Hg, CPP <60 mm Hg, and SjO ₂ <50% were associated with worse outcomes. |

Abbreviations: CPP=cerebral perfusion pressure, DRS=disability rating scale, ED=emergency department, GCS=Glasgow Coma Scale, GOS=Glasgow Outcome Scale, GOS-E=Extended Glasgow Outcome Scale, ICP=intracranial pressure, ICU=intensive care unit, SBP=systolic blood pressure, SjO₂= jugular venous oxygen saturation, TBI=traumatic brain injury.

***Reference new to the 4th Edition.**

Two new Class 3 studies were included as evidence for this topic. One (N=60) was a prospective study conducted in a single Level 1 trauma center in the United States.⁵ The other (N=6,801) was a retrospective analysis of individual patient data collected from three observational studies and eight RCTs (the IMPACT database).⁶ Findings from both of these studies suggested that the previously-defined SBP level for hypotension of below 90 mm Hg should be re-examined, and that maintenance of higher levels might result in better outcomes.

The Class 3 studies from the 3rd Edition of these guidelines are listed in Table 15-3.

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16. Intracranial Pressure Thresholds

INTRODUCTION

Intracranial pressure (ICP) is the pressure inside the cranial vault and is affected by intracranial contents, primarily brain, blood, and cerebrospinal fluid. The intracranial volume is constant.¹ Since the intracranial vault is a fixed space, ICP increases with an increase in brain volume and cerebral blood volume, increased cerebrospinal fluid production, and or decreased cerebrospinal fluid clearance.¹⁻³ Mass lesions such as tumors, hemorrhagic lesions, cerebral edema, or obstruction of venous and or CSF return can increase ICP. The Monro-Kellie hypothesis states that under normal conditions, the intracranial compartment space, cerebral blood volume, and volume inside the cranium are fixed volumes.⁴ If any of these component volumes increase, then compensation must occur to maintain ICP within normal range. Typically, these compensatory measures include displacement of CSF and venous blood downward into the spinal spaces and decrease in blood volume. These compensatory measures allow for ICP to be maintained within the normal range of 0-10 mm Hg.^{4,5}

As mass lesions occupy more volume, intracranial compliance (change in cerebral volume/intracranial pressure) decreases, and elastance (change in cerebral pressure/cerebral volume) increases.⁵ A critical threshold is reached when space-occupying lesions can no longer expand without neuronal injury, herniation, and brain death. It is important to remember that the idea of ICP, while important in itself, must also be considered in the context of its inverse relationship with cerebral perfusion pressure, which is discussed elsewhere.

RECOMMENDATIONS*

Level I and II A

- There was insufficient evidence to support a Level I or II A recommendation for this topic.

Level II B

- Treating ICP above 22 mm Hg is recommended because values above this level are associated with increased mortality.

Level III

- A combination of ICP values and clinical and brain CT findings may be used to make management decisions.

*The committee is aware that the results of the RESCUEicp trial⁶ may be released soon after the publication of these Guidelines. The results of this trial may affect these recommendations and may need to be considered by treating physicians and other users of these Guidelines. We intend to update these recommendations after the results are published if needed. Updates will be available at <https://braintrauma.org/coma/>.

Changes from Prior Edition

A new Class 2 study provides evidence for the current recommendation, which replaces the Level II recommendation of the 3rd Edition of these guidelines. The study that supported the 3rd Edition recommendation⁷ was found to be Class 3 in relation to the ICP Monitoring topic. (It remains Class 2 in relation to barbiturates. See Part II. Monitoring for details.)

EVALUATION OF THE EVIDENCE

Quality of the Body of Evidence

The studies identified for this topic (Table 16-1) address two questions: (1) what are the ICP thresholds to target or avoid? and (2) what key factors need to be considered in addition to ICP when making management decisions? For the first question, one Class 2 study (Table 16-2) with a comparatively large sample size (N=459) provides an overall low quality of the body of evidence about the target values for ICP when treating patients with severe TBI.⁸ The concern is that, except in extraordinary cases (e.g., a large multi-site randomized trial with definitive results), the finding of a single study may be reversed by subsequent research.

Two new studies,^{9, 10} and nine from the 3rd Edition of these guidelines,^{7,11-18} provide Class 3 evidence about target values for ICP. Of these, three^{11,12,14} address the second question on which key factors need to be considered in addition to ICP when making management decisions. The included studies provide a low-quality body of evidence for the Level III recommendation.

The remaining Class 3 studies are reported in Table 16-3 and the summary section below, but are not included in the assessment of the body of evidence and were not used to inform the recommendations.

Table 16-1. Quality of the Body of Evidence (Intracranial Pressure Thresholds)

| Topic | Number of Studies | Meta-Analysis | Number of Subjects | Class of Studies (1 or 2) | Consistency (High, Moderate, Low) | Directness (Direct or Indirect) | Precision (High, Moderate, Low) | Quality of Evidence (High, Moderate, Low, or Insufficient) |
|--|------------------------------------|---------------|--------------------|---------------------------|-----------------------------------|---------------------------------|---------------------------------|--|
| COMPONENTS OF OVERALL QUALITY – Class 2 | | | | | | | | |
| ICP Threshold ⁸ | 1 Cohort 0 RCT | NA | 459 | 2 | NA | Direct | Moderate | Low |
| COMPONENTS OF OVERALL QUALITY – Class 3 | | | | | | | | |
| Factors other than ICP to consider ^{11,12,14} | 2 Retro-spective 1 Pro-spective | NA | 352 | 3 | NA | Direct | NA | Low |

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

Applicability

The single study included for the Level IIB recommendation used data from one hospital in Cambridge, England, collected over 17 years (1992 to 2009, N=459).⁸ There is a risk that practice patterns specific to this site and/or changes in practice over time might have influenced the results. The two studies included for the Level III recommendation were from single centers, had small to moderate sample sizes, and the patients received different treatments consistent with their clinical course. The applicability of this information is low.

SUMMARY OF THE EVIDENCE

Process

Of eight new, potentially relevant studies reviewed, five were excluded because they did not meet the inclusion criteria for this topic (Appendix F). One was rated Class 2 and was included as evidence.⁸ The remaining two were rated Class 3.^{9, 10} These and nine Class 3 studies from the 3rd Edition were included as evidence for this topic.^{7, 11-18}

Class 2 Study

The evidence from the Class 2 study of intracranial pressure thresholds is summarized in Table 16-2.

Table 16-2. Summary of Evidence – Class 2 Study (Intracranial Pressure Thresholds)

| Reference Study Topic | Study Design, N, and Outcomes | Data Class | Results Conclusion |
|---|---|------------|--|
| ICP Thresholds to Target or Avoid | | | |
| Sorrentino, 2012* ⁸ ICP/CPP/PRx Threshold | Retrospective Cohort N=459 Mortality Favorable/Unfavorable Outcomes | Class 2 | <u>ICP threshold</u> 22 mm Hg for ICP for reduced mortality 18 mm Hg for favorable outcomes in women and older patients <u>CPP threshold</u> 70 mm Hg for mortality and favorable outcome <u>PRx threshold</u> 0.25 for reduced mortality 0.05 for increase in favorable outcomes |

Abbreviations: CPP=cerebral perfusion pressure, ICP=intracranial pressure, N=total sample size, PRx=Pressure-Reactivity Index.

* Reference new to the 4th Edition

Using a database including 459 patients meeting criteria that were admitted with TBI to the Neuroscience Critical Care Unit of Cambridge, UK, Sorrentino et al., 2012 identified threshold values for ICP, CPP, and pressure-reactivity index (PRx).⁸ The PRx is the Pearson moving correlation coefficient between mean ICP and mean BP calculated using the ICM+[®] software for brain monitoring (ICM+, University of Cambridge Enterprise, Cambridge, UK).¹⁹ Data were collected from 1992 through 2009. Analysis consisted of sequential chi-square distributions in which patients were dichotomized into survivors or not and GOS 1 to 3 vs. 4 and 5). ICP was examined in steps of 1 in order to identify the ICP level that returned the highest chi square score. This was interpreted as having the best discriminative value between patient outcomes.

For ICP, the identified threshold was 22 mm Hg for both mortality and favorable outcome for all patients (Chi square=58.18, p<0.001 and 18.15, p<0.001). When subgroups for age and sex were analyzed, the threshold did not change for mortality, but it decreased to 18 mm Hg for favorable outcomes for patients over 55 years of age and women of all ages. Given the sub-group analysis may not have been adequately powered, and this finding is limited to one study, the data are not used to support a recommendation about ICP targets that vary by age or gender.

Class 3 Studies

The evidence from the Class 3 studies of intracranial pressure thresholds is summarized in Table 16-3.

Table 16-3. Summary of Evidence – Class 3 Studies (Intracranial Pressure Thresholds)

| Reference Study Topic | Study Design, N, and Outcomes | Data Class | Results Conclusion |
|--|--|------------|---|
| New Studies | | | |
| Kostic 2011* ⁹ Compared ICP vs. no ICP for mortality | RCT N=61 ICP monitored=32 (52.5%) Single Center in Serbia. | Class 3 | No significant difference in the survival rate between the two groups ($\chi^2=2.11$; $p=0.15$; $p>0.05$). Average ICP was 27 mm Hg for patients who died and 18 mm Hg for patients who survived. |
| Kuo 2006* ¹⁰ Determine thresholds of ICP and CPP during surgery that were predictive of outcomes. | Prospective Observational N=30 Single Center in Taiwan. GOS at 3 months post-injury | Class 3 | Initial ICP for unfavorable outcomes was 47.4 ± 21.4 mm Hg, resulting in a CPP of 22.8 ± 12.83 mm Hg. Initial ICP for favorable outcomes was 26.4 ± 10.1 mm Hg, resulting in a CPP of 48.8 ± 13.4 mm Hg. CPP had the largest area under the ROC curve in all stages of the operation, corresponding to intraoperative CPP thresholds of 37 mm Hg (initial), 51.8 mm Hg (intraoperative) and 52 mm Hg (after scalp closure). |
| Studies from 3rd Edition | | | |
| Andrews 1988 ¹¹ Determine the effect of hematoma location on outcome. | Retrospective review of the clinical course and CT scans of 45 patients with supratentorial intracerebral hematomas to determine the effect of hematoma location on clinical course and outcome. | Class 3 | Signs of herniation were significantly more common with temporal or temporoparietal lesions. Clot size of 30 cc was the threshold value for increased incidence of herniation. Factors other than ICP (such as location of mass lesion) must be considered in guiding treatment. |
| Chambers 2001 ¹² Assess the effect of CT classification on the utility of ICP thresholds | Prospective series of 207 adult patients with ICP and CPP monitoring were analyzed using ROC curves to determine if there were significant thresholds for the determination of outcome. | Class 3 | The sensitivity for ICP rose for values >10 mm Hg, but it was only 61% at 30 mm Hg. ICP cut off value for all patients was 35 mm Hg, but ranged from 22 to 36 for different CT classifications. It may be inappropriate to set a single target ICP, as higher values may be tolerated in certain CT classifications. |

| Reference Study Topic | Study Design, N, and Outcomes | Data Class | Results Conclusion |
|---|---|-------------------|--|
| Eisenberg 1988 ⁷ Determine if outcomes were better for patients whose ICP could be controlled | Prospective, multicenter study wherein 73 severe TBI patients, whose ICP was not controllable using “conventional therapy” were randomly assigned to a high-dose pentobarbital vs. placebo-control regimen. Dependent variable was ability to control ICP below 20 mm Hg. | Class 3 | The outcome for study patients whose ICP could be kept below 20 mm Hg using either regimen was significantly better than those whose ICP could not be controlled. |
| Marmarou 1991 ¹³ Identify what threshold values were associated with outcomes. | Retrospective analysis from the Traumatic Coma Data Bank. 428 patients who met ICP monitoring criteria were analyzed for monitoring parameters that determined outcome and their threshold values. | Class 3 | Using logistic regression, the threshold value of 20 mm Hg was found to best correlate with outcome at 6 months. The proportion of hourly ICP reading greater than 20 mm Hg was a significant independent determinant of outcome. The four centers used ICP treatment thresholds of 20-25 mm Hg. The degree to which this confounds the regression statistics is unclear. The incidence of morbidity and mortality resulting from severe TBI is strongly related to ICP control wherein 20 mm Hg is the most predictive threshold. |
| Marshall 1979 ¹⁴ Evaluate the effectiveness of an ICP threshold of 15 mm Hg | Retrospective review of 100 consecutively admitted severe TBI patients from the Traumatic Coma Data Bank. | Class 3 | Patients managed with a regimen including ICP monitoring using a threshold of 15 mm Hg had improved outcome vs. published reports using less ICP-intensive therapy. |
| Narayan 1982 ¹⁵ Assess the impact of a 20mm Hg threshold for ICP | Retrospective analysis of the courses of 207 consecutively admitted severe TBI patients to a single center. Management included aggressive attempts to control ICP using a threshold of 20 mm Hg. | Class 3 | Outcome was significantly correlated with the ability to control ICP. ICP control using a threshold of 20 mm Hg as a part of an overall aggressive treatment approach to severe TBI associated with improved outcome. |
| Ratanalert 2004 ¹⁶ Compare the impact of ICP thresholds of 20 and 25 mm Hg. | Prospective study of 27 patients, randomly selected into groups of ICP treatment thresholds of ≥ 20 (n=13) or ≥ 25 (n=14) mm Hg. Treatment protocols were similar between groups with CPP kept >70 and $SjO_2 >54\%$. | Class 3 | No difference in outcome between ICP thresholds of 20 or 25 mm Hg. |

| Reference Study Topic | Study Design, N, and Outcomes | Data Class | Results Conclusion |
|--|---|------------|---|
| Saul 1982 ¹⁷ Compare mortality for patients treated using or not using a strict protocol | A single center series of 127 severe TBI patients whose ICP treatment was initiated at 20-25 mm Hg, not using a strict treatment protocol, was compared with a subsequent group of 106 patients with similar injury characteristics who received treatment under a strict protocol at an ICP threshold of 15 mm Hg. | Class 3 | The 46% mortality in the first group was significantly greater than the 28% mortality in the second group. Suggests an increase in mortality if ICP maintained above a threshold between 15 and 25 mm Hg. |
| Schreiber 2002 ¹⁸ Identify the ICP level that is associated with higher mortality | 233 patients with ICP monitoring were analyzed from a prospectively collected database of 368 patients from a single center. Potentially predictive parameters were analyzed to determine their impact on survival. | Class 3 | An opening ICP of ≥ 15 mm Hg was identified as one of five risk factors associated with higher mortality. |

Abbreviations: CPP=cerebral perfusion pressure, CT=computed tomography, ICP=intracranial pressure, N=total sample size, PRx=pressure-reactivity index, SjO₂= jugular venous oxygen saturation.

*** References new to the 4th Edition**

Class 3 studies also provided evidence on ICP thresholds to target or avoid. Of the two Class 3 studies included since the 3rd Edition of these guidelines, one was an RCT in which patients were randomized to ICP monitoring or no ICP monitoring (N=61).⁹ Authors reported average ICP for survivors and non-survivors to be 18 mm Hg and 27 mm Hg, respectively. Due to inadequate randomization and allocation concealment and lack of blinding, this RCT was rated Class 3. The second study reported initial ICP thresholds *during surgery* predictive of favorable outcomes versus unfavorable outcomes (GOS at 3 months post-injury were 26.4 ± 10.1 mm Hg and 47.4 ± 21.4 mm Hg, respectively; N=30).¹⁰

Of the nine Class 3 studies maintained from the 3rd Edition, four were retrospective,^{11,13-15} four were prospective,^{7,12,16,18} and one was a prospective before/after study.¹⁷ A total of 1,447 patients were observed. Seven provided information about the association between ICP thresholds and outcomes but were not used to support a recommendation due to the availability of higher quality information.

Three Class 3 studies that provide information about the utility of information from CT scans to augment decisions about target ICP threshold in some patients are used to support the Level III recommendation in these guidelines.^{11,12,14} Patients can herniate at intracranial pressures less than 20-25 mm Hg. The likelihood of herniation depends on the location of an intracranial mass lesion. In the report by Marshall et al., 1979 pupillary abnormalities occurred with ICP values as

low as 18 mm Hg.¹⁴ Therefore, at all points, any chosen threshold must be closely and repeatedly corroborated with the clinical exam and CT imaging in an individual patient.

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17. Cerebral Perfusion Pressure Thresholds

INTRODUCTION

Cerebral perfusion pressure (CPP) is the difference between the mean arterial blood pressure and intracranial pressure (ICP). CPP can only be calculated when the ICP is known, and this should be factored into the decision about whether to place an ICP monitor. CPP has long been considered a valuable measure in attempting to optimize the care of the traumatically brain injured, as it is, at least to some degree, a surrogate measure for the delivery of nutrients to the brain. Moreover, it is believed that CPP is the blood pressure metric to which brain autoregulatory mechanisms respond.¹ To this point, some literature has suggested that ICP elevation can be tolerated as long as acceptable CPP values are maintained.

Views on the optimal CPP have evolved over the years. Rosner¹ argued for very high CPP values, the rationale being that it would help to restore the injured brain's autoregulatory capacity.¹ However, Robertson et al. found that CPP values higher than 70 mm Hg were associated with elevated risk for respiratory complications and poorer outcome.² Recent years have seen increased attention to patients' pressure autoregulatory status with the view that patients with intact autoregulation are best served by higher CPP values while pressure-passive patients with dysfunctional pressure autoregulation do better with lower CPP values. It has also been suggested that an optimal CPP value may need to be tailored to individual patients, and that achieving this level throughout the course of a patient's care could be associated with better outcomes,³ although further confirmatory research is needed.

RECOMMENDATIONS

Level I and II A

- There was insufficient evidence to support a Level I or II A recommendation for this topic.

Level II B

- The recommended target cerebral perfusion pressure (CPP) value for survival and favorable outcomes is between 60 and 70 mm Hg. Whether 60 or 70 mm Hg is the

minimum optimal CPP threshold is unclear and may depend upon the patient's autoregulatory status.

Level III

- Avoiding aggressive attempts to maintain CPP above 70 mm Hg with fluids and pressors may be considered because of the risk of adult respiratory failure.

Changes from Prior Edition

In the 3rd Edition of these guidelines, CPP monitoring and thresholds were combined into one section. In this edition, they are reported separately with new evidence added. Of the 11 publications included in the section about CPP in the 3rd Edition, four provided information about monitoring and are addressed in that topic, and one was eliminated because it is not comparative and thus does not meet the criteria for this review. Seven are summarized in this topic (one was used for both CPP topics). Seven new Class 3 studies were also included. Two new Class 2 studies were added to the body of evidence for the 4th Edition, and the recommendations were revised to incorporate the results of these studies. One study rated Class 2 in the 3rd Edition² was reevaluated and rated Class 3.

EVALUATION OF THE EVIDENCE

Quality of the Body of Evidence

The body of evidence consisted of two Class 2 cohort studies, one Class 3 RCT, and 13 Class 3 cohort studies (Table 17-1). The major weakness in the body of evidence was the lack of consistency in what the studies tested, as well as in the results. The smaller, older RCT did not find a difference in neurological outcomes between treatment protocols with two different CPP thresholds (50 mm Hg vs. 70 mm Hg).² The two Class 2 cohort studies both reported better outcomes with higher CPP, but they identified different thresholds (60 mm Hg and 70 mm Hg).^{4,5} For this reason, the quality of evidence is considered low and the Level II B recommendation of a target CPP is not precise.

A re-analysis of the RCT² data identified an association between the negative effects also seen in the trial with the use of pressors.⁶ The other 12 Class 3 studies^{3,7-17} were variable in their designs and inconsistent in their results. For this reason, the quality of the body of evidence is low and the Level III recommendation is limited to stating that CPP below 50 should be avoided.

Table 17-1. Quality of the Body of Evidence (Cerebral Perfusion Pressure Thresholds)

| Topic | Number of Studies | Meta-Analysis | Number of Subjects | Class of Studies | Consistency (High, Moderate, Low) | Directness (Direct or Indirect) | Precision (High, Moderate, Low) | Quality of Evidence (High, Moderate, Low, or Insufficient) |
|--|----------------------|-----------------------------------|--------------------|---|-----------------------------------|---------------------------------|---------------------------------|--|
| COMPONENTS OF OVERALL QUALITY – Class 2 and 3 | | | | | | | | |
| CPP target for positive outcomes ^{2, 4,5} | 2 Cohort 1 RCT | Different designs and comparisons | 2,405 | Cohort studies: Class 2 RCT: Class 3 | Low | Direct | Moderate | Low |
| CPP threshold ^{3, 7-17} | 12 Cohort | Different designs and comparisons | 2,024 | 3 | Low | Direct | Low | Low |
| Negative impact of elevating CPP with pressors and fluids ^{2,6} | 1 Re-analysis of RCT | NA | 189 | 3 | NA | Direct | Moderate | Low |

Abbreviations: CPP=cerebral perfusion pressure, NA=not applicable, RCT=randomized controlled trial.

Applicability

The Class 3 RCT and one Class 2 observational study were conducted at single sites,^{2, 4} while the other Class 2 study included multiple hospitals in New York State.⁵ The two Class 2 retrospective studies^{4,5} have large sample sizes. They were conducted over several years; however, because patients in the group above the target threshold as well as those in the group below the target threshold would be subjected to the same changes in practice over these periods, this may not be an issue in terms of applicability.

SUMMARY OF THE EVIDENCE

Process

Of the 14 new, potentially relevant studies reviewed, five were excluded because they did not meet the inclusion criteria for this topic (see Appendix F). Of the remaining nine, two were rated Class 2^{4,5} and seven were rated Class 3.⁷⁻¹³ These and seven additional studies from the 3rd Edition^{2,3,6,14-17} were included as evidence for this topic.

Class 2 Studies

The evidence from the Class 2 studies of CPP thresholds is summarized in Table 17-2.

Table 17-2. Summary of Evidence – Class 2 Studies (Cerebral Perfusion Pressure Thresholds)

| Reference, Study Topic | Study Design, N, and Outcomes | Data Class | Results Conclusion |
|---|---|------------|--|
| New Studies | | | |
| Allen et al., 2014* ⁵ Identification of age-specific CPP thresholds related to short-term survival | Retrospective cohort N=1,757 (18 years old and older) Mortality 14 days post-injury | Class 2 | Survivors/Non-survivors # (%) CPP high (>60) 701(84.0%)/134 (16.1%) CPP 50-60 562 (83.6%)/110 (16.4%) CPP low (<50) 147 (62.3%)/89 (37.7%). RR: low to high 2.35 (1.88, 2.95), p<0.0001. Survival is better for adults with high CPP vs. adults with low CPP. |
| Sorrentino et al., 2012* ⁴ ICP/CPP/PRx thresholds | Retrospective cohort N=459 | Class 2 | CPP 70 mm Hg for mortality and favorable outcome ICP thresholds 22 mm Hg for ICP for reduced mortality, 18 mm Hg for favorable outcomes in women and older patients. PRx 0.25 for mortality, 0.05 for favorable outcome. |

Abbreviations: CPP=cerebral perfusion pressure, ICP=intracranial pressure, N=total sample size, PRx=Pressure-reactivity Index, RCT=randomized controlled trial, RR=relative risk.

*** References new to the 4th Edition.**

Allen et al. analyzed data on all patients with severe TBI (Glasgow Coma Scale [GCS] 3-8 following resuscitation) included in the New York State TBI-trac© database. The objectives were to determine if CPP thresholds should be age-specific, and which thresholds are best for children and adolescents. In addition, they analyzed the data for adults. Patients who had no time periods with CPP below 60 mm Hg had higher survival rates than patients who had any time periods below 50 mm Hg. Patients with CPP between 50 and 60 mm Hg were not significantly different from the >60 group in terms of survival. The researchers acknowledge that higher CPP may increase the risk of acute respiratory distress syndrome (ARDS) based on other research, but they do not report information on this risk based on their data and analysis.⁵

Sorrentino et al., 2012 identified threshold values for ICP, CPP, and pressure-reactivity index (PRx) using a database of 763 patients admitted with TBI to the Neuroscience Critical Care Unity of Cambridge, UK. Data was collected from 1992 through 2009; the analysis consisted of sequential chi-square distributions in which patients were dichotomized into survivors or not, Glasgow Outcome Scale (GOS) of 1 to 3 versus 4 to 5, and CPP in steps of 5 mm Hg. For both mortality and neurological outcomes, 70 mm Hg was the optimal threshold for adults; however, in the subgroup of patients >55 years old, the identified threshold was 75 mm Hg. In addition, the study found no difference in outcomes for patients with CPP ≥ 70 compared with those < 70 for the subset with preserved auto regulation (PRx < 0.05); but for the subset with impaired regulation (PRx ≥ 0.05), those with CPP < 70 had significantly poorer outcomes.⁴

Class 3 Studies

The evidence from the Class 3 studies of CPP thresholds is summarized in Table 9-2.

Table 17-3. Summary of Evidence – Class 3 Studies (Cerebral Perfusion Pressure Thresholds)

| Reference, Study Topic | Study Design, N, and Outcomes | Data Class | Results Conclusion |
|---|--|------------|---|
| New Studies | | | |
| Chang 2009* ⁷ Brain tissue hypoxia PbrO ₂ CPP | Retrospective Cohort N=27 Single Level 1 Trauma Center in the United States Dichotomized GOS-E and FSE at 6-9 months post-injury | Class 3 | RR of poor outcome for subjects having at least 20% of hourly PbrO ₂ values below 20 from 2.8 to 4.6. CPP below 60 mm Hg was associated with a significant risk of hypoxia RR 3.01 (95% CI 2.51 to 3.61), p<0.0001. |
| Elf 2005* ⁸ CPP | Prospective Cohort N=81 Severe=72 Single University Hospital in Sweden Mailed questionnaire at 6 months post-injury based on GOS (with telephone follow-up) - dichotomized | Class 3 | <u>OR of favorable outcome</u> CPP <60 mm Hg= OR 1.55 (95% CI 1.10 to 2.19), p<0.05 CPP >70 mm Hg= OR 0.71 (95% CI 0.51 to 0.99), p<0.05 CPP >80 mm Hg= OR 0.69 (95% CI 0.49 to 0.98), p<0.05. |

| Reference, Study Topic | Study Design, N, and Outcomes | Data Class | Results Conclusion |
|--|---|------------|--|
| Huang 2006* ⁹ CPP >70 mm Hg and >60 mm Hg | Retrospective Cohort N=213 84 – ICP 77 – CPP > 70 52 – CPP > 60 Single University Hospital in Taiwan Dichotomized GOS at 6 months post-injury | Class 3 | No difference in outcomes between threshold groups. In the >70 and >60 groups, the mortality rate was 14.3% and 13.5%, respectively (p=0.55), the frequency of unfavorable outcomes was 22.1% and 17.3%, respectively (p=0.38), and the frequency of favorable outcomes was 63.7% and 69.2%, respectively (p=0.32). |
| Johnson 2011* ¹⁰ Compared outcomes for patients with impaired vs. intact cerebral pressure autoregulation (CPA) at <50, <60, >70, and >80 mm Hg | Prospective Cohort N=58 Single University Hospital in Sweden Dichotomized GOS at 6 months post-injury | Class 3 | No significant difference in outcome was seen between patients with more intact CPA when divided by level of CPP. In patients with more impaired CPA, CPP <50 mm Hg and CPP <60 mm Hg were associated with favorable outcome, whereas CPP >70 mm Hg and CPP >80 mm Hg were associated with unfavorable outcome. |
| Kuo 2006* ¹¹ Determine thresholds of ICP and CPP <i>during surgery</i> that were predictive of outcome. | Prospective Observational N=30 Single Center in Taiwan. GOS at 3 months post-injury | Class 3 | Initial ICP for unfavorable outcomes was 47.4 ± 21.4 mm Hg, resulting in a CPP of 22.8 ± 12.83 mm Hg. Initial ICP for favorable outcomes was 26.4 ± 10.1 mm Hg, resulting in a CPP of 48.8 ± 13.4 mm Hg. CPP had the largest area under the ROC curve in all stages of the operation, corresponding to intraoperative CPP thresholds of 37 mm Hg (initial), 51.8 mm Hg (intraoperative), and 52 mm Hg (after scalp closure). |
| Lin 2008* ¹² Assessed relationship between outcomes and CPP levels for patients with and without ICP monitoring, and higher vs. lower GCS (6-8 and 3-5) | Retrospective Cohort N=305 Eight Centers in Taiwan Mortality and dichotomized GOS at 3 months post-injury | Class 3 | Significantly lower mortality and better outcome for patients with GCS 3-5 when CPP was maintained >70 mm Hg, (p<0.05). |

| Reference, Study Topic | Study Design, N, and Outcomes | Data Class | Results Conclusion |
|--|--|------------|--|
| Zweifel 2008* ¹³ Assessed pressure reactivity (PRx) and outcomes | Retrospective Cohort N=398 Single Center in Cambridge, U.K. Mortality and GOS at 6 months post-injury | Class 3 | Optimal CPP for each patient was calculated based on the pressure reactivity index. Patients whose mean CPP varied above or below the optimal CPP were less likely to have a favorable outcome. 69% mortality in patients with PRx >0.25; <20% in patients with PRx <0.25 (p<0.0001). |
| Studies from 3rd Edition | | | |
| Changaris 1987 ¹⁴ | Retrospective analysis of the relationship between 1 year outcomes and initial CPP in 136 patients with severe TBI | Class 3 | All patients with CPP <60 mm Hg on the second post-injury day died; more patients had a good outcome than died when CPP was >80 mm Hg. |
| Clifton 2002 ¹⁵ | Retrospective review of 393 patients from the multicenter randomized hypothermia trial, comparing 6-month outcome with ICP, MAP, CPP, and fluid balance. | Class 3 | Poor outcome was associated with CPP <60 mm Hg. No benefit to maintaining CPP >70 mm Hg. |
| Contant 2001 ⁶ | Retrospective analysis of the factors related to the occurrence of ARDS in the 189 adults with severe TBI from the RCT comparing CPP- with ICP-targeted. | Class 3 | 5-fold increase in risk of ARDS in CPP group strongly related to use of pressors. |
| Juul 2000 ¹⁶ | Retrospective review of the 427 adult patients in the Selfotel RCT of the influence of ICP and CPP on neurological deterioration and 6-month outcome. | Class 3 | CPPs greater than 60 mm Hg had no significant influence on outcome. |
| McGraw 1989 ¹⁷ | Retrospective analysis of the relationship between 1-year outcomes and initial CPP in 221 patients with severe TBI | Class 3 | The likelihood of good outcomes was significantly higher and of death significantly lower if CPP was >80 mm Hg |
| Robertson 1999 ² Comparison of CBF protocol (CPP kept at >70 mm Hg and PaCO ₂ was kept at approximately 35 torr [4.67 kPa]) vs. ICP management protocol (CPP was kept at >50 mm Hg and hyperventilation to a PaCO ₂ of 25-30 torr [3.33-4.00 kPa]) | RCT (2-month time blocks randomized) N=189 CBF=100 ICP=89 Neurologic outcome at 6 months | Class 3 | No difference in neurologic outcome. CBF (higher CPP) had few jugular desaturations. ICP group had more jugular desaturations but these were rapidly managed. CBF group had more systemic complications: Adult respiratory distress syndrome was 5 times greater in the CBF-targeted group, p=0.007. |

| Reference, Study Topic | Study Design, N, and Outcomes | Data Class | Results Conclusion |
|---------------------------|--|------------|---|
| Steiner 2002 ³ | Prospective observation of CPP and outcome at 6 months for 114 adults with moderate or severe TBI. | Class 3 | Optimal CPP for each patient was calculated based on the pressure reactivity index. Patients whose mean CPP varied above or below the optimal CPP were less likely to have a favorable outcome. |

Abbreviations: ARDS=acute respiratory distress syndrome, CBF=cerebral blood flow, CPP=cerebral perfusion pressure, FSE=Functional Status Examination, GCS=Glasgow Coma Scale, GOS-E=Extended Glasgow Outcome Scale, ICP=intracranial pressure, PaCO₂=partial pressure of arterial carbon dioxide; RCT=randomized controlled trial, TBI=traumatic brain injury.

Note: Different abbreviations such as pBtO₂/PbtO₂ and P_iO₂ are used to mean brain tissue oxygen monitoring and brain tissue oxygen tension; we use PbrO₂ for consistency which may differ from what the study authors used.

One Class 3 study from the 3rd Edition of these guidelines contributes evidence for the recommendations for this topic. In order to randomize treatment in one hospital ICU, Robertson et al. randomly assigned 2 different protocols to 2-month time blocks. In the cerebral blood flow (CBF) protocol, CPP was maintained above 70 mm Hg. In the ICP-targeted protocol, CPP was maintained above 50 mm Hg. The proportion of patients with good recovery or moderate disability was not significantly different at 3 or 6 months (3 months: CPP 31.9%, ICP 37.0%, p=0.554; 6 months: CPP 39.8%, ICP 49.3%, p=0.49), but 15% of the CPP group developed ARDS compared with 3.3% of the ICP group (p=0.007). The primary outcome was jugular venous desaturation, which was more frequent in the ICP protocol group (OR 2.367, SE 0.8106, p=0.012).² Although the evidence is insufficient to contribute to a recommendation, avoiding CPP <50 mm Hg may be considered. (Ancillary monitoring of cerebral blood flow, oxygenation, or metabolism may facilitate CPP management.) Of the 14 Class 3 studies included for this topic, one was an RCT, one reanalyzed the RCT data, four were prospective, and eight were retrospective. Sample sizes ranged from 27 to 427; a total of 2,592 patients were observed. Outcomes included mortality; the GOS, Extended GOS, Functional Status Examination, and neurological outcomes spanning 3, 6, 9, and 12 months; and rates of ARDS. Findings were inconsistent (Table 17-3) and cannot be used to support a more detailed Level III recommendation.

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18. Advanced Cerebral Monitoring Thresholds

INTRODUCTION

The goal of the medical management of severe traumatic brain injury (TBI) is to ensure that nutrient delivery to the brain is optimized through the period of abnormal physiology and brain swelling that follows the injury. The only way to be assured that this is being achieved to the greatest extent possible is to measure brain metabolites which provide reassurance that the needs of oxidative metabolism are being met.

Historical means of examining brain health, such as the Kety-Schmidt method, which remains a gold standard assay for cerebral blood flow and metabolism,¹ as well as xenon-CT, which informs the former, were cumbersome.² Both provide information about large brain regions, as does jugular venous O₂ monitoring (S_jO₂). In recent decades, invasive monitors have been developed that monitor brain pressure, oxygenation (PbrO₂), and blood flow on a continuous or nearly continuous basis.³ Microdialysis techniques allow measurement of metabolites in the brain's extracellular fluid. Intracranial pressure is a clinically important surrogate measure of brain health discussed elsewhere in these guidelines.

Substantial gaps in our knowledge currently exist regarding how the data provided by advanced cerebral monitors should be used. These gaps are substantially greater for some such technologies than others. Studies published to date have attempted to explore putative thresholds of prognostic significance; however, uncertainty remains as to the precise thresholds that should be employed, and if the notion of a threshold best characterizes the relationship with outcome. For regional monitors, there is insufficient understanding of how specific brain regions and distance from focal lesions affect measurements.⁴ Moreover, placement of these monitors with stereotactic precision is not currently feasible for these devices. It is critical to consider these limitations and knowledge gaps when examining the literature supporting use of these technologies for patient care.

RECOMMENDATIONS

Level I and II

- There was insufficient evidence to support Level I or II recommendation for this topic.

Level III

- Jugular venous saturation of <50% may be a threshold to avoid in order to reduce mortality and improve outcomes.

Changes from Prior Edition

In the 3rd Edition of these guidelines, monitoring and thresholds were combined into one section. In this 4th Edition, they are reported separately, and this topic has been renamed Advanced Cerebral Monitoring (ACM) Thresholds. The Level III recommendation from the 3rd Edition about jugular venous saturation has been maintained. The Level III recommendation from the 3rd Edition about brain tissue oxygen monitoring has been revised based on reconsideration of the body of evidence.

EVALUATION OF THE EVIDENCE

Quality of the Body of Evidence

While there has been an increase in the number of studies published about ACM, there is not yet sufficient evidence about threshold values to target or avoid specific to the individual subtypes of ACM to inform Level I or II recommendations (Table 18-1).

Table 18-1. Quality of the Body of Evidence (Advanced Cerebral Monitoring Thresholds)

| Topic | Number of Studies | Meta-Analysis | Number of Subjects | Quality of Studies (Class 1 or 2) | Consistency (High, Moderate, Low) | Directness (Direct or Indirect) | Precision (High, Moderate, Low) | Quality of Evidence (High, Moderate, Low, or Insufficient) |
|--|-------------------------|---------------|--------------------|-----------------------------------|-----------------------------------|---------------------------------|---------------------------------|--|
| COMPONENTS OF OVERALL QUALITY – Class 2 | | | | | | | | |
| PbrO ₂ monitoring ⁵ | 1 Retro-spective, 0 RCT | NA | 32 | 2 | NA | Direct | Low | Insufficient |
| AVDO ₂ monitoring ⁶ | 1 Retro-spective 0 RCT | NA | 55 | 2 | NA | Direct | Low | Insufficient |

| Topic | Number of Studies | Meta-Analysis | Number of Subjects | Quality of Studies (Class 1 or 2) | Consistency (High, Moderate, Low) | Directness (Direct or Indirect) | Precision (High, Moderate, Low) | Quality of Evidence (High, Moderate, Low, or Insufficient) |
|--|---|---------------|--------------------|-----------------------------------|-----------------------------------|---------------------------------|---------------------------------|--|
| COMPONENTS OF OVERALL QUALITY – Class 3 | | | | | | | | |
| PbrO ₂ monitoring ⁷⁻¹¹ | 4 Pro-spective, 1 Retro-spective, 0 RCT | NA | 222 | 3 | Moderate | Direct | Low | Insufficient |
| AVDO ₂ monitoring ¹²⁻¹⁵ | 3 Pro-spective, 1 Retro-spective, 0 RCT | NA | 972 | 3 | Low | Direct | Low | Low |
| Cerebral autoregulation ^{16,17} | 1 Pro-spective, 1 Retro-spective | NA | 84 | 3 | Moderate | Direct | Low | Insufficient |

Abbreviations: NA=not applicable, RCT=randomized controlled trial.

Note: Different abbreviations such as pBtO₂/PbtO₂ and P_iO₂ are used to mean brain tissue oxygen monitoring and brain tissue oxygen tension; we use PbrO₂ for consistency, which may differ from what the study authors used.

Applicability

The included Class 2 studies^{5,6} were conducted at single sites and have small sample sizes, which could limit their applicability. The Class 3 studies are larger and more varied, but the four new studies added to this edition are all single-center studies conducted in the United States, Germany, and Israel. Given that their overall quality is low, applicability is less of a concern.

SUMMARY OF THE EVIDENCE

Process

Of the 48 new, potentially relevant studies reviewed, 42 were excluded because they did not meet the inclusion criteria for this topic (see Appendix F). Of the remaining six, two Class 2 studies^{5,6} and four Class 3 studies^{7,8,16,17} were included as evidence for this topic. Seven Class 3 studies from the 3rd Edition were also included for this topic.⁹⁻¹⁵

Class 2 Studies

The evidence from the Class 2 studies of advanced cerebral monitoring thresholds is summarized in Table 18-2.

Table 18-2. Summary of Evidence: Class 2 Studies (Advanced Cerebral Monitoring Thresholds)

| Reference, Study Topic | Study Design, N, and Outcomes | Data Class | Results Conclusion |
|--|--|------------|--|
| Brain Tissue Oxygen Monitoring | | | |
| Eriksson, 2012 ^{*5} To determine the value of brain tissue oxygenation (PbrO ₂) most predictive of survival | Retrospective Cohort N=32 Survived=22 Died=10 Survival in 72 hours | Class 2 | Mortality is higher when PbrO ₂ remains below 29 mm Hg in the 1st 72 hours. (F=12.898), p<0.001. |
| Jugular Bulb Monitoring of Arteriovenous Oxygen Content Difference | | | |
| Chierigato, 2007 ^{*6} Determine values of measures available from a jugular bulb monitoring associated with early death | Retrospective Cohort N=55 Survived=43 Early death=12 Brain death within 48 hours | Class 2 | AVD pPO ₂ and eRQ ranges were wider in patients who died in univariate analysis but did not predict outcome in multivariate model. Lactate variables were better predictors of death than AVDO ₂ and CO ₂ related indexes. |

Abbreviations: AVDO₂=arteriovenous oxygen content difference, PbrO₂=brain tissue oxygenation.

Note: Different abbreviations such as pBtO₂/PbtO₂ and P_iO₂ are used to mean brain tissue oxygen monitoring and brain tissue oxygen tension; we use PbrO₂ for consistency, which may differ from what the study authors used.

* **References new to the 4th Edition.**

Brain Tissue Oxygen Monitoring (PbrO₂)

Eriksson et al., 2012⁵ collected data hourly from both ICP and PbrO₂ monitors for the first 72 hours of monitoring in 32 patients and compared values for those who survived with those who died. The PbrO₂ values were significantly higher in survivors at 8, 12, 20-44, 52-60, and 72 hours (p<0.05), while ICP and CPP were not significantly different. The threshold most predictive of mortality was 29 mm Hg, with survivors having a longer period of time with PbrO₂ ≥29 during the first 72 hours of monitoring (hours, 52.2 ± 20.1 vs. 26.8 ± 16.1, p=0.001).

Jugular Bulb Monitoring of Arteriovenous Oxygen Content Difference (AVDO₂)

Chierigato et al., 2007⁶ analyzed data from blood samples of 55 patients taken with a retrograde jugular catheter during the 48 hours post-injury. Patients who died within the 48 hours (21.8%) due to TBI were compared with those who survived (78.2%). These samples were used to measure arteriovenous pCO₂ difference (AVDpCO₂), estimated respiratory quotient (eRQ), arteriovenous lactate difference (AVDL), and lactate oxygen index (LOI). The lactate variables were more clearly related to early death than isolated AVDpCO₂ widening and increases in eRQ.

Over time, the AVDP_{CO2} normalized in the patients who survived, suggesting that isolated measures of arteriovenous pCO₂ are not specific for global cerebral ischemia, but that monitoring over time could predict outcomes.

Class 3 Studies

The evidence from the Class 3 studies of advanced cerebral monitoring thresholds is summarized in Table 18-3.

Table 18-3: Summary of Evidence: Class 3 Studies (Advanced Cerebral Monitoring Thresholds)

| Reference Study Topic | Study Design, N, and Outcomes | Data Class | Results Conclusion |
|--|---|------------|---|
| New Studies | | | |
| Brain Tissue Oxygen Monitoring | | | |
| Chang 2009* ⁷ Assessed thresholds for PbrO ₂ and CPP | Retrospective Cohort N=27 Single Level 1 Trauma Center in the United States Dichotomized GOS-E and FSE (Functional Status Examination) at 6-9 months post-injury | Class 3 | RR of poor outcome for subjects having at least 20% of hourly PbrO ₂ values below 20 mm Hg from 2.8 to 4.6. CPP below 60 mm Hg was associated with a significant risk of hypoxia RR 3.01 (95% CI 2.51 to 3.61), p<0.0001. |
| Stiefel 2006* ⁸ Assessed PbrO ₂ levels and mortality | Prospective Cohort N=25 Single Level I Trauma Center in the United States Mortality | Class 3 | Mortality was 30% when brain O ₂ was greater than 25 mm Hg; 43% if the O ₂ level was less than 20 mm Hg; and 50% when it was less than 15 mm Hg. When the brain tissue O ₂ level was less than 20 mm Hg and did not improve during resuscitation, the mortality rate was 60%. |
| Cerebral Autoregulation Monitoring | | | |
| Sanchez-Porras 2012* ¹⁶ Assessed relationship between low-frequency pressure reactivity (L-PRx) values and outcomes | Retrospective Cohort N=29 Single University Hospital in Germany Mortality and GOS at 6 months post-injury | Class 3 | Critical value to avoid for averaged (for each patient) L-PRx is >0.2. 83.3% fatality for patients >0.2. Patients with fatal outcome had an averaged L-PRx of 0.4 while survivors had an averaged L-PRx of 0.03. Significant correlation between L-PRx and GOS at 6 months (r=-0.556, p=0.002). Significant difference in L-PRx values between survivors and non-survivors (p=0.001). |

| Reference Study Topic | Study Design, N, and Outcomes | Data Class | Results Conclusion |
|--|---|------------|--|
| Soustiel 2005* ¹⁷ Assessed CBF measurements with TCD | Prospective Cohort N=55 Single Hospital in Israel Dichotomized GOS at 3 months post- injury | Class 3 | 71.4% of patients with poor outcome had CBF levels below 35 mL/100g ⁻¹ /min ⁻¹ on admission in comparison with patients of favorable outcome in whom only 16.7% had such low CBF values (<i>p</i> =0.0007). |
| Studies from 3rd Edition | | | |
| Brain Tissue Oxygen Monitoring | | | |
| Bardt 1998 ⁹ | Prospective, observational study of 35 severe TBI (GCS ≤8) patients who underwent monitoring of brain tissue oxygen. Outcome was assessed by GOS at 6 months post-injury. | Class 3 | Time spent with a PbrO ₂ <10 was related to outcome as follows: Patients (n=12) with PbrO ₂ <10 mm Hg for <30 minutes had rates of: Favorable outcome: 73% Unfavorable outcome: 18% Death: 9% Patients (n=23) with PbrO ₂ <10 mm Hg for >30 minutes had rates of: Favorable outcome: 22% Unfavorable outcome: 22% Death: 56%. Low PbrO ₂ values and the duration of time spent with low PbrO ₂ are associated with mortality. |
| Valadka 1998 ¹⁰ | Prospective, observational study of 34 TBI patients who underwent monitoring of brain tissue oxygen. Outcome was assessed by GOS at 3 months post-injury. | Class 3 | The likelihood of death increased with increasing duration of time below PbrO ₂ of 15 mm Hg or with occurrence of any value below 6 mm Hg. Low PbrO ₂ values and the duration of time spent with low PbrO ₂ are associated with mortality. |

| Reference Study Topic | Study Design, N, and Outcomes | Data Class | Results Conclusion |
|---|---|------------|---|
| Van den Brink 2000 ¹¹ | Prospective, observational study of 101 severe TBI (GCS \leq 8) who underwent monitoring of brain tissue oxygen. Outcome was assessed by GOS at 6 months post-injury. | Class 3 | <p>Patients with initially low values (<10 mm Hg) of PbrO₂ for more than 30 minutes had higher rates of mortality and worse outcomes than those whose PbrO₂ values were low for less than 30 minutes. Time spent with a low PbrO₂ was related to outcome as follows:</p> <ul style="list-style-type: none"> PbrO₂ <5 mm Hg of 30 minutes duration was associated with a 50% risk of death. PbrO₂ <10 mm Hg of 1 hour 45 minutes duration was associated with a 50% risk of death. PbrO₂ <15 mm Hg of 4 hours duration was associated with a 50% risk of death. <p>Low PbrO₂ values and the duration of time spent with low PbrO₂ are associated with mortality. A 50% risk of death was associated with a PbrO₂ less than 15 mm Hg lasting longer than 4 hours.</p> |
| Jugular Bulb Monitoring of Arteriovenous Oxygen Content Difference | | | |
| Cormio 1999 ¹² | Retrospective analysis of 450 TBI patients who underwent jugular venous saturation monitoring in which the relationship of elevated SjO ₂ to GOS at 3 or 6 months was studied. The relationship of SjO ₂ to CBF measured by Kety-Schmidt method was also studied. | Class 3 | <p>Patients in group with mean SjO₂ >75% had significantly higher CBF. Patients in group with mean SjO₂ >75% had significantly worse outcomes (death or vegetative state in 49% and severe disability in 26%) compared with those with mean SjO₂ between 74 to 56%.</p> <p>High SjO₂ values may be associated with poor outcomes.</p> |
| Robertson, 1993 ¹³ | Prospective, observational study of SjO ₂ monitoring in 116 TBI patients (100 with closed head injury and 16 with penetrating head injury) in which desaturation episodes (SjO ₂ <50%) were monitored and correlated to GOS at 3 months post-injury. | Class 3 | <p>The number of episodes of desaturation were found to be associated with mortality as follows:</p> <ul style="list-style-type: none"> no desaturation episodes: mortality 18% one desaturation episode: mortality 46% multiple desaturation episodes: mortality 71%. <p>Episodes of desaturation are related to mortality and GOS at 3 months.</p> |

| Reference Study Topic | Study Design, N, and Outcomes | Data Class | Results Conclusion |
|--------------------------------------|--|------------|--|
| Robertson et al., 1995 ¹⁴ | Prospective, observational study of continuous SjO ₂ monitoring during first 5-10 days after injury in 177 TBI patients with GCS ≤8 in which episodes of desaturation (SjO ₂ <50%) were correlated with GOS at 3 months post-injury. | Class 3 | <p>Causes of desaturation are about equally divided between systemic and cerebral causes.</p> <p>39% of patients had at least one episode of desaturation (112 episodes in 69 patients)</p> <p>Systemic causes (hypotension, hypoxia, hypocarbia, and anemia) were responsible for 51 episodes, while cerebral causes (elevated ICP, vasospasm) were responsible for 54 episodes. The number of desaturation episodes were related to outcome as follows:</p> <p>Good recovery/moderate disability No episodes: 44% One episode: 30% Multiple episodes: 15%</p> <p>Severe disability/vegetative state No episodes: 35% One episode: 33% Multiple episodes: 15%</p> <p>Death No episodes: 21% One episode: 37% Multiple episodes: 69%</p> <p>Episodes of desaturation are common and are related to mortality and GOS at 3 months.</p> |
| Stocchetti 2004 ¹⁵ | Prospective observational study of 229 severe TBI patients measuring AVDO ₂ and SjO ₂ every 12 hours. | Class 3 | <p>At 6 months post injury, favorable outcomes group had significantly higher mean AVDO₂ (4.3 vol %; sd 0.9) than severe disability/vegetative group (3.8 vol %; sd 1.3) or group that died (3.6 vol %; sd 1) (p=0.001). AVDO₂ was a significant and independent predictor of outcome.</p> |

Abbreviations: CBF=cerebral blood flow, CPP=cerebral perfusion pressure, ICP=intracranial pressure, GCS=Glasgow Coma Scale, N=total sample size, PRx=Pressure-Reactivity Index

Note: Different abbreviations such as AJDO₂, and ajDO₂ are used to mean arterio-jugular difference of oxygen content; we use AVDO₂ for consistency, which may differ from what the study authors used.

Different abbreviations such as pBtO₂/PbtO₂ and P_iO₂ are used to mean brain tissue oxygen monitoring and brain tissue oxygen tension; we use PbrO₂ for consistency, which may differ from what the study authors used.

Different abbreviations such as SjvO₂ and S_jVO₂ are used to mean jugular venous saturation and jugular venous O₂ monitoring; we use SjO₂ for consistency, which may differ from what the study authors used.

* **Reference new to the 4th Edition**

Brain Tissue Oxygen Monitoring (PbrO₂)

Of the five Class 3 studies that addressed thresholds for PbrO₂ monitoring, four were prospective⁸⁻¹¹ and one was retrospective.⁷ All were from single centers. Outcomes included mortality, GOS-E and FSE measured between 6 and 9 months post-injury, and GOS measured at 3 and 6 months. A total of 222 patients were observed across studies, with sample sizes ranging from 25 to 101. One⁷ identified a PbrO₂ value of <20 mm Hg as a threshold to avoid. One⁸ showed increasingly poor outcomes as thresholds moved from <25 to <20 and <15 mm Hg. Three⁹⁻¹¹ suggested that longer duration of time at thresholds <10 and 15 mm Hg is associated with poorer outcomes.

Jugular Bulb Monitoring of Arteriovenous Oxygen Content Difference (AVDO₂)

Of the four Class 3 studies that addressed thresholds for AVDO₂ monitoring, three were prospective¹³⁻¹⁵ and one was retrospective.¹² Three were conducted in single centers,¹²⁻¹⁴ while one collected data in two hospitals.¹⁵ Outcomes included mortality and GOS measured at 3 and 6 months. A total of 972 patients were observed, with sample sizes ranging from 116 to 450. Cormio¹² found increased mortality and poor outcomes to be associated with a mean SjO₂ >75%. Stocchetti¹⁵ found a decreased mortality and better outcomes to be associated with higher mean AVDO₂ values. The two Robertson studies^{13,14} suggest that a SjO₂ value of ≤50% is a critical threshold to avoid.

Cerebral Autoregulation Monitoring

Both of the two Class 3 studies that addressed thresholds for cerebral autoregulation monitoring were from single centers. One retrospective study¹⁶ (N=29) found an association between mortality and L-PRx >0.2. The other prospective study¹⁷ (N=55) found an association between poor outcomes at 3 months post-injury and cerebral blood flow (CBF) levels below 35 mL/100g⁻¹/min⁻¹ on admission.

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Future Research

Management of patients with traumatic brain injury (TBI) is not a function of the application of individual treatments. No treatment or management approach exists independent of other treatments and approaches, or independent of the ecology. The design of meaningful and effective future research needs to be consistent with this clinical reality. The brain trauma community needs to design and engage in a systematic process for developing a research agenda that begins with thoughtful conversations about scope, topics, management environments, and research methods. The Living Guidelines Methods Team has proposed the development of a process to accomplish this goal. The process should include (1) identification and refinement of topics for individual studies that could serve to fill critical gaps in the guidelines, (2) improvement of individual study designs, and (3) incorporation of state-of-the-art methods for synthesizing literature, assessing bodies of evidence, and generating guidelines.

Topic Selection and Refinement

Topics addressed in this edition—in particular those for which no recommendation was made—provide a place to begin. However, listing all the unanswered questions and stating that more research is needed is a passive approach that will not advance the field or improve patient outcomes. For this reason, rather than repeat what is missing for each topic, the Methods Team plans to supplement the guidelines with an integrated Topic Refinement and Future Research process as part of the transition to Living Guidelines, which will result in a proposed research agenda.

To accomplish this, we need to monitor the field and add new topics as they become relevant. Additionally, for each existing topic we need to reexamine both the questions *and* the unexamined assumptions that have become established parameters in our process. For example, we currently limit studies for our guidelines to those with patient populations with an initial Glasgow Coma Scale (GCS) of 3 to 8. As we saw in assessing Deep Vein Thrombosis Prophylaxis for this edition, the decision to administer chemoprophylaxis is not always related to the patient's initial GCS. Consequently, that inclusion criterion might be inappropriate for this topic and may result in exclusion of studies with relevant data.

We need to approach topics systematically and with an open mind. We need to look back into the past and identify the unexamined assumptions that have driven the articulation of our key questions to date. Then we need to look at present and promising future developments, expanding to include other disciplines, to redefine the territory for key research questions. Concurrently, we should access any new information that may become available from the large comparative effectiveness research projects being conducted in both adult and pediatric populations. Findings from these studies could help us move from the current focus on individual treatments to a more ecologically valid model for generating guidelines.

Methods—Individual Studies

As stated in the Introduction section, we could begin the critical self-examination of our research methods by returning to the recommendations of the Clinical Trials in Head Injury Study Group.¹ That will only be useful if done inside a full recognition of the current paradigm for conducting clinical research. Unfortunately, the realities of conducting clinical research sometimes compromise sound scientific methods. Moving from a pilot to a full scale study may include:

- Revision of and heterogeneity in inclusion criteria, to increase sample size
- Revision of the protocol for delivering the intervention
- An increase in number of centers—to increase sample size and to speed recruitment in order to decrease study duration—resulting in a lack of standardized management across multiple centers
- Expanded data collection to meet multiple agency requirements
- Outcome measures that may not be clinically relevant
- Shortened time to complete follow-up
- Effect size requirements that may be statistically, but not clinically, relevant
- Budget constraints

The rationale for subjecting an effective single-center trial to the variability encountered in a large multi-center trial is valid. Ideally, a treatment should be effective across various clinical environments. However, failure at the multi-center level could be the result of factors other than,

or in addition to, lack of a robust treatment effect. Variability in research protocols, patient assessments, and data collection and management could be washing out the potential effects of the interventions we are studying.

Also in the spirit of critical self-examination is this question: What does our community need to do to produce a substantial and permanent shift in the quality of the studies we are generating? The direct approach of wagging the evidence-based finger is not changing research practice. What is in the background of our world view and frame of reference for research that is influencing our selection of research models and designs? How does the current paradigm for brain trauma allow for the persistence of studies that employ designs and protocols we know in advance will not produce strong evidence? Discovery at this contextual level will be necessary, but not sufficient, for the generation of strong evidence.

Methods—Systematic Reviews and Guidelines Development

In addition to a systematic and integrated approach to topic refinement and future research needs, we will continue to develop and use the most advanced methods available for our evidence reviews and generation of guidelines recommendations. Thus, there will be changes over time. In this edition, we improved our fidelity to the pre-specified inclusion criteria. We added an assessment of the quality of the body of available evidence to address specific questions, and used the overall quality and applicability to support recommendations. In the future, we will be examining our criteria for inclusion as well the criteria used to rate the quality of individual studies, the quality of the body of evidence, and applicability. As we continue this work, we will consider new methods as they become available and incorporate those that help us advance our mission to strengthen the evidence base related to TBI.

To do this, we will be reaching out to various stakeholders. We will draw on the collective expertise of multiple communities to develop a framework for guideline development that explicitly incorporates all steps from topic identification, through topic refinement, evidence synthesis, development of recommendations, and dissemination, to the prioritization of future research.

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Conclusion

Often, the available evidence is not sufficient to generate guidelines addressing the most critical questions faced by clinicians and patients. While there have been some major developments in severe traumatic brain injury (TBI) management, for some topics in this edition it was not possible to make new evidence-based recommendations. The options are to wait for better evidence to be produced, or to situate our reviews and guidelines in a larger enterprise. Our vision is a recursive structure for the reviews and guidelines to contribute to the development and execution of a research agenda that can provide the evidence base for better guidelines. We anticipate that this agenda will also promote the development and use of increasingly rigorous research methods in individual studies as well as reviews.

As outlined in the Introduction section, this edition differs from prior editions in several ways. First, we are moving from a static document to a “living guideline” model that will better meet the needs of the brain trauma community. Second, the Brain Trauma Foundation guidelines have been integrated into the Brain Trauma Evidence-based Consortium (B-TEC). In that context, the guidelines will contribute to, and benefit from, the realization of the mission of B-TEC to cause a paradigm shift in the assessment, diagnosis, treatment, and prognosis of brain trauma.

Appendices

Appendix A. Major Changes from 3rd to 4th Edition

Changes in the approach and methodology from the 3rd to this current 4th Edition are outlined in the Introduction and Methods sections. Within each topic, text describing the changes is included immediately following the Recommendations.

The table below lists the major changes for each topic.

| <i>Topic</i> | <i>Change</i> | <i>Explanation</i> |
|---|--|--|
| Treatments | | |
| Decompressive Craniectomy | New topic for 4th Edition. | This topic was part of the surgical guidelines. It has been added as it is an increasingly common treatment in the management of severe TBI. |
| Prophylactic Hypothermia | Meta-analysis was not repeated and the current evidence synthesis is now qualitative. | When reviewed according to current standards, treatments in studies were considered clinically different and not appropriate for meta-analysis. |
| Hyperosmolar Therapy | This topic focused on the comparative effectiveness of different hyperosmolar agents. ----- Eisenberg, 1988 is no longer included in this topic. | This is currently a routine therapy and the more urgent, clinically relevant question is which hyperosmolar agent to use. ----- This study is a Class 2 study of barbiturates. It is not Class 2 for this topic. |
| Cerebrospinal Fluid Drainage | New topic for 4th Edition. | This topic has been added as it is used in current practice to reduce ICP. It is anticipated that the evidence base will grow as the use and study of CSF drainage increases in TBI. |
| Ventilation Therapies | This title was changed from Hyperventilation. | This reflects the expansion of the search and will allow the inclusion of related therapies in the future. |
| Anesthetics, Analgesics, and Sedatives | No major change. | NA |
| Steroids | No major change. | Six-month outcomes from the CRASH trial were added to the evidence table and text. |
| Nutrition | New recommendations and addition of new studies. | Additions to recommendations were based on new evidence identified for this update. |

| <i>Topic</i> | <i>Change</i> | <i>Explanation</i> |
|--|---|--|
| Infection Prophylaxis | Scope limited to TBI-related issues (not general infection prevention). | Recommendations added based on included evidence. Evidence added about oral care. Level II Recommendations about the use of antibiotics for intubation has been deleted. Presently, using a course of antibiotics for this purpose would be considered a questionable treatment option, given the potential harms due to development of resistant organisms. |
| Anti-seizure Prophylaxis | No change in recommendations. Notation added that some evidence is indirect. | The Class 2 studies included in the 3rd Edition—Temkin, 1990 and 1999—include patients with both moderate and severe TBI, and the studies do not report the results separately. By our definition, this is indirect evidence and is now evaluated as such. |
| Deep Vein Thrombosis Prophylaxis | Scope limited to TBI-specific risk and treatment issues, though indirect evidence was used. | Much of the evidence is not TBI-specific. However, as this is an important issue in the management of TBI, it was maintained, and indirect evidence was used to inform recommendations. |
| Monitoring | | |
| Intracranial Cerebral Pressure Monitoring | Clarification of scope and questions for this topic. ----- Studies from prior editions that were re-classified for this topic are not included. | Prior editions addressed several questions in this section. The topic is now focused on whether monitoring results in better outcomes. ----- Eisenberg 1988 and Palmer 2001 are no longer included as they did not meet the current inclusion criteria. |
| Cerebral Perfusion Pressure Monitoring | CPP Monitoring was made its own section. | Monitoring and thresholds were split into separate sections in this edition to clarify the scope and allow for different quality assessment criteria. |
| Advance Cerebral Monitoring | Renamed. | The name was changed from Brain Oxygen Monitoring in order to accurately reflect that several types of monitoring could be included. |
| Thresholds | | |

| <i>Topic</i> | <i>Change</i> | <i>Explanation</i> |
|--|--|--|
| Blood Pressure Thresholds | Blood Pressure Thresholds was made its own section. Studies from pre-hospital care are no longer included. | Vasser 1990, 1991, and 1993 are studies of pre-hospital care and are no longer included. |
| ICP Thresholds | Eisenberg, 1988 is no longer included in this topic. | Eisenberg, 1988 is not included for this topic. This study is a Class 2 study of barbiturates. |
| Cerebral Perfusion Thresholds | CPP Thresholds was made its own section. | We split monitoring and thresholds into separate sections to clarify the scope and allow for different quality assessment criteria. |
| Advanced Cerebral Monitoring Thresholds | Name changed and scope clarified. | The name was changed from Brain Oxygen Monitoring in order to accurately reflect that several types of monitoring could be included. |

Abbreviations: CPP=cerebral perfusion pressure, CRASH=Corticosteroid Randomization After Significant Head Injury Trial, CSF=cerebrospinal fluid, ICP=intracranial pressure, NA=not applicable, TBI=traumatic brain injury.

Appendix B. Research Team

Methods Team

| | |
|---------------------|--|
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| | |
|---------------------------------|--|
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Appendix C. Analytic Frameworks

Treatments

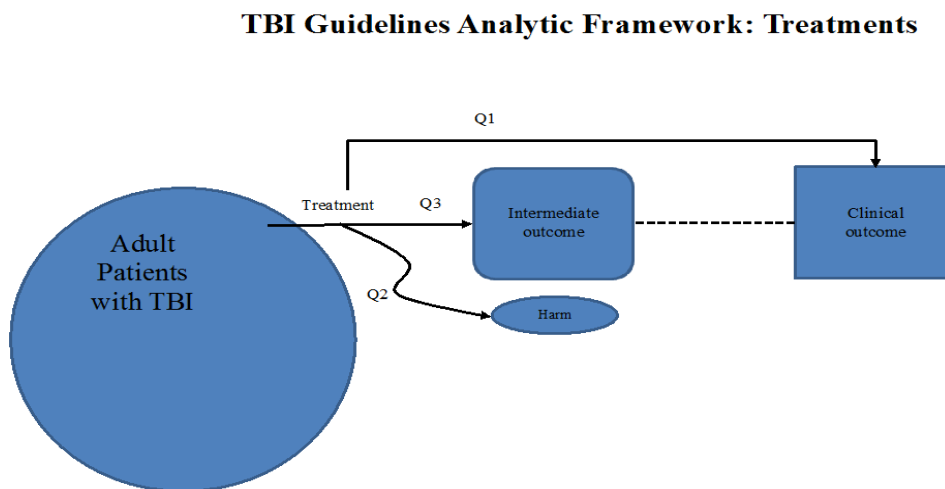
The analytic framework for treatments is presented in **Figure 1**. The general population is Adults with traumatic brain injury (TBI). For each treatment, the questions are:

Q1: Does the treatment affect clinical outcomes, defined as mortality and neurological function?

Q2: Does the treatment cause harms?

Q3: Does the treatment affect intermediate outcomes?

Figure 1.



For Decompressive Craniectomy (DC) as a treatment, the questions are:

Q1: Does DC reduce mortality or improve neurological outcomes?

Q2: Does DC cause harms?

Q3: Does DC lower ICP (an intermediate outcome)?

For each question, there may be more specific sub-questions. For DC there is research about the best size of the DC. Similarly, appropriate intermediate outcomes vary according to the treatment and are specified in the text of each treatment section.

Monitoring

Monitoring provides information that is used to make treatment decisions. As such, monitoring per se does not influence outcomes. Some studies follow the path from monitoring to changes in treatment, then from changes in treatment to outcomes (represented by the line for Q1, analytic framework for monitoring, **Figure 2**). This could include instances in which the treatment is controlled as part of the study or in which treatment variables are used to either define the study population or as controls for confounding. Other studies do not examine changes in treatment as a result of monitoring, but go directly from monitoring to outcome. This is depicted as Q4. The “black box” in Q4 indicates that some treatment happened, but the study does not track or consider what treatment was provided or how the ICP information affected treatment.

To summarize the questions are:

Q1: Does the monitoring affect treatment and ultimately impact clinical outcomes, defined as mortality and neurological function?

Q2: Does monitoring lead to treatment that causes harms?

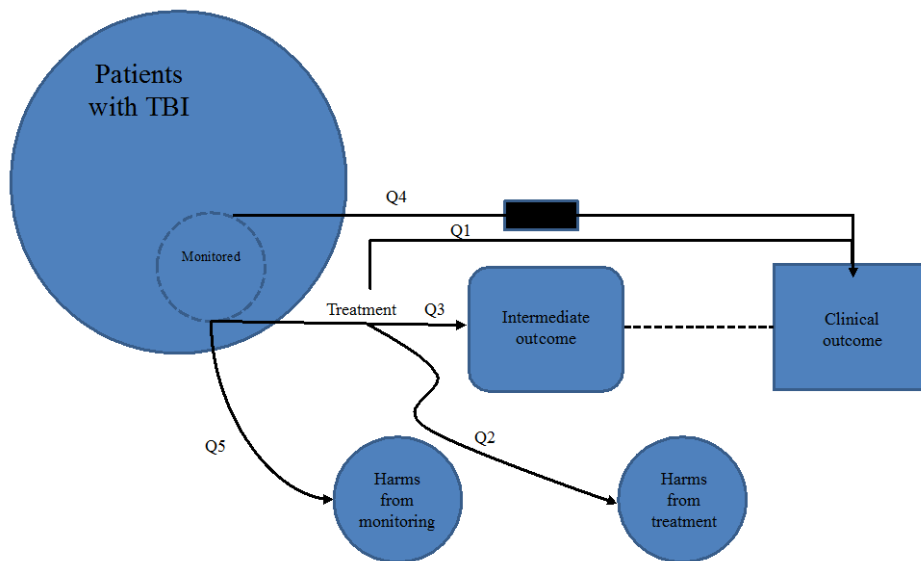
Q3: Does monitoring affect the treatment that then affects intermediate outcomes?

Q4: Is monitoring associated with changes in outcomes? In this case the impact on treatment is not measured, hence the “black box.”

Q5: Does monitoring cause harms?

Figure 2.

TBI Guidelines Analytic Framework: Monitoring



Thresholds

Threshold questions ask what values should be targeted or avoided when managing severe TBI. For example, when is intracranial pressure (ICP) high? Or what blood pressure (BP) and cerebral perfusion pressure (CPP) levels are ideal? The studies may be exploratory, in that they strive to identify a value, or they may be confirmatory, striving instead to confirm a previously identified value. While the types of studies used to identify or confirm threshold values differ from studies of interventions, the questions are similar. This is represented in **Figure 3**.

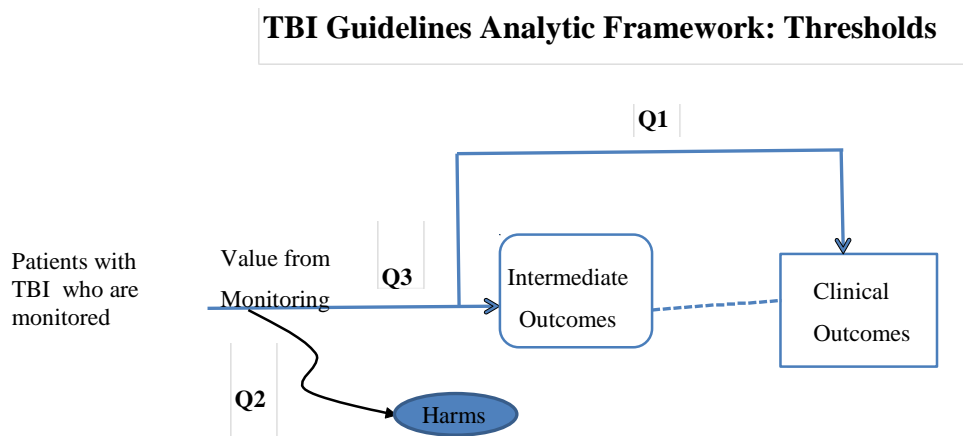
In threshold studies the population is patients with TBI who are monitored. The questions are:

Q1: What value is associated with better clinical outcomes?

Q2: What value is associated with worse outcomes or harm?

Q3: What value is associated with intermediate outcomes?

Figure 3.



Appendix D. Search Strategies

Decompressive Craniotomy

- 1 exp Craniocerebral Trauma/
- 2 ((head or brain\$) adj injur\$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, unique identifier]
- 3 1 or 2
- 4 intracranial hypertension.mp. or exp Intracranial Hypertension/
- 5 3 and 4
- 6 limit 5 to "all adult (19 plus years)"
- 7 limit 6 to english language
- 8 su.fs.
- 9 drain\$.mp.
- 10 cerebrospinal fluid shunts.mp. or exp Cerebrospinal Fluid Shunts/
- 11 neurosurgery.mp. or exp Neurosurgery/
- 12 shunt\$.mp.
- 13 exp Neurosurgical Procedures/
- 14 (craniot\$ or craniectom\$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
- 15 8 or 9 or 10 or 11 or 12 or 13 or 14
- 16 7 and 15
- 17 limit 16 to yr="2001 – 2013"

Prophylactic Hypothermia

- 1 exp Brain Injuries/
- 2 hypertherm\$.mp.
- 3 hypotherm\$.mp.
- 4 ((brain or cerebr\$) adj3 temperature\$).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
- 5 2 or 3 or 4
- 6 1 and 5
- 7 limit 6 to humans
- 8 limit 7 to English language
- 9 7 not 8
- 10 limit 9 to abstracts
- 11 8 or 10
- 12 exp "Outcome and Process Assessment (Health Care)"/
- 13 11 and 12
- 14 limit 11 to clinical trial
- 15 13 or 14
- 16 (2006\$ or 2007\$ or 2008\$ or 2009\$ or 2010\$ or 2011\$ or 2012\$ or 2013\$).ed.
- 17 15 and 16

Hyperosmolar Therapy

- 1 exp Brain Injuries/
- 2 ((brain\$ or cerebr\$) adj3 (trauma\$ or injur\$)).mp.
- 3 1 or 2
- 4 hyperosmol\$.mp.
- 5 “Osmolar Concentration”
- 6 saline.mp. or exp Sodium Chloride
- 7 (hyperton\$ adj3 saline).mp.
- 8 5 and 6
- 9 4 or 7 or 8
- 10 3 and 9
- 11 (2006\$ or 2007\$ or 2008\$ or 2009\$ or 2010\$ or 2011\$ or 2012\$ or 2013\$).ed.
- 12 10 and 11

CSF Drainage

- 1 exp Craniocerebral Trauma/
- 2 head injur\$.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
- 3 brain injur\$.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
- 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 adult (19 plus years)”
- 12 limit 11 to yr=”1980 –2013”

Hyperventilation

- 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 (2006\$ or 2007\$ or 2008\$ or 2009\$ or 2010\$ or 2011\$ or 2012\$ or 2013\$).ed.
- 10 8 and 9

Anesthetics

- 1 exp Brain Injuries/
- 2 cerebral perfusion pressure.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
- 3 1 and 2
- 4 (2006\$ or 2007\$ or 2008\$ or 2009\$ or 2010\$ or 2011\$ or 2012\$ or 2013\$).ed.
- 5 3 and 4
- 6 exp Craniocerebral Trauma/
- 7 exp Intracranial Pressure/
- 8 exp Intracranial Hypertension/
- 9 exp Intracranial Hypotension/
- 10 7 or 8 or 9
- 11 exp ANESTHETICS/
- 12 exp BARBITURATES/
- 13 exp PROPOFOL/
- 14 exp ETOMIDATE/
- 15 thiopentol.mp.
- 16 exp PENTOBARBITAL/
- 17 11 or 12 or 13 or 14 or 15 or 16
- 18 exp ANESTHESIA/
- 19 17 or 18
- 20 6 and 10 and 19
- 21 propofol infusion syndrome.mp.
- 22 20 or 21
- 23 limit 22 to human
- 24 limit 23 to english language
- 25 limit 23 to abstracts
- 26 24 or 25
- 27 (2006\$ or 2007\$ or 2008\$ or 2009\$ or 2010\$ or 2011\$ or 2012\$ or 2013\$).ed.
- 28 26 and 27

Analgesics

- 1 exp ANALGESICS/
- 2 exp “Hypnotics and Sedatives”/
- 3 propofol.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
- 4 exp phenothiazines/
- 5 exp central nervous system depressants/
- 6 1 or 2 or 3 or 4 or 5
- 7 exp Craniocerebral Trauma/
- 8 exp “SEVERITY OF ILLNESS INDEX”/ or exp INJURY SEVERITY SCORE/ or exp TRAUMA SEVERITY INDICES/

- 9 (severe or severity).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
- 10 exp Intensive Care Unites/ or exp Critical Care/
- 11 8 or 9 or 10
- 12 6 and 7 and 11
- 13 limit 12 to (english language and humans)
- 14 (2006\$ or 2007\$ or 2008\$ or 2009\$ or 2010\$ or 2011\$ or 2012\$ or 2013\$).ed.
- 15 13 and 14

Barbiturates

- 1 exp Craniocerebral Trauma/
- 2 exp BARBITURATES/
- 3 etomidate.mp.
- 4 pentobarbital.mp.
- 5 thiopental.mp.
- 6 2 or 3 or 4 or 5
- 7 1 and 6
- 8 exp Intracranial Hypertension/dt [Drug Therapy]
- 9 6 and 8
- 10 7 or 9
- 11 (2006\$ or 2007\$ or 2008\$ or 2009\$ or 2010\$ or 2011\$ or 2012\$ or 2013\$).ed.
- 12 10 and 11

Steroids

- 1 exp Craniocerebral Trauma/
- 2 exp STEROIDS/
- 3 1 and 2
- 4 (2006\$ or 2007\$ or 2008\$ or 2009\$ or 2010\$ or 2011\$ or 2012\$ or 2013\$).ed.
- 5 3 and 4

Nutrition

- 1 exp Craniocerebral Trauma/
- 2 exp nutrition/
- 3 1 and 2
- 4 exp Nutrition Therapy/
- 5 1 and 4
- 6 exp Energy Metabolism/
- 7 1 and 6
- 8 nutritional requirements/
- 9 1 and 8
- 10 exp nutrition assessment/
- 11 1 and 10

- 12 exp Craniocerebral Trauma/dh [Diet Therapy]
- 13 exp Dietary Supplements/
- 14 1 and 13
- 15 exp Craniocerebral Trauma/me [Metabolism]
- 16 (diet\$ or nutrit\$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
- 17 15 and 16
- 18 7 and 16
- 19 exp feeding methods/
- 20 1 and 19
- 21 exp vitamins/
- 22 1 and 21
- 23 3 or 5 or 9 or 11 or 12 or 14 or 17 or 18 or 20 or 22
- 24 limit 23 to human
- 25 limit 24 to english language
- 26 24 not 25
- 27 limit 26 to abstracts
- 28 25 or 27
- 29 (2006\$ or 2007\$ or 2008\$ or 2009\$ or 2010\$ or 2011\$ or 2012\$ or 2013\$).ed.
- 30 28 or 29

Infection Prophylaxis

- 1 exp Craniocerebral Trauma/
- 2 exp Central Nervous System Infections/
- 3 exp Craniocerebral Trauma/co [Complications]
- 4 exp Central Nervous System Infections/pc [Prevention & Control]
- 5 2 and 3
- 6 1 and 4
- 7 5 or 6
- 8 1 and 2
- 9 exp Anti-Infective Agents/
- 10 exp Antibiotic Prophylaxis/
- 11 9 or 10
- 12 8 and 11
- 13 exp Catheterization/
- 14 exp Catheters, Indwelling/
- 15 exp Ventriculostomy/
- 16 exp Cerebrospinal Fluid Shunts/
- 17 exp monitoring, physiologic/ and exp intracranial pressure/
- 18 13 or 14 or 15 or 16 or 17
- 19 8 and 18
- 20 2 and 11 and 18
- 21 7 or 12 or 19 or 20

- 22 limit 21 to humans
- 23 limit 22 to english language
- 24 22 not 23
- 25 limit 24 to abstracts
- 26 23 or 25
- 27 (2006\$ or 2007\$ or 2008\$ or 2009\$ or 2010\$ or 2011\$ or 2012\$ or 2013\$).ed.
- 28 26 and 27

Ventilator Associated Pneumonia

- 1 exp Pneumonia, Ventilator-Associated
- 2 exp Ventilators, Mechanical
- 3 exp Cross Infection
- 4 exp Infection Control
- 5 exp Pneumonia/ep, et, pc
- 6 3 or 4 or 5
- 7 2 and 6
- 8 1 or 7
- 9 prevalence
- 10 Cross-Sectional Studies
- 11 9 or 10
- 12 8 and 11
- 13 exp Iatrogenic Disease
- 14 exp Disease Transmission, Infectious
- 15 13 or 14
- 16 exp pneumonia
- 17 2 and 15 and 16
- 18 12 or 17
- 19 iatrogen\$.mp.
- 20 2 and 16 and 19
- 21 20 not 18
- 22 8 and 15
- 23 12 or 22
- 24 exp Craniocerebral Trauma
- 25 ((head or brain\$ or cereb\$ or skull\$ or crani\$) adj3 (injur\$ or wound\$ or traum\$ or damag\$)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
- 26 24 or 25
- 27 8 and 26
- 28 23 or 27
- 29 limit 28 to yr="2001 – 2013"

Anti-seizure Prophylaxis

- 1 seizure\$.mp.
- 2 head injur\$.mp.
- 3 1 and 2
- 4 (2006\$ or 2007\$ or 2008\$ or 2009\$ or 2010\$ or 2011\$ or 2012\$ or 2013\$).ed.
- 5 3 and 4

ICP Monitoring

- 1 exp Craniocerebral Trauma/
- 2 exp Intracranial Pressure/
- 3 exp Intracranial Hypertension/
- 4 1 and 2
- 5 1 and 3
- 6 exp Intracranial Pressure/ and exp Monitoring, Physiologic/
- 7 1 and 6
- 8 (2006\$ or 2007\$ or 2008\$ or 2009\$ or 2010\$ or 2011\$ or 2012\$ or 2013\$).ed.
- 9 7 and 8

ICP Thresholds

- 1 (intracranial hypertension or icp or intracranial pressure).mp.
- 2 head injur\$.mp.
- 3 (treatment or management or resuscitation).mp.
- 4 (threshold or level).mp.
- 5 1 and 2 and 3 and 4
- 6 limit 5 to humans
- 7 (2006\$ or 2007\$ or 2008\$ or 2009\$ or 2010\$ or 2011\$ or 2012\$ or 2013\$).ed.
- 8 6 and 7

Cerebral Perfusion Monitoring and Thresholds

- 1 exp Brain Injuries/
- 2 cerebral perfusion pressure.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
- 3 1 and 2
- 4 (2006\$ or 2007\$ or 2008\$ or 2009\$ or 2010\$ or 2011\$ or 2012\$ or 2013\$).ed.
- 5 3 and 4

Brain Oxygen Monitoring and Thresholds

- 1 exp Craniocerebral Trauma/
- 2 exp Craniocerebral Trauma/bl, cf, pa, pp, ra, ri, en, us, ur, me, mi [Blood, Cerebrospinal Fluid, Pathology, Physiopathology, Radiography, Radionuclide Imaging, Enzymology, Ultrasonography, Urine, Metabolism, Microbiology]

- 3 exp Monitoring, Physiologic/
- 4 1 and 3
- 5 exp Oxygen/
- 6 1 and 5
- 7 limit 6 to humans
- 8 3 and 7
- 9 2 and 5
- 10 9 not 8
- 11 limit 10 to humans
- 12 Microdialysis/
- 13 1 and 12
- 14 monitor\$.mp.
- 15 1 and 5 and 14
- 16 4 or 13 or 15
- 17 limit 16 to humans
- 18 17 or 7
- 19 exp Oxygen Consumption/
- 20 1 and 19
- 21 limit 20 to humans
- 22 18 or 21
- 23 limit 22 to “all adult (19 plus years)”
- 24 limit 23 to (case reports or letter)
- 25 23 not 24
- 26 (2006\$ or 2007\$ or 2008\$ or 2009\$ or 2010\$ or 2011\$ or 2012\$ or 2013\$).ed.
- 27 25 and 26

Blood Pressure and Oxygenation

- 1 exp Craniocerebral Trauma/
- 2 hypoxia.mp.
- 3 hypotension.mp.
- 4 2 or 3
- 5 1 and 2
- 6 limit 5 to human
- 7 (field or pre-hospital).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
- 8 (treatment or management or resuscitation).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
- 9 1 and 7 and 8
- 10 6 or 9
- 11 (2006\$ or 2007\$ or 2008\$ or 2009\$ or 2010\$ or 2011\$ or 2012\$ or 2013\$).ed.
- 12 10 and 11

Appendix E. Inclusion and Exclusion Criteria

| Inclusion Criteria | Exclusion Criteria |
|---|--|
| Population (note: population criteria may be relaxed and studies used as indirect evidence if no direct evidence is available). | |
| Human subjects | Animal or mechanical simulations; not human subjects |
| 85% of population must be: | if more than 15% are: |
| Adults | Children |
| Traumatic brain injury, non-penetrating | Brain injury not from trauma (e.g., stroke) or penetrating injury (gun shot, foreign object) or mixed pathology without separation of outcomes |
| In-hospital | Prehospital or outpatient treatment |
| GCS 3-8; or results presented for subgroup with this GCS | GCS \geq 9 with no results presented by GCS subgroups |
| N \geq 25 | N<25 |
| Interventions | |
| Decompressive Craniectomy | Studies of type of bone flap replacement |
| Prophylactic Hypothermia | |
| Hyperosmolar Therapy | |
| Cerebrospinal Fluid Drainage | |
| Ventilation Therapy | Hyperbaric O ₂ |
| Anesthetics, Analgesics and Sedatives | |
| Steroids | |
| Nutrition | |
| Infection Prophylaxis | |
| Deep Vein Thrombosis | |
| Anti-Seizure Prophylaxis | |
| ICP Monitoring | |
| CPP Monitoring | |
| Advanced Cerebral Monitoring | |
| Blood Pressure Thresholds | |
| ICP Thresholds | |
| CPP Thresholds | |
| Advanced Cerebral Monitoring Thresholds | |
| Comparator/Study Designs | |
| Two or more groups defined by differences in intervention (or monitoring or thresholds) and compared on an included outcome | Purely prognostic studies (non-treatment factors that affect outcome) that are not thresholds |

| Inclusion Criteria | Exclusion Criteria |
|---|--|
| Randomized controlled trials, cohort studies, case control studies | Descriptive studies (e.g., natural history or characteristics of the injury or of course of treatment) |
| Cohort Studies, Retrospective or Prospective | Case studies, case series |
| Case Control Studies | Assessments of Technologies (differences, cost, feasibility of use) |
| | Studies that assess the psychometrics of a measure (validity, reliability, etc.) |
| | New drug or device efficacy trials |
| Outcomes | |
| Mortality (inpatient or post discharge) | Physiologic measures without a link to an included outcome |
| Morbidity/Harms (e.g., pneumonia, bleeding, infection, ischemia, re operation etc.) | |
| Function (GOS other functional measure) | |
| Health services use (length of stay in hospital, in ICU etc.) | |
| Change in ICP (for treatments explicitly aimed at lowering ICP) | |
| Publication | |
| English | Not English |
| Publication date: 2000 or later (for updated topics) | Studies published prior to 2000 |
| Research study | Editorial, comments, letters |

Appendix F. Excluded Studies

Decompressive Craniotomy

1. Al-Jishi A, Saluja RS, Al-Jehani H, Lamoureux J, Maleki M, Marcoux J. Primary or secondary decompressive craniectomy: different indication and outcome. *Can J Neurol Sci* 2011;38(4):612-20.
2. Albanese J, Leone M, Alliez JR, et al. Decompressive craniectomy for severe traumatic brain injury: Evaluation of the effects at one year. *Crit Care Med*. 2003;31:2535-2538.
3. Aarabi B, Hesdorffer DC, Ahn ES, Aresco C, Scalea TM, Eisenberg HM. Outcome following decompressive craniectomy for malignant swelling due to severe head injury. *J Neurosurg*. Apr 2006;104:469-479.
4. Bao YH, Liang YM, Gao GY, Pan YH, Luo QZ, Jiang JY. "Bilateral decompressive craniectomy for patients with malignant diffuse brain swelling after severe traumatic brain injury: a 37-case study." *J Neurotrauma* 2010;27(2):341-347.
5. Chibbaro S, Tacconi L. Role of decompressive craniectomy in the management of severe head injury with refractory cerebral edema and intractable intracranial pressure. Our experience with 48 cases. *Surg Neurol* 2007;68(6):632-8
6. Daboussi A, Minville V, Leclerc-Foucras S, Geeraerts T, Esquerre JP, Payoux P, Fourcade O. "Cerebral hemodynamic changes in severe head injury patients undergoing decompressive craniectomy. [Erratum appears in J Neurosurg Anesthesiol. 2010 Apr;22(2):157]." *J Neurosurg Anesthesiol* 2009;21(4):339-45.
7. De Bonis P, Pompucci A, Mangiola A, Paternoster G, Festa R, Nucci CG, et al. Decompressive craniectomy for elderly patients with traumatic brain injury: it's probably not worth the while. *J Neurotrauma* 2011;28(10):2043-8.
8. Eberle BM, Schnuriger B, Inaba K, Gruen JP, Demetriades D, Belzberg H. Decompressive craniectomy: surgical control of traumatic intracranial hypertension may improve outcome. *Injury* 2010;41(9):894-8.
9. Faleiro RM, Faleiro LC, Caetano E, et al. "Decompressive craniotomy: prognostic factors and complications in 89 patients." *Arq Neuropsiquiatr* 2008;66(2B):369-373.
10. Howard JL, Cipolle MD, Anderson M, et al. "Outcome after decompressive craniectomy for the treatment of severe traumatic brain injury." *J Trauma* 2008;65(2):380-385; discussion 385-386.
11. Kim KT, Park JK, Kang SG, et al. Comparison of the effect of decompressive craniectomy on different neurosurgical diseases. *Acta Neurochir* 2009;151(1):21-30.
12. Leitgeb J, Erb K, Mauritz W, et al. Severe traumatic brain injury in Austria V: CT findings and surgical management. *Wiener Klinische Wochenschrift* 2007;119:56-63.
13. Liu B, Tian Y, Zhang Y, Zhang W. Therapeutic effect analysis of acute traumatic brain injuries. *Neurological Research* 2008;30(6):594-7.
14. Meier U, Lemcke J, Reyer T, Grawe A. "Decompressive craniectomy for severe head injury in patients with major extracranial injuries." *Acta Neurochir* 2006;Suppl 96:373-376.
15. Morgalla MH, Will BE, Roser F, Tatagiba M. "Do long-term results justify decompressive craniectomy after severe traumatic brain injury?" *J Neurosurg* 2008;109(4):685-690.

16. Paci GM, Sise MJ, Sise CB, et al. Preemptive craniectomy with craniotomy: what role in the management of severe traumatic brain injury? *J Trauma* 2009;67:531-536.
17. Rubiano AM, Villarreal W, Hakim EJ, et al. Early decompressive craniectomy for neurotrauma: an institutional experience. *Ulusal Travma ve Acil Cerrahi Dergisi = Turkish Journal of Trauma & Emergency Surgery: TJTES* 2009;15(1):28-38.
18. Schneider GH, von Helden A, Lanksch WR, Unterberg A. "Continuous monitoring of jugular bulb oxygen saturation in comatose patients--therapeutic implications." *Acta Neurochir (Wien)*. 1995;134(1-2):71-75.
19. Timofeev I, Czosnyka M, Nortje J, et al. Effect of decompressive craniectomy on intracranial pressure and cerebrospinal compensation following traumatic brain injury. *J Neurosurg* 2008;108:66-73.
20. Whitfield PC, Patel H, Hutchinson PJ, et al. "Bifrontal decompressive craniectomy in the management of posttraumatic intracranial hypertension." *Br J Neurosurg* 2001;15(6):500-7.
21. Williams RF, Magnotti LJ, Croce MA, et al. "Impact of decompressive craniectomy on functional outcome after severe traumatic brain injury." *J Trauma* 2009;66(6):1570-1574; discussion 1574-1576.

Prophylactic Hypothermia

1. McIlvoy L. The impact of brain temperature and core temperature on intracranial pressure and cerebral perfusion pressure. *J Neurosci Nurs* 2007;39:324-331.
2. Polderman KH, Rijnsburger ER, Peerdeman SM, Girbes AR. Induction of hypothermia in patients with various types of neurologic injury with use of large volumes of ice-cold intravenous fluid. *Crit Care Med* 2005;33:2744-2751.
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3rd Edition Class 3 Excluded Studies

| Topic | Study | Reason |
|--------------|-----------------------|---|
| Hyperosmolar | Becker and Vries 1972 | Descriptive |
| Hyperosmolar | James 1980 | Descriptive |
| Hyperosmolar | Marshall 1978 | Descriptive |
| Hyperosmolar | Mendelow 1985 | Descriptive |
| Hyperosmolar | Miller 1975 | Descriptive |
| Hyperosmolar | Muizelaar 1984 | Descriptive |
| Ventilation | Bouma 1992 | Case Series |
| Ventilation | Marion 1991 | Case Series |
| Ventilation | Sioutos 1995 | Case Series |
| Ventilation | Sheinberg 1992 | Case Series |
| Ventilation | Imberti 2002 | Case Series |
| Ventilation | Oertel 2002 | Case Series |
| Nutrition | Clifton 1986 | Study measured energy expenditure. |
| VAP | Holloway 1996 | Per clinical investigators – not current practice |
| VAP | Sundbarg 1996 | Per clinical investigators – not current practice |
| DVT | Black 1986 | Descriptive |
| DVT | Gerlach 2003 | Descriptive |
| DVT | Kleindienst 2003 | Descriptive |
| DVT | Norwood 2002 | Descriptive |

| Topic | Study | Reason |
|---------------|----------------|---|
| ICP | Howells 2005 | Not comparison of ICP –compares ICP oriented protocol with CPP-oriented protocol. |
| ICP | Saul 1982 | Not comparison of ICP reports on Thresholds. |
| ICP | Timofeev 2006 | Not comparison of ICP – reports on pre/postsurgical ICP. |
| ICP | Eisenberg 1988 | Included in Barbiturates; removed from other topics. |
| ICP | Palmer 2001 | No comparison group |
| ICP | Eisenberg 1990 | Not topic specific |
| ICP | Lobato 1986 | Not topic specific |
| ICP | Marmarou 1991 | Not topic specific |
| ICP | Miller 1981 | Not topic specific |
| ICP | Narayan 1982 | Not topic specific |
| ICP | Lee 1998 | Not topic specific |
| ICP | Miller 2004 | Not topic specific |
| ICP | Poca 1998 | Not topic specific |
| ICP | Narayan 1981 | Prognosis |
| ICP | Servadei 2002 | Prognosis |
| ACM | Schneider 1995 | Case series |
| ACM | Tolias 2004 | Not topic specific |
| BP Thresholds | Cooke 1995 | Data not related to outcomes. |
| BP Thresholds | Narayan 1982 | About ICP |

| Topic | Study | Reason |
|----------------|----------------|---|
| BP Thresholds | Vasser 1990 | Pre-hospital |
| BP Thresholds | Vasser 1991 | Pre-hospital |
| BP Thresholds | Vasser 1993 | Pre-hospital |
| ACM Thresholds | Schneider 1995 | Case Series, does not report thresholds |
| ACM Thresholds | Cruz 1998 | No threshold data |
| ACM Thresholds | LeRoux 1997 | No threshold data |

Abbreviations: ACM=advanced cerebral monitoring, BP=blood pressure, DVT = deep vein thrombosis, ICP = intracranial pressure, VAP = ventilator-associated pneumonia.

Appendix G. Criteria for Quality Assessment of Individual Studies

| Criteria | Study Design or Type | | |
|--|----------------------|---------------|-----------|
| | RCT | Observational | Threshold |
| Adequate random assignment | X | | |
| Allocation concealment | X | | |
| Groups similar at baseline | X | | |
| Outcome assessors blinded | X | | |
| Adequate sample size | X | X | X |
| No differential loss to follow-up | X | | |
| Follow-up $\geq 85\%$ | X | X | X |
| Intention to treat analysis | X | | |
| Baseline differences between eligible excluded and eligible included | X | | |
| Maintenance of comparable groups | X | | |
| Comparison of two or more groups must be clearly distinguished | | X | |
| Non-biased selection of patients | | X | X |
| Blind or independent assessment of outcomes | | X | X |
| Use of reliable/concrete outcomes | | X | X |
| Accurate ascertainment of cases | | X | X |
| Adequate control for potential confounders | | X | |

| Criteria | Study Design or Type | | |
|--|----------------------|---------------|-----------|
| | RCT | Observational | Threshold |
| Rationale for threshold value provided: either criteria stated a priori or specified that value would be derived from the data | | | X |
| Monitoring technology is the same or equivalent for all patients | | | X |
| Treatment protocol is similar for similar patients (e.g., all patients at certain values received the same interventions) | | | X |

Class 1 Evidence is derived from randomized controlled trials. However, some may be poorly designed, lack sufficient patient numbers, or suffer from other methodological inadequacies that render them Class 2 or 3.

Class 2 Evidence is derived from cohort studies including prospective, retrospective, and case-control. Comparison of two or more groups must be clearly distinguished. Class 2 evidence may also be derived from flawed RCTs.

Class 3 Evidence is derived from case series, databases or registries, case reports, and expert opinion. Class 3 evidence may also be derived from flawed RCTs, cohort, or case-control studies.

Appendix H. Quality of the Body of Evidence Assessment

Quality of the Body of Evidence Ratings and Criteria

Ratings

The overall assessment is whether the quality of the body of evidence is high, moderate, low, or insufficient. The definitions for these are:

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

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

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

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

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

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

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

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

Criteria:

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

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

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

Directness: Directness can have different definitions. We define it as whether the study population is the same as the population of interest and whether the study includes clinical rather than intermediate outcomes. Indirect is noted if the population differs; for example if the study includes both moderate and severe TBI or patients with stroke or TBI and does not separate the results by these population characteristics, or if the outcomes are not mortality or neurological function. As outlined in Methods, indirect evidence was only included if no direct evidence was found.

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

Appendix I. Hypothermia Interventions Detail

Included in the table below are details about the hypothermia intervention in the studies considered for Meta-analysis. Based on this information it was determined that the interventions differed in clinically important ways.

| Characteristics of the Hypothermia Intervention | Aibiki, 2000 | Clifton, 1993 | Clifton, 2001 | Clifton, 2011 | Jiang, 2000 | Liu, 2006 | Marion, 1997 | Qiu, 2005 |
|--|---------------------|----------------------|--|----------------------|------------------------------|---------------------------------|------------------------------|--------------------|
| Cooling duration | 3-4 days | 48 hours | 48 hours | 48 hours | 3-14 days | 3 days | 24 hours | 4.3 days (average) |
| Target cooling temperature (degrees C) | 32-33 | 32-33 | Bladder temp of 33 then 32.5 to 34.0 | 33 | 33-35 | 33-35 | 32-33 | 33-35 |
| Rate of rewarming | 1°C per day | 1°C per 4 hours | no faster than 0.5°C per 2-hour period | 0.5°C every 2 hours | No greater than 1°C per hour | Allowed to return spontaneously | No greater than 1°C per hour | Natural rewarming |