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Reviewed for evidence-based integrity and endorsed by the American Association of Neurological Surgeons and the Congress of Neurological Surgeons.

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Guidelines for the Management of Severe Traumatic Brain Injury, Fourth Edition

The scope and purpose of this work is 2-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 think it is important to have evidence-based recommendations 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. The complete guideline document, which summarizes and evaluates the literature for each topic, and supplemental appendices (A-I) are available online at https://www.braintrauma.org/coma/guidelines.

KEY WORDS: Severe traumatic brain injury, Adults, Critical care, Evidence-based medicine, Guidelines, Systematic review

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In the Fourth Edition of the "Brain Trauma Foundation's Guidelines for the Management of Severe Traumatic Brain Injury," there are 189 publications included as evidence to support 28 recommendations covering 18 topics. The publication reports on 5 Class 1 studies, 46 Class 2 studies, 136 Class 3 studies, and 2 meta-analyses. This synopsis provides an overview of the process, includes the updated recommendations, and describes the new evidence added. The complete guideline document, which summarizes and evaluates the literature for each topic, and supplemental appendices (A-I) are available online at https://www.braintrauma.org/coma/guidelines.

During the past 20 years, the brain trauma community's approach to guideline development has evolved as the science and application of evidence-based medicine has advanced. This new iteration of the guidelines reflects the most current methodologic standards and establishes more rigorous procedures for future work. As a result, the guidelines include 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. Details on the changes within each topic from the Third[1] to this Fourth Edition are listed in Appendix A in the complete Fourth Edition Guidelines and are described in the sections on each topic in the comprehensive guideline document. These are available online at https://www.braintrauma.org/coma/guidelines.

Despite these improvements, the recommendations are limited in many areas, reflecting persisting gaps in the evidence base for severe traumatic brain injury (TBI) management. Although there have been numerous new publications in the field since the Third Edition of the Guidelines was published in 2007,[1] many repeat the same methodologic flaws found in previous research. The comprehensive guideline document includes an examination of the current condition of brain trauma clinical research, outlines how this condition is defining and shaping the future, and proposes a solution in establishing a formal evidence-based consortium.

ABBREVIATIONS: TBI, traumatic brain injury; **RESCUEicp,** Randomised Evaluation of Surgery with Craniectomy for Uncontrollable Elevation of ICP

Scope of the Guidelines

The guidelines address treatment interventions, monitoring, and treatment thresholds that are specific to TBI or that address a risk that is greater in patients with TBI. The guidelines are 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.

Developing protocols that integrate TBI-specific, evidence-based recommendations with general best practices for trauma patients, and that provide guidance, suggestions, or options in areas of TBI management where the evidence is insufficient, is outside the scope of these guidelines. These recommendations are intended to provide the foundation on which protocols can be developed that are appropriate to different treatment environments.

Living Guidelines

This Fourth Edition of the Guidelines is transitional. We do not intend to produce a Fifth 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 change 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.

The first test of this approach will involve incorporating the results of the RESCUEicp (Randomised Evaluation of Surgery with Craniectomy for Uncontrollable Elevation of ICP) study, which was published just after the completion of this edition. This study is a randomized, controlled trial that evaluates decompressive craniectomy as a secondary procedure, after ICP-targeted medical therapies have failed.[2] The results of this trial will be evaluated and may impact recommendations related to decompressive craniectomy as well as ICP thresholds.

METHODS

The development of guidelines encompasses 2 major activities: first, a systematic review and synthesis of evidence; and second, the derivation of recommendations.

Systematic Evidence Review and Synthesis

Literature Search and Review

Our literature search protocol is detailed in the comprehensive guideline document, and the search strategies are in Appendix D to the same document. Both documents are available online at https://www.braintrauma.org/coma/guidelines.

The key criteria for including studies in the review were as follows: the population was adult patients with severe TBI (defined as Glasgow Coma Scale Score of 3-8), and the study assessed an included outcome (mortality; neurologic function; or appropriate, selected, intermediate outcomes for the topic). Differences were resolved via consensus or by a third reviewer. Detailed inclusion criteria and a list of studies excluded after full-text review are in the comprehensive guideline document in Appendices E and F.

Quality Assessment and Data Abstraction of Individual Studies

All included studies were assessed for potential bias, which is a systematic approach to assessing the internal validity or quality of studies. The criteria used in the Third 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 threshold studies (see Appendix G for a complete list of the quality criteria used for individual studies). Key data elements then were extracted from each study. These were provided to the guideline panel and summarized by topic in the guideline document (see summary by topic in the comprehensive guideline document available online at https://www.braintrauma.org/coma/guidelines). Class 1 is the highest class and is limited to good-quality randomized trials. Class 2 includes moderate-quality randomized controlled trials and good-quality cohort or case-control studies. Class 3 is the lowest class and is given to low-quality randomized controlled trials, moderate- to low-quality cohort or case control studies, and case series and other non-comparative designs.

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, after the Recommendations and preceding the Evidence Summary, which can be found in the comprehensive guideline document available online at https://www.braintrauma.org/coma/guidelines.

Quality of the Body of Evidence

Assessing the quality of the body of evidence involves 4 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 in the Methods section of the comprehensive guideline document, 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 topic section in the comprehensive guideline document (https://braintrauma.org/coma/guidelines).

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). Refer to the comprehensive guideline document available online at https://www.braintrauma.org/coma/guidelines for a complete definition of Applicability. In this edition, we consider the applicability of individual studies in the Quality of the Body of Evidence and Applicability section immediately after the recommendations.

Derivation of Recommendations

Development of Recommendations

Class 1, 2, and 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 the ability to translate the evidence into recommendations. Even if a recommendation was not made, the evidence was included to acknowledge its place in the body of evidence and make it accessible for future consideration. As new studies are generated and added to the evidence base, we expect to see changes in the assessment of the quality of the body of evidence.

Level of Recommendations

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 IIA recommendations were based on a moderate-quality body of evidence.
- Level IIB 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 the distinction between a Level IIB or a Level III recommendation. Level IIB recommendations were based on a body of evidence with Class 2 studies that provided direct evidence but were of overall low quality. Level III recommendations were based on Class 3 studies or on Class 2 studies providing only indirect evidence.

Consideration of applicability could result in a Level III recommendation (eg, a "moderate-quality body of evidence" with significant applicability concerns). In this edition, applicability alone was not used to downgrade a recommendation. Currently, there is a lack of standards and developed methods in this area, so we elected to cite applicability issues that were identified and discussed by the authors.

"Insufficient" was used in cases in which the body of evidence was insufficient to support a recommendation because there were no studies identified or because the body of evidence had major quality limitations. If the evidence was insufficient, no recommendation was made.

RECOMMENDATIONS

Revised Recommendations

There are now 28 evidence-based recommendations; 14 are new or changed from the previous edition, while 14 have not changed. These include 1 Level I, 7 Level IIA, 10 Level IIB, and 10 Level III recommendations. There are 7 Third Edition recommendations that are restated here but are no longer substantiated by evidence meeting current standards.

Tables 1, 2, and 3 provide the recommendations for treatments, monitoring, and thresholds, respectively. In these tables, the recommendations in bold are new or have been revised; those in regular text have not changed. The comprehensive guideline document available online includes a section on each topic consisting of an Introduction, Recommendations, Evaluation of the Evidence, and Summary of the Evidence (including narrative and evidence tables).

Treatment Recommendations

Table 1 contains the recommendations for 11 treatments that are either specific to the in-hospital management of severe TBI or are related to risks experienced by patients with TBI. The topics that are included reflect current practice but are expected to change as new treatments are developed that may replace or complement existing treatments.

Decompressive craniectomy and cerebrospinal fluid drainage are new topics to this edition, so the recommendations for these topics also are new. Other changes include revision of the hypothermia, nutrition and infection prophylaxis recommendations, and a statement in the seizure prophylaxis topic that there is not yet sufficient evidence to support a recommendation about levetiracetam, despite its widespread use. The recommendations for anesthetics have not changed, but we updated the reference to the Food and Drug Administration warning that high doses of propofol can increase the risk of morbidity.[3] A list of the 41 studies that constitute the new evidence informing these recommendations is cited by topic in Table 4.[4-44]

Monitoring Recommendations

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. These recommendations are related to the influence on patient outcomes of 3 types of monitoring: ICP, cerebral perfusion pressure monitoring, and advanced cerebral monitoring. Although 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 technology-based 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.

Table 2 contains revised recommendations for all 3 types of monitoring. New evidence cited in Table 4 has led to revisions to

TABLE 1. Updated Treatment Recommendations[a,b]

Topic	Recommendations
Decompressive craniectomy	Level IIA
	• **Bifrontal DC is not recommended to improve outcomes as measured by the GOS-E score at 6 mo 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 min within a 1-h period that are refractory to first-tier therapies. However, this procedure has been demonstrated to reduce ICP and to minimize days in the 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 trial[2] were released soon after the completion 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 if needed. Updates will be available at https://braintrauma.org/coma/guidelines.
Prophylactic hypothermia	Level IIB
	• **Early (within 2.5 h), short-term (48 h post-injury), prophylactic hypothermia is not recommended to improve outcomes in patients with diffuse injury.**
Hyperosmolar therapy	Recommendations from the prior (Third) Edition not supported by evidence meeting current standards.
	Mannitol is effective for control of raised ICP at doses of 0.25 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 neurologic deterioration not attributable to extracranial causes.
Cerebrospinal fluid drainage	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 GCS <6 during the first 12 h after injury may be considered.**
Ventilation therapies	Level IIB
	• Prolonged prophylactic hyperventilation with $PaCO_2$ of ≤25 mm Hg is not recommended.
	Recommendations from the prior (Third) Edition not supported by evidence meeting current standards.
	Hyperventilation is recommended as a temporizing measure for the reduction of elevated ICP.
	Hyperventilation should be avoided during the first 24 h after injury when CBF often is reduced critically.
	If hyperventilation is used, SjO_2 or $BtpO_2$ measurements are recommended to monitor oxygen delivery.
Anesthetics, analgesics, and sedatives	Level IIB
	• 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.[3]
Steroids	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.
Nutrition	Level IIA
	• **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 IIB
	• **Transgastric jejunal feeding is recommended to reduce the incidence of ventilator-associated pneumonia.**
Infection prophylaxis	Level IIA
	• Early tracheostomy is recommended to reduce mechanical ventilation days when the overall benefit is thought 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 PI oral care is not recommended to reduce ventilator-associated pneumonia and may cause an increased risk of acute respiratory distress syndrome.**

(Continues)

TABLE 1. ***Continued***

Topic	Recommendations
	Level III
	• **Antimicrobial-impregnated catheters may be considered to prevent catheter-related infections during external ventricular drainage.**
Deep vein thrombosis Prophylaxis	Level III
	• LMWH or low-dose unfractioned 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.
Seizure prophylaxis	Level IIA
	• 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 d of injury), when the overall benefit is thought 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 compared with phenytoin regarding efficacy in preventing early post-traumatic seizures and toxicity.**

[a] $BtpO_2$, brain tissue O_2 partial pressure; CBF, cerebral blood flow; CSF, cerebrospinal fluid drainage; DC, decompressive craniectomy; EEG, electroencephalogram; EVD, external ventricular drainage; GCS, Glasgow Coma Scale; GOS-E, Glasgow Outcome Scale—Extended; ICP, intracranial pressure; ICU, intensive care unit; LMWH, low molecular weight heparin; $PaCO_2$, partial pressure of arterial carbon dioxide; PI, povidone-iodine; PTS, posttraumatic seizures; RESCUEicp trial, Randomised Evaluation of Surgery with Craniectomy for Uncontrollable Elevation of ICP trial; SjO_2, jugular venous oxygen saturation; TBI, traumatic brain injury.

[b] Bold: New or revised recommendations.

the ICP and cerebral perfusion pressure monitoring recommendations.

Threshold Recommendations

These recommendations are related to threshold values for parameters that are monitored during the in-hospital management of patients with severe TBI. In this Fourth Edition, we include thresholds for blood pressure, ICP, cerebral perfusion pressure, and advanced cerebral monitoring. 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.

DISCUSSION

New Evidence

In updating the recommendations, 102 articles were added to the body of evidence. These fall into 3 categories. The 41 studies listed in Table 4 contributed to additions or changes to the recommendations. Table 4 lists these by topic and includes basic information about the studies, including study design, the number of patients included (N), and the data class. More details, including outcomes and results, are included in the evidence tables and narrative in the comprehensive guideline document available online at https://www.braintrauma.org/coma/guidelines.

Another 27 studies present new evidence, but, for various reasons (eg, single studies with small samples, inconsistent results across studies, lack of precision), they were assessed as insufficient to support adding or changing a recommendation. The remaining 34 new studies met the inclusion criteria, but they supplement the findings of the previous research that informed existing recommendations and did not change the findings or the strength of evidence. All the included studies are cited and discussed in the comprehensive guideline document available online at https://www.braintrauma.org/coma/guidelines.

Future Research

Management of patients with TBI is not a function of the application of individual treatments. No treatment or management approach exists independent of other treatments and approaches, or independent of the ecology. 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 process should include (1) identification and refinement of topics for studies that could serve to fill critical gaps in the guidelines, (2) improvement of study designs, and (3) incorporation of state-of-the-art methods for synthesizing literature, assessing bodies of evidence, and generating guidelines.

TABLE 2. Updated Monitoring Recommendations[a,b]

Topic	Recommendations
Intracranial pressure monitoring	Level IIB
	• **Management of severe TBI patients using information from ICP monitoring is recommended to reduce in-hospital and 2-week post-injury mortality.**
	Recommendations from the prior (Third) Edition not supported by evidence meeting current standards.
	ICP should be monitored in all salvageable patients with a TBI (GCS 3-8 after resuscitation) and an abnormal CT scan. An abnormal CT scan of the head is one that reveals hematomas, contusions, swelling, herniation, or compressed basal cisterns.
	ICP monitoring is indicated in patients with severe TBI with a normal CT scan if ≥2 of the following features are noted at admission: age >40 years, unilateral or bilateral motor posturing, or SBP <90 mm Hg.
Cerebral perfusion pressure monitoring	Level IIB
	• **Management of severe TBI patients using guidelines-based recommendations for CPP monitoring is recommended to decrease 2-wk mortality.**
Advanced cerebral monitoring	Level III
	• Jugular bulb monitoring of $AVDO_2$, as a source of information for management decisions, may be considered to reduce mortality and improve outcomes at 3 and 6 mo post-injury.

[a] $AVDO_2$, arteriovenous oxygen content difference; CPP, cerebral perfusion pressure; CT, computed tomography; GCS, Glasgow Coma Scale; ICP, intracranial pressure; SBP, systolic blood pressure; TBI, traumatic brain injury.
[b] Bold: New or revised recommendations.

Individual Studies

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.[45] They encouraged (in part):

- Identification and testing of specific (appropriate) subgroups of patients with TBI
- 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. That only will 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 the number of research 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 worldview 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 use designs and protocols we know in advance will not produce strong evidence? Discovery at this contextual level

TABLE 3. Updated Recommendations: Thresholds[a,b]

Topic	Recommendations
Blood pressure thresholds	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 >70 years old may be considered to decrease mortality and improve outcomes.**
Intracranial pressure thresholds	Level IIB
	• **Treating ICP >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 trial[2] were released after the completion 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 if needed. Updates will be available at https://braintrauma.org/coma/guidelines.
Cerebral perfusion pressure thresholds	Level IIB
	• **The recommended target 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 autoregulatory status of the patient.**
	Level III
	• Avoiding aggressive attempts to maintain CPP >70 mm Hg with fluids and pressors may be considered because of the risk of adult respiratory failure.
Advanced cerebral monitoring thresholds	Level III
	• Jugular venous saturation of <50% may be a threshold to avoid in order to reduce mortality and improve outcomes.

[a]CPP, cerebral perfusion pressure; CT, computed tomography; ICP, intracranial pressure; RESCUEicp trial, Randomised Evaluation of Surgery with Craniectomy for Uncontrollable Elevation of ICP; SBP, systolic blood pressure.
[b]Bold: New or revised recommendations.

will be necessary, but not sufficient, for the generation of strong evidence.

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 Effectiveness Research, which is being promoted by funding agencies and adopted by large consortium efforts in the brain trauma research community. However, at the operational level, Comparative Effectiveness Research still is subject to many of the same vulnerabilities as traditional research, because it is accomplished using randomized controlled trials and observational studies. A transition to a new focus on Comparative Effectiveness Research must be accompanied by consistent adherence to evidence-based protocols.

CONCLUSION

Often, the available evidence is not sufficient to generate guidelines addressing the most critical questions faced by clinicians and patients. Although there have been some major developments in severe TBI management, for other 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 that includes ongoing publication monitoring, systematic reviews and synthesis, and guidelines that then contribute back to the development and execution of a research agenda that can provide the evidence base for more comprehensive guidelines. We anticipate that this agenda also will promote the development and use of increasingly rigorous research methods in individual studies as well as reviews. A detailed and comprehensive future research agenda is provided in the comprehensive guideline document available online at https://www.braintrauma.org/coma/guidelines.

Disclosures

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TABLE 4. New Studies Added to Evidence Supporting Revisions to Recommendations[a]

Topic	Reference	Study Design and Sample Size (N)	Data Class
Treatments			
Decompressive craniectomy	Cooper et al, *N Engl J Med,* 2011[4]	RCT (N = 155)	1
	Jiang et al, *J Neurotrauma,* 2005[5]	RCT (N = 486)	2
	Qiu et al, *Crit Care,* 2009[6]	RCT (N = 74)	2
Hypothermia	Clifton et al, *Lancet Neurol,* 2011[7]	RCT (N = 97)	1
Cerebrospinal fluid drainage	Nwachuku et al, *Neurocrit Care,* 2013[8]	Retrospective cohort (N = 62)	3
	Griesdale et al, *Can J Neurol Sci,* 2010[9]	Retrospective cohort (N = 171)	3
Nutrition	Chourdakis et al, *J Parenter Enteral Nutr,* 2012[10]	RCT (N = 59)	2
	Hartl et al, *J Neurosurg,* 2008[11]	Retrospective cohort (N = 797)	2
	Lepelletier et al, *J Neurosurg Anesthesiol,* 2010[12]	Retrospective cohort (N = 161)	2
	Dhandapani et al, *Surg Neurol Int,* 2012[13]	Prospective cohort (N = 67)	3
	Acosta-Escribano et al, *Intensive Care Med,* 2010[14]	RCT (N = 104)	2
Infection prophylaxis	Seguin et al, *Crit Care Med,* 2006[15]	RCT (N = 98)	2
	Seguin et al, *Crit Care Med,* 2014[16]	RCT (N = 179)	1
	Ratilal et al, *Cochrane Databse Syst Rev,* 2011[17]	Meta-analysis 17 studies (N = 2134)	Moderate
	Wang et al, *Crit Care,* 2013[18]	Meta-analysis 8 studies (N = 3038)	Moderate
Deep vein thrombosis prophylaxis	Daley and Brown, *Am Surg,* 2015[19]	Retrospective cohort (N = 271)	3
	Kwiatt et al, *J Trauma Acute Care Surg,* 2012[20]	Retrospective cohort (N = 1215)	3
	Mohseni et al, *J Emerg Trauma Shock,* 2012[21]	Retrospective case-control (N = 78)	3
	Scudday et al, *J Am Coll Surg,* 2011[22]	Retrospective cohort (N = 812)	3
Monitoring			
Intracranial pressure monitoring	Alali et al, *J Neurotrauma,* 2013[23]	Retrospective cohort (N = 10 628)	2
	Chesnut et al, *N Engl J Med,* 2012[24]	RCT (N = 324)	1
	Farahvar et al, *J Neurosurg,* 2012[25]	Retrospective cohort (N = 1304)	2
	Gerber et al, *J Neurosurg,* 2013[26]	Retrospective cohort (N = 2320)	2
	Talving et al, *J Neurosurg,* 2013[27]	Prospective cohort (N = 216)	2
	Haddad et al, *Anaesth Intensive Care,* 2011[28]	Retrospective cohort (N = 477)	3
	Kostic et al, *Med Pregl,* 2011[29]	RCT (N = 61)	3
	Liew et al, *Med J Malaysia,* 2009[30]	Prospective cohort (N = 72)	3
	Mauritz et al, *Intensive Care Med,* 2008[31]	Prospective cohort (N = 1856)	3
	Shafi et al, *J Trauma,* 2008[32]	Retrospective cohort (N = 1646)	3
Cerebral perfusion pressure monitoring	Gerber et al, *J Neurosurg,* 2013[26]	Retrospective cohort (N = 2320)	2
Thresholds			
Blood pressure thresholds	Berry et al, *Injury,* 2012[33]	Retrospective cohort (N = 15 733)	2
	Brenner et al, *J Trauma Acute Care Surg,* 2012[34]	Prospective cohort (N = 60)	3
	Butcher et al, *J Neurotrauma,* 2007[35]	Retrospective cohort (N = 6801)	3
Intracranial pressure thresholds	Sorrentino et al, *Neurocrit Care,* 2012[36]	Retrospective cohort (N = 459)	2
Cerebral perfusion pressure thresholds	Allen et al, *Pediatr Crit Care Med,* 2014[37]	Retrospective cohort (N = 1757)	2
	Sorrentino et al, *Neurocrit Care,* 2012[36]	Retrospective cohort (N = 459)	2
	Chang et al, *Crit Care Med,* 2009[38]	Retrospective cohort (N = 27)	3
	Elf et al, *Neurosurgery,* 2005[39]	Prospective cohort (N = 81)	3
	Huang et al, *Surg Neurol,* 2006[40]	Retrospective cohort (N = 213)	3
	Johnson et al, *Neurosurgery,* 2011[41]	Prospective cohort (N = 58)	3
	Kuo et al, *J Clin Neurosci,* 2006[42]	Prospective cohort (N = 30)	3
	Lin et al, *Acta Neurochirg Suppl,* 2008[43]	Retrospective cohort (N = 305)	3
	Zweifel et al, *Neurosurgery,* 2008[44]	Retrospective cohort (N = 398)	3

[a]N, sample size; RCT, randomized controlled trial.

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APPENDICES

All appendices are available online at https://www.braintrauma.org/coma/guidelines.

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