Chapter 1. Introduction

I. RECOMMENDATIONS

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

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

After rigorous application of the criteria for including studies that were prespecified by the guidelines committee, we found 27 new publications for the second edition. However, 25 publications that were included in the 2003 document failed to meet the more rigorous criteria in this second edition (Appendix A). Key reasons for excluding publications were 1) no clear specification of admission Glasgow Coma Scale score; 2) inclusion of patients with pathologies other than severe TBI; 3) inclusion of adult patients without analysis of data by age; and 4) failure to include a relevant health outcome such as mortality or function or even an important surrogate outcome such as intracranial pressure. For example, a recent study by Bar-Joseph et al (13) on the use of ketamine as a sedative in pediatric brain injury could not be included as evidence because the admission Glasgow Coma Scale was not specified, and the sample included children with pathologies other than severe TBI.

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

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

We rated the quality of randomized controlled trials using predefined criteria designed to assess study design factors that are widely accepted as important indicators of internal validity: use of adequate randomization, allocation concealment, and blinding methods; similarity of compared groups at baseline; maintenance of comparable groups; use of an intention-to-treat analysis; overall follow-up rate of ≥85%; and no differential loss to follow-up. We used separate predefined criteria to rate the quality of cohort and case–control studies designed to reflect the most important aspects of those study designs: nonbiased patient selection methods, identification and ascertainment of events, adequate sample size, follow-up rate of at least 85%, and use of adequate statistical methods to control for potentially confounding variables.

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

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

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

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

Chapter	First Edition	Second Edition
Cerebral Perfusion Pressure	Level II—A CPP >40 mm Hg in children with TBI should be maintained Level III—A CPP between 40 and 65 mm Hg probably represents an age-related continuum for the optimal treatment threshold; there may be exceptions to this range in some infants and neonates Level III—Advanced cerebral physiological monitoring may be useful to define the optimal CPP in individual instances Level III—Hypotension should be avoided	Level III—A minimum CPP of 40 mm Hg may be considered in children with TBI Level III—A CPP threshold 40–50 mm Hg may be considered; there may be age-specific thresholds with infants at the lower end and adolescents at the upper end of this range
Hyperosmolar Therapy	Level III—Hypertonic saline is effective for control of increased ICP after severe head injury; effective doses as a continuous infusion of 3% saline range between 0.1 and 1.0 mL/kg of body weight per hour, administered on a sliding scale; the minimum dose needed to maintain ICP <20 mm Hg should be used Level III—Mannitol is effective for control of increased ICP after severe TBI; effective bolus doses range from 0.25 g/kg of body weight to 1 g/kg of body weight Level III—Euvolemia should be maintained by fluid replacement; a Foley catheter is recommended in these patients to avoid bladder rupture Level III—Serum osmolarity should be maintained below 320 mOsm/L with mannitol use, whereas a level of 360 mOsm/L appears to be tolerated with hypertonic saline, even when used in combination with mannitol	Level II—Hypertonic saline should be considered for the treatment of severe pediatric TBI associated with intracranial hypertension; effective doses for acute use range between 6.5 and 10 mL/kg Level III—Hypertonic saline should be considered for the treatment of severe pediatric TBI associated with intracranial hypertension; effective doses as a continuous infusion of 3% saline range between 0.1 and 1.0 mL/kg of body weight per hour, administered on a sliding scale; the minimum dose needed to maintain ICP <20 mm Hg should be used; serum osmolarity should be maintained below 360 mOsm/L Footnote below recommendations: although mannitol is commonly used in the management of raised ICP in pediatric TBI, no studies meeting inclusion criteria were identified for use as evidence for this topic
Temperature Control	Level III—Extrapolated from the adult data, hyperthermia should be avoided in children with severe TBI Level III—Despite the lack of clinical data in children, hypothermia may be considered in the setting of refractory intracranial hypertension	Level II—Moderate hypothermia (32–33°C) beginning early after severe TBI for only 24 hrs duration should be avoided Level II—Moderate hypothermia (32–33°C) beginning within 8 hrs after severe TBI for up to 48 hrs' duration should be considered to reduce intracranial hypertension Level II—If hypothermia is induced for any indication, rewarming at a rate of >0.5°C per hour should be avoided Level III—Moderate hypothermia (32–33°C) beginning early after severe TBI for 48 hrs duration may be considered
Hyperventilation	Level III—Mild or prophylactic hyperventilation ($Paco_2$ <35 mm Hg) in children should be avoided Level III—Mild hyperventilation ($Paco_2$ 30–35 mm Hg) may be considered for longer periods for intracranial hypertension refractory to sedation and analgesia, neuromuscular blockade, cerebrospinal fluid drainage, and hyperosmolar therapy Level III—Aggressive hyperventilation ($Paco_2$ <30 mm Hg) may be considered as a second-tier option in the setting of refractory hypertension; cerebral blood flow, jugular venous oxygen saturation, or brain tissue oxygen monitoring is suggested to help identify cerebral ischemia in this setting Level III—Aggressive hyperventilation therapy titrated to clinical effect may be necessary for brief periods in cases of cerebral herniation or acute neurologic deterioration	Level III—Avoidance of prophylactic severe hyperventilation to a $Paco_2$ <30 mm Hg may be considered in the initial 48 hrs after injury Level III—If hyperventilation is used in the management of refractory intracranial hypertension, advanced neuromonitoring for evaluation of cerebral ischemia may be considered

Table 1.—*Continued*

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

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

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

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

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

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

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

[c]There were no publications that met the inclusion criteria for this topic.

[d]This topic is addressed in the *Guidelines for the Management of Severe Traumatic Brain Injury, Third Edition* (15).

[e]The critical pathway will be developed and published as a separate document.

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