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Severe Traumatic Brain Injury in Children – A Vision for the Future

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Traumatic brain injury (TBI) remains the most common cause of death and disability in children from the developed world. Evidenced-based guidelines have been published for children with severe TBI [1], yet the practicality of these guidelines to inform clinical practice is limited by insufficient information. There are currently no Level 1 recommendations and only 4 Level 2 recommendations – 3 of which are therapies/maneuvers to avoid (immune-enhanced diet, steroids and therapeutic hypothermia). The 3 largest randomized, controlled trials (RCTs) for children with severe TBI have been performed to test the utility of early, therapeutic hypothermia – and all have failed to demonstrate that the intervention positively impacted the primary outcomes of the studies [2–4]. Moreover, the remainder of the evidenced-based guideline consists of Level 3

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recommendations that “may be considered”, largely because the studies informing these topics were (i) developed in a single center, (ii) retrospective in nature with limited ability to obtain detailed follow-up or (iii) significantly limited in study design [5]. For adults with severe TBI, multi-centered RCTs have almost universally failed to prove their primary hypothesis encompassing pharmacological therapies, therapeutic medical maneuvers and surgical procedures [6–8].

New paths for clinical care and research for TBI have emerged. The IMPACT study team, led by Dr. Maas and colleagues, combined more than a dozen clinical studies and determined that inter-center variations in outcomes were prominent and likely overwhelmed the therapeutic intervention under study [9]. Concurrently, Dr. Manley and colleagues embarked on studies to more thoroughly categorize the nature of the injuries by using biomarkers and neuroimaging [10–12]. These efforts – now comprising the Collaborative European Neurotrauma Effectiveness Research in TBI (CENTER-TBI) study and the Transforming Research and Clinical Knowledge in Traumatic Brain Injury (or TRACK-TBI) study – are designed to better understand the entire spectrum of the disease (Table 1).

For children, we chose another approach. Because of the lethality of TBI in children and the dearth of specific recommendations for treatments, we chose to compare the effectiveness of strategies for therapies that are (i) part of the evidenced-based guidelines and (ii) in clinical use today. In preparation for our study that we call ADAPT (Approaches and Decisions for Acute Pediatric TBI), we found that the basic aspects of care that are outlined within the guidelines are applied in substantially varied ways in the leading TBI centers [13]. Therefore, we chose 3 TBI topics – intracranial hypertension therapies (cerebrospinal fluid diversion and hyperosmolar therapies), secondary insult detection/treatment (hyperventilation and hypoxia [based on brain tissue oxygen monitoring]) and metabolic support (nutrition administration and glucose control) – and developed hypotheses to answer some of these unanswered questions. To date, over 800 children (inclusion criteria: Glasgow Coma Scale score [GCS] $\geq$ 8, diagnosis of TBI, age $<$ 18 y, placement of an intracranial pressure [ICP] monitor; exclusion criteria: pregnancy) have been consecutively enrolled at 49 clinical sites in the US, Europe, South Africa, India, Australia and New Zealand. Using statistical methods commonly employed within comparative effectiveness research including propensity scoring, we anticipate generating level 2 evidence for all of the primary hypotheses – more such recommendations than have been generated within the guidelines to date. Moreover, since this study design requires the understanding and control of many co-variables, we anticipate significant other information regarding other aspects of TBI care.

We believe ADAPT – which will be approximately 5 times larger than any previous study of this patient population - will serve to provide clinicians with contemporary evidence valuable for caring for children with severe TBI and future researchers with information regarding basic aspects of care that can be used to standardize patient care and allow future randomized trials to detect possible experimental signals. With the conclusion of our enrollment of 1000 children in the summer of 2016, we look forward to presenting our findings as rapidly as possible to the intensive care community.

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Table 1

Ongoing observational studies in traumatic brain injury within the US and Europe

Ongoing Clinical Study	Population Under Study	Number of Subjects Projected	Overall Goals
Approaches and Decisions for Acute Pediatric Traumatic Brain Injury (ADAPT Trial)	Children (age < 18) with severe TBI (GCS = 8) with ICP monitor placed	N = 1000	Compare the effectiveness of therapies that are in clinical use (ICP therapies, secondary insults, metabolic support) in children (www.ADAPTTrial.org)
Collaborative European Neurotrauma Effectiveness Research In TBI (CENTER-TBI)	Entire age spectrum and entire injury severity spectrum (divided into subjects discharged from Emergency Department, admitted to hospital ward and admitted to intensive care unit)	N = 6000 subjects in full study; ~20,000 in registry study	10 specific aims to better characterize TBI as a disease, describe it in a European context and identify the most effective clinical interventions for managing TBI (https://www.centertbi.eu)
Transforming Research and Clinical Knowledge in Traumatic Brain Injury (TRACK-TBI)	Entire age spectrum and entire injury severity spectrum (divided into subjects discharged from Emergency Department, admitted to hospital ward and admitted to intensive care unit)	N = 3300 subjects	Collect and analyze detailed clinical data on subjects – including CT/MRI imaging, blood biospecimens and detailed clinical outcomes to develop a precision medicine-based database for advancement of the understanding of TBI as a disease (https://tracktbi.ucsf.edu)