Childs Nerv Syst (2017) 33:1663–1667
DOI 10.1007/s00381-017-3530-y

SPECIAL ANNUAL ISSUE

Challenges and opportunities for pediatric severe TBI—review of the evidence and exploring a way forward

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Received: 30 June 2017 / Accepted: 6 July 2017

Abstract Traumatic brain injury (TBI) is a leading killer of children in the developed and developing world. Despite evidence-based guidelines and several recent clinical trials, the progress in developing best practices for children with severe TBI has been slow. This article describes (i) the burden of the disease, (ii) the inadequacies of the evidence-based guidelines, (iii) the failure of the largest clinical trials to prove their primary hypotheses, and (iv) possible advances from an observational cohort study called the Approaches and Decisions for Acute Pediatric TBI (ADAPT) Trial that has recently completed enrollment.

Keywords Children · Pediatric neurotrauma · Severe traumatic brain injury · Pediatric neurocritical care · Comparative effectiveness research · Evidenced-based guidelines

Burden of disease

The burden of TBI for children is enormous—even when only considering children with the most severe injuries. In the 11 years from 1997 to 2007, the US CDC reports that 73,276 children died from TBI [1]. An analysis of the Kid's Inpatient Database—utilizing discharge data from >3000 hospitals in 30 states—found more than 29,000 cases of hospitalized children with TBI, 4907 with severe TBI, a mortality rate of 24.2% [2] and $2.56 billion in acute hospital costs [3]. Internationally, the impact of TBI on child health is similarly large [4–6]. Our understanding of the long-term effect of severe TBI on children's health is difficult to fully appreciate. One study estimates that at least 145,000 children were living with a TBI-related disability in 2005 [7] and the overall total life costs (medical costs and productivity losses) of injuries for children <14 years of age were $60.4 billion [8].

The paradox

The author Joseph Heller popularized the term "Catch-22," broadly defined as a dilemma or difficult circumstance from which there is no escape because of mutually conflicting or dependent conditions. In our estimation, the field of severe TBI management appears to be in a similar situation at this time. Most clinicians would argue that a properly executed, randomized-controlled trial (RCT) would provide the best evidence for the efficacy of a proposed therapy. However, an important factor to the success of such an RCT would be to standardize as many of the clinical practices already in use except for the experimental therapy—as well as standardizing the populations of subjects under study based on patient and disease characteristics. Standardizing clinical practices across institutions would be most effective by applying strong recommendations from the literature that exists at the time of the planning of the RCT. The successful RCTs and rigorous guidelines would lead toward a consensus standard of care that could be altered as new information is generated. As outlined below, the interconnected circumstances of the field

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Table 1 Summary of randomized controlled trials for children with severe TBI

Study	Therapy	N	Quality	Outcome	Result
Kloti, 1987	Dexamethasone	24	Class II	6 mo GOS	No difference
Fanconi, 1988	Dexamethasone	25	Class II	6 mo GOS	No difference
Fisher, 1992	HTS (3%)	18	Class II	ICP	Decreased ICP
Simma, 1998	HTS (1.7%)	35	Class II	Mortality	No difference
Taylor, 2001	Decompressive Surgery	27	Class III	6 mo GOS	No statistical difference in GOS, decreased ICP at 48 h
Adelson, 2005	Hypothermia	75	Class III	Complications	No difference
Briassoulis, 2006	Immune diet	40	Class II	Mortality	No difference
Hutchison, 2008	Hypothermia	225	Class II	Mortality	Trend toward ↑mortality
Adelson, 2013	Hypothermia	77	Class II	Mortality	No difference
Beca, 2015	Hypothermia	50	Class II	PCPC, Safety	No difference

of pediatric neurotrauma care have hampered advances in the field up to this point.

Randomized controlled trials in children with severe TBI

Ten substantive randomized controlled trials [9–18] have been conducted in children with severe TBI (defined as age <18 years and Glasgow Coma Scale [GCS] score ≤8) over the past several decades, with 3 large, multi-centered studies completed in the last 10 years (Table 1). These 3 most recent trials all studied therapeutic hypothermia to improve overall outcome of the children and all demonstrated the difficulties in performing RCTs in the current environment. Hypothermia Pediatric Head injury Trial (Hyp-HIT) is the largest RCT conducted in children with severe TBI (n = 225) and represents a milestone achievement for the field [15]. The study was completed over 7 years in 17 clinical centers in Canada, Europe, and Australia and failed to find a beneficial effect of 24 h of therapeutic hypothermia. In performing the study, the experimental group had a greater incidence of hypotension and increased use of vasopressor support—both leading to lower cerebral perfusion pressure at critical times during the study. Moreover, hyperosmolar therapies were used much more commonly in the normothermia group while both children from both groups were exposed to hyperventilation (~40% of subjects). The Cool Kids Trial randomized children to receive 48 h of hypothermia or normothermia initially from 12 US sites which was expanded to sites within the USA, UK, and Australia after enrollment goals were not obtained [10]. The study was stopped for futility by the DSMB after approximately 3 years of enrollment and 77 patients randomized. As part of the study, the Executive Committee of Cool Kids proposed a treatment strategy for intracranial hypertension and other aspects of care based on the evidence-based guidelines to the study sites. However, several study sites expressed concerns that they did not routinely follow these practices related to glucose management, sedation practices, and other aspects of care. Ultimately, the clinical protocol became suggestions for sites to follow rather than mandates based on the sponsors' desire to determine if hypothermia could be effective in the "real world." Most recently, Beca and colleagues published a phase II RCT for hypothermia of slightly longer duration in 8 centers in Australia and New Zealand [11]. Over a 3.5-year period of enrollment, 764 children were screened that resulted in 50 evaluable children. All of these studies demonstrate the extreme difficulty in identifying patients in a timely enough manner to randomize children (generally within 6–8 h of injury), logistical problems of getting procedures implemented in sites located in a wide variety of countries and the need to screen many more patients to.

Evidence-based guidelines

For children with severe TBI, evidence-based guidelines were first published in 2003 [19] and have been revised in 2012 [20]. For the most recent guidelines, an expert panel (15 clinicians including pediatric neurosurgeons, emergency medicine physicians, intensivists, anesthesiologists, neurologists and surgeons and 3 methodologists) was selected by the Brain Trauma Foundation based on their expertise. This panel determined topics for inclusion within the guidelines based on (i) the sufficiency of the evidence within the topic and (ii) the link between the topic and outcomes. Based on these criteria, 15 topics (Table 2) were selected including 8 medical interventions (hyperosmolar therapies, temperature, CSF diversion, barbiturates, hyperventilation, corticosteroids, analgesia/sedation/neuromuscular blockade, and nutrition/glucose). A doctoral-level librarian performed extensive literature searches to identify articles that met the inclusion criteria—clearly defined patient population of children with severe TBI,

Table 2 Summary of guidelines topics

Indications for ICP monitoring	Hyperosmolar therapy	Hyperventilation
Threshold for ICP	Temperature control	Corticosteroids
Threshold for CPP	CSF diversion	Sedatives, NM blockade
Advanced neuromonitoring	Barbiturates	Glucose/nutrition
Neuroimaging	Decompressive Craniectomy	Antiseizure prophylaxis

identifiable independent variables (treatments) and dependent variables (outcomes), adequate sample size—for each topic. Level I, II, and III recommendations were made for therapies that "must be done," "should be considered," and "may be considered," respectively. The guidelines underwent peer review by 14 external reviewers and were reviewed and endorsed by 10 associations/societies including AAP—Section on Neurological Surgery, American Association of Neurological Surgeons, Society of Critical Care Medicine, Child Neurology Society, European Society of Pediatric and Neonatal Intensive Care and the Paediatric Intensive Care Society-UK.

The new guidelines shed light on our inadequate knowledge of treatments for pediatric TBI. Specifically, there was insufficient evidence to support a Level I recommendation for any of the topics. Moreover, there was evidence to support only 4 Level II recommendations for medical therapies—(i) the use of corticosteroids is not recommended to improve outcome or reduce ICP, (ii) moderate hypothermia beginning early after severe TBI for only 24 h should be avoided, (iii) an immune-enhanced diet should be avoided, and (iv) HTS should be considered for treatment of intracranial hypertension. In summary, the existing literature cannot recommend that a clinician "must do" any aspect of the 15 therapies or maneuvers identified by the pediatric neurotrauma community. Importantly, there is only evidence that a clinician "should consider" use of HTS during intracranial hypertension episodes with the remaining 3 level II recommendations (hypothermia, steroids, immune-enhanced diets) suggesting that therapies should be avoided. Analysis of the level III recommendations offers clinicians little guidance as well (Table 3). As an example, the guidelines can only recommend that ICP monitoring "may be considered" and can only suggest that a threshold of 20 mmHg "may be considered". However, many of the other recommendations are predicated on providing therapies during intracranial hypertension—which would not be diagnosed without the ICP monitor providing the necessary data and the clinician deciding on an appropriate threshold for ICP. Furthermore, basic questions regarding therapies that are widely believed to improve outcome and must be answered by the clinician caring for a child with severe TBI—Will CSF diversion lead to improved outcome? Are hyperosmolar therapies effective? Does prophylactic hyperventilation harm recovery? Should new methods to monitor for brain hypoxia be utilized? How many calories are needed for optimal recovery? When should glucose be administered?—remain unaddressed by the guidelines. This lack of evidence frustrates evidence-based clinical decision-making for all children with TBI and introduces uncontrollable variability into research protocols that attempt to standardize practices at multiple sites to successfully detect an experimental signal of a prospective therapy.

Table 3 Level III recommendations from the evidence-based guidelines

Topic	Level III recommendations
ICP monitoring indications	"ICP monitoring may be considered…in severe TBI"
ICP threshold	"Treatment of ICP may be considered at a threshold of 20 mm Hg"
CPP threshold	"A minimum CPP of 40 mm Hg may be considered.."
CPP threshold	"A CPP threshold of 40 – 50 mm Hg may be considered. There may be age-specific thresholds.."
Advanced Neuromonitoring	"If brain oxygenation monitoring is used, maintenance of PbO2 ≥10 mm Hg may be considered.."
Neuroimaging	"In the absence of neurological deterioration..obtaining a routine repeat CT scan..may not be indicated.."
Hyperosmolar therapy	"Hypertonic saline may be considered for treatment of.intracranial hypertension..Serum osmolarity should be maintained below 360 mOsm/L."
Cerebrospinal fluid Drainage	"CSF drainage may be considered..The addition of a lumbar drain may be considered."
Barbiturates	"High-dose barbiturate therapy may be considered.."
Decompressive craniectomy	"Decompressive craniectomy. .may be considered.."
Hyperventilation	"Avoidance of prophylactic severe hyperventilation to a PaCO2 <30 may be considered.."
Analgesics, Sedatives, NMB	"Etomidate may be considered.."
Glucose, nutrition	"In the absence of outcome data, the specific approach to glycemic control.. should be left to the treating physician"
Antiseizure prophylaxis	"Prophylactic treatment with phenytoin may be considered.."

Approaches and decisions for acute pediatric TBI (ADAPT) trial

The ADAPT Trial was designed to start to address the problems outlined above by understanding how therapies that are

already in clinical use are associated with outcomes. Thus, ADAPT is an observational cohort study that intends to use statistical techniques common to comparative effectiveness research to develop new level II recommendations for the guidelines. The topics chosen included Tier 1 therapies for intracranial hypertension management (cerebrospinal fluid [CSF] diversion, hyperosmolar therapies, hyperventilation) and basic aspects of neurocritical care (hypoxia management [as measured by the partial pressure of brain oxygen (PbO_2) monitoring], nutritional support and glucose management). For each topic, a primary and secondary hypothesis was generated and it is anticipated that ADAPT will generate up to 12 new Level II guidelines recommendations based on these a priori defined hypotheses. Importantly, these hypotheses will determine which of the currently used strategies within the topics are associated with improved neurological outcome (measured by the Glasgow Outcome Scale Extended for Pediatrics [GOS-E Peds] at 6 months after injury). If compelling enough, these level II recommendations may become new standards of care for years to come. As an example, if ADAPT demonstrates that initiation of nutritional support within a given number of days after TBI is associated with improved outcomes, this might be interpreted by the TBI community as sufficient evidence to adopt this approach as a standard for both clinical care and research protocols. Alternatively, findings from ADAPT could generate preliminary data that compels additional studies. In another example, PbO_2 monitoring may be found to be associated with improved outcome after ADAPT is fully analyzed. In this instance, it might be necessary to perform further studies to develop a standard approach that is adopted by the pediatric neurotrauma community.

ADAPT was begun in July 2013 and steady progress has been made. Fifty-one clinical centers in 8 countries participated in patient enrollments, with enrollment of 1000 consecutive subjects completed in approximately 2.5 years. The last subjects were enrolled in September 2016 and primary outcomes were completed in late March 2017. Analysis of the primary hypotheses of the study will be completed after data cleaning and audits of all clinical sites are completed (anticipated for fall 2017). However, significant preliminary findings have already been published. In a survey of clinical sites participating in ADAPT, we found that significant variations of the *medical goals* of the clinical sites exist, let alone what actually gets accomplished in subjects within ADAPT [21]. In this analysis, we found that while sites generally targeted an ICP of 20 mmHg for their care, there were significant differences in strategies regarding all of the ADAPT hypotheses. We anticipate that completion of ADAPT will demonstrate even greater variation in clinical practices. We conducted a survey regarding EEG monitoring and treatment of seizures that demonstrated sites that utilize protocols report using fewer medications for treating electrographic abnormalities that are detected [22]. We have also published two analyses of subjects within the study—both analyses performed on the first 200 subjects enrolled in the study. In an analysis of the GCS scores that qualified subjects for ADAPT—documented by the providers who determined the need for ICP monitoring—validated that GCS scores incrementally predicted mortality in a tripartite distribution (GCS 3 vs. 4–5 vs. 6–8) [23]. Lastly, we demonstrated that variations in characteristics between children who had suffered from accidental and abusive head trauma [24].

Future plans

As stated previously, we anticipate publishing a number of reports regarding our primary hypotheses in the coming months that will expand the guidelines. We believe that these reports will serve as a basis for developing standards of care as well as new hypotheses to be tested. Given the large database, we also anticipate publishing findings on other aspects of the guidelines including mortality and disability prediction models, sedation practices, Tier 2 therapies (barbiturates, hypothermia, decompressive surgery for intracranial hypertenstion), fluid balance, ICP/CPP thresholds among others. We believe that understanding these findings—along with a better understanding of characterizing the disease of severe TBI—offers the best opportunity to make a difference in the field.

Acknowledgements Investigators for the ADAPT Study are Shruti Agrawal, Addenbrookes Hospital, Cambridge, UK; Sarah Mahoney, Alder Hey Children's NHS Foundation Trust, Liverpool, UK; Deepak Gupta, All India Institute of Medical Sciences, New Delhi, India; John Beca, Auckland DHB Charitable Trust, Starship Children's Hospital, Auckland, NZ; Laura Loftis, Baylor College of Medicine, Houston, TX; Kevin Morris, Birmingham Children's Hospital NHS Foundation Trust, Birmingham, UK; Lauren Piper, Levine Children's Hospital, Charlotte, NC; Anthony Slater, Children's Health Queensland Hospital and Health Service, Brisbane, Australia; Karen Walson, Children's Healthcare of Atlanta, Atlanta, GA; Tellen Bennett, Children's Hospital Colorado, Denver, CO; Todd Kilbaugh, Children's Hospital of Philadelphia, Philadelphia, PA; AM Iqbal O'Meara, Children's Hospital of Richmond, Richmond, VA; Nathan Dean, Children's National Medical Center, Washington, DC; Ranjit S. Chima, Cincinnati Children's Hospital Medical Center, Cincinnati, OH; Katherine Biagas, Columbia University, New York, NY; Enno Wildschut, Erasmus Medical Center, Rotterdam, Netherlands; Mark Peters, Great Ormond St Hospital NHS Foundation Trust, London, UK; Kerri LaRovere, Boston Children's Hospital, Boston, MA; Joan Balcells, Hospital Vall d'Hebron, Barcelona, Spain; Courtney Robertson, John Hopkins University, Baltimore, MD; Shira Gertz, Joseph M. Sanzari Children's Hospital at Hackensack University Medical Center, Hackensack, NJ; Akash Deep, King's College Hospital NHS Foundation Trust, London, UK; Sian Cooper, Leeds Teaching Hospitals NHS Trust, Leeds, UK; Mark Wainwright, Lurie Children's Hospital, Chicago IL; Sarah Murphy, Massachusetts General Hospital, Boston, MA; John Kuluz, Miami Children's Hospital, Miami, FL; Warwick Butt, Murdoch Children's Research Institute, Royal Children's Hospital, Melbourne, Australia; Nicole O'Brien, Nationwide Children's Hospital,

Columbus, OH; Neal J. Thomas, Pennsylvania State University, Hershey, PA; Sandra Buttram, Phoenix Children's Hospital, Phoenix, AZ; Simon Erickson, Princess Margaret Hospital, Perth, Australia; J. Mahil Samuel, Royal Manchester Children's Hospital NHS Foundation Trust, Manchester, UK; Rachel Agbeko, The Newcastle Upon Tyne Hospitals NHS Foundation Trust, Newcastle, UK; Richard Edwards, University Hospital Bristol NHS Foundation Trust, Bristol, UK; Kesava Ananth Ramakrishnan, University Hospital Southampton NHS Foundation Trust, Southampton, UK; Margaret Winkler and Santiago Borasino, University of Alabama at Birmingham, Birmingham, AL; Joanne Natale, University of California, Davis, Sacramento, CA; Christopher Giza, University of California, Los Angeles, Los Angeles, CA; Mary Hilfiker and David Shellington, University of California, San Diego, San Diego, CA; Anthony Figaji, Red Cross War Memorial Children's Hospital, Cape Town, South Africa; Elizabeth Newell, University of Iowa Children's Hospital, Iowa City, IA; Edward Truemper, University of Nebraska Medical Center and Nebraska Medical Center, Omaha, NE; Robert Clark, University of Pittsburgh, Pittsburgh, PA; Kit Newth, Children's Hospital of Los Angeles, Los Angeles, CA; Nadeem Shafi, LeBonheur Children's Hospital, Memphis, TN; Darryl Miles, University of Texas Southwestern Medical Center, Dallas, TX; Michelle Schober, University of Utah, Jerry Zimmerman, University of Washington, Seattle, WA; Peter Ferrazzano, University of Wisconsin, Madison, WI; Jose Pineda, Washington University—St. Louis, St. Louis, MO; and Ajit Sarnik, Wayne State University, Detroit, MI.

Compliance with ethical standards

Conflict of interest The authors have no conflicts of interest to report except for the grant funding from NIH.

Funding Research reported in this publication was supported by the National Institute of Neurological Disorders and Stroke of the National Institutes of Health under Award Number U01 NS081041. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

References

1. Coronado VG et al (2011) Surveillance for traumatic brain injury-related deaths—United States, 1997-2007. MMWR Surveill Summ 60(5):1–32
2. Stanley RM et al (2012) US estimates of hospitalized children with severe traumatic brain injury: implications for clinical trials. Pediatrics 129(1):e24–e30
3. Shi J et al (2009) Costs, mortality likelihood and outcomes of hospitalized US children with traumatic brain injuries. Brain Inj 23(7): 602–611
4. Stocchetti N et al (2010) Traumatic brain injury in pediatric patients. Minerva Anestesiol 76(12):1052–1059
5. Tasker RC et al (2011) Severe head injury in children: intensive care unit activity and mortality in England and Wales. Br J Neurosurg 25(1):68–77
6. Tude Melo JR et al (2010) Mortality in children with severe head trauma: predictive factors and proposal for a new predictive scale. Neurosurgery 67(6):1542–1547
7. Zaloshnja E et al (2008) Prevalence of long-term disability from traumatic brain injury in the civilian population of the United States, 2005. J Head Trauma Rehabil 23(6):394–400
8. Corso P et al (2006) Incidence and lifetime costs of injuries in the United States. Inj Prev 12(4):212–218
9. Adelson PD et al (2005) Phase II clinical trial of moderate hypothermia after severe traumatic brain injury in children. Neurosurgery 56(4):740–754 discussion 740-54
10. Adelson PD et al (2013) Comparison of hypothermia and normothermia after severe traumatic brain injury in children (Cool Kids): a phase 3, randomised controlled trial. Lancet Neurol 12(6):546–553
11. Beca J et al (2015) Hypothermia for traumatic brain injury in children-a phase II randomized controlled trial. Crit Care Med 43(7):1458–1466
12. Briassoulis G et al (2006) Temporal nutritional and inflammatory changes in children with severe head injury fed a regular or an immune-enhancing diet: a randomized, controlled trial. Pediatr Crit Care Med 7(1):56–62
13. Fanconi S et al (1988) Dexamethasone therapy and endogenous cortisol production in severe pediatric head injury. Intensive Care Med 14(2):163–166
14. Fisher B, Thomas D, Peterson B (1992) Hypertonic saline lowers raised intracranial pressure in children after head trauma. J Neurosurg Anesthesiol 4(1):4–10
15. Hutchison JS et al (2008) Hypothermia therapy after traumatic brain injury in children. N Engl J Med 358(23):2447–2456
16. Kloti J et al (1987) Dexamethasone therapy and cortisol excretion in severe pediatric head injury. Childs Nerv Syst 3(2):103–105
17. Simma B et al (1998) A prospective, randomized, and controlled study of fluid management in children with severe head injury: lactated Ringer's solution versus hypertonic saline. Crit Care Med 26(7):1265–1270
18. Taylor A et al (2001) A randomized trial of very early decompressive craniectomy in children with traumatic brain injury and sustained intracranial hypertension. Childs Nerv Syst 17(3):154–162
19. Adelson PD et al (2003) Guidelines for the acute medical management of severe traumatic brain injury in infants, children, and adolescents. Chapter 1: introduction. Pediatr Crit Care Med 4(3 Suppl): S2–S4
20. Kochanek PM et al (2012) Guidelines for the acute medical management of severe traumatic brain injury in infants, children, and adolescents—second edition. Pediatr Crit Care Med 13(Suppl 1): S1–82
21. Bell MJ et al (2013) Differences in medical therapy goals for children with severe traumatic brain injury—an international study. Pediatr Crit Care Med 14(8):811–818
22. Kurz JE et al (2016) Variation in anticonvulsant selection and electroencephalographic monitoring following severe traumatic brain injury in children—understanding resource availability in sites participating in a comparative effectiveness study. Pediatr Crit Care Med 17(7):649–657
23. Murphy S, et al. (2017) Tripartite stratification of the Glasgow coma scale in children with severe traumatic brain injury and mortality: an analysis from a multi-center comparative effectiveness study. J Neurotrauma
24. Miller Ferguson, N., et al. (2017) Abusive head trauma and mortality-an analysis from an international comparative effectiveness study of children with severe traumatic brain injury. Crit Care Med