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Differences in Medical Therapy Goals for Children With Severe Traumatic Brain Injury— An International Study

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Abstract

Objectives—To describe the differences in goals for their usual practice for various medical therapies from a number of international centers for children with severe traumatic brain injury.

Design—A survey of the goals from representatives of the international centers.

Setting—Thirty-two pediatric traumatic brain injury centers in the United States, United Kingdom, France, and Spain.

Patients—None.

Interventions—None.

Measurements and Main Results—A survey instrument was developed that required free-form responses from the centers regarding their usual practice goals for topics of intracranial hypertension therapies, hypoxia/ischemia prevention and detection, and metabolic support.

Cerebrospinal fluid diversion strategies varied both across centers and within centers, with roughly equal proportion of centers adopting a strategy of continuous cerebrospinal fluid diversion and a strategy of no cerebrospinal fluid diversion. Use of mannitol and hypertonic saline for hyperosmolar therapies was widespread among centers (90.1% and 96.9%, respectively). Of centers using hypertonic saline, 3% saline preparations were the most common but many other concentrations were in common use. Routine hyperventilation was not reported as a standard goal and 31.3% of centers currently use Pb_{O_2} monitoring for cerebral hypoxia. The time to start nutritional support and glucose administration varied widely, with nutritional support beginning before 96 hours and glucose administration being started earlier in most centers.

Conclusions—There were marked differences in medical goals for children with severe traumatic brain injury across our international consortium, and these differences seemed to be greatest in areas with the weakest evidence in the literature. Future studies that determine the superiority of the various medical therapies outlined within our survey would be a significant advance for the pediatric neurotrauma field and may lead to new standards of care and improved study designs for clinical trials.

Keywords

cerebral hypoperfusion; hypoxia; intracranial hypertension; pediatric neurocritical care; pediatric traumatic brain injury; secondary Injuries

Over the past decade, a number of international efforts have been made to improve the care and outcomes of children with severe traumatic brain injury (TBI)—the leading cause of death of children and responsible for billions of dollars of medical and societal costs each year (1–6). In 2003, the first edition of the *Guidelines for the Medical Management of Traumatic Brain Injury in Infants, Children and Adolescents* was published (7), which included evidence-based recommendations along with expert opinions. This landmark work was updated in 2012, with slight modifications of the topics reviewed and a diminished emphasis on expert opinion (8). Although influential, these guidelines emphasize that the neurotrauma literature is insufficient to provide firm recommendations regarding a host of medical decisions (Table 1) that are important in caring for children with severe TBI—including the superiority/inferiority of cerebrospinal fluid (CSF) diversion strategies, the relative effectiveness of various hyperosmolar therapies, the ability of hypoxia/ischemia monitoring strategies to improve outcomes, the timing and quantity of nutritional support, and the decisions on glucose administration and management. All of these decisions are likely to have some effect on overall outcomes, yet the current literature cannot discern their relative importance or impact on the overall outcomes.

During this time span, randomized controlled trials (RCTs) have failed to provide more substantive evidence for the guidelines. The Canadian Critical Care Trials Group and the Pediatric Traumatic Brain Injury Consortium: Hypothermia carried out a total of three studies to determine the efficacy of therapeutic hypothermia in children with severe TBI (9, 10)—all of which failed to demonstrate efficacy. Significant variability in medical goals between centers has been suggested as a reason for the failure of these trials, and this pattern was previously observed in an RCT of hypothermia for adult TBI victims (11). For example, the use of hypertonic saline for intracranial hypertension was significantly greater in

children randomized to normothermia in the Hyp-HIT study—potentially introducing a bias into the study that was uncontrollable by the study investigators.

We hypothesize substantial variations in medical goals for children with severe TBI in the overall pediatric neurotrauma community and have performed a survey of these goals for this article. We speculate that these variations may play a role in differences in outcomes observed between centers in routine care as well as in clinical studies. We assembled an international consortium of clinical centers that also agreed to participate in a planned comparative effectiveness study of medical therapies for pediatric TBI.

METHODS

This study was submitted to the Institutional Review Board (IRB) of the University of Pittsburgh for their consideration and deemed to be exempt from IRB review. An international consortium of pediatric TBI participants was recruited from a variety of sources (members of the recently formed Pediatric Neurocritical Care Research Group [<http://www.pncrg.org>], site principal investigators from the “Cool Kids” Trial and the Hyp-HIT study, and investigators within the ESPNIC [European Society of Pediatric and Neonatal Intensive Care] Neurocritical Care section). All potential participants were asked to report on the usual practices employed at their institution.

A survey instrument to determine current practices regarding intracranial hypertension therapies, hypoxia/ischemia monitoring strategies, and metabolic issues was generated (Table 2). In order to estimate how many children the participating institutions cared for with severe TBI—and therefore, to approximate the relative value of the survey—respondents were asked to audit the number of cases of severe TBI their institution had admitted in the past 3 years. For this audit, inclusion criteria (age ≥ 18 yr, severe TBI with Glasgow Coma Scale score ≤ 8 , and placement of intracranial pressure [ICP] monitor) and exclusion criteria (pregnancy, penetrating injury, and unknown mechanism) were applied. Respondents were asked to describe the goals for the usual practices that occur at their centers regarding the questions listed in Table 2. These answers were given in free form and respondents were free to explain their practices without interpretation and *did not represent any form of medical record review*. We chose the topics for the survey for a number of reasons. All of the topics were aspects of the most recent version of the pediatric TBI guidelines—with the requisite requirement that the topics within the guideline were deemed to be important in TBI outcomes. We were primarily considering medical therapies that were necessary for routine care of all children with severe TBI and tailored our inquiries to those topics. We considered inquiring about sedation and neuromuscular blockade usage within the survey, but felt that the existing literature demonstrating the relationship between these agents and outcomes was still extremely preliminary. Large intracenter variation was likely for these agents, making the information provided by the participants less reliable than those for the other topics. Similarly, we did not study antiseizure prophylaxis due to lack of evidence that it may change overall outcomes. For other topics, particularly corticosteroids and hypothermia, sufficient data exist within the literature to generate substantive recommendations, and therefore, these topics were not surveyed. Lastly, we did not study neurological imaging and decompressive surgery, as these are not medical therapies for

pediatric TBI. Results were collated and reported for the 18 different questions. Responses were analyzed overall and stratified based on institution size and location (United States vs international center).

RESULTS

A total of 32 centers were recruited from the United States, United Kingdom, Spain, and France (Appendix 1), and all centers that agreed to participate completed the survey. To demonstrate the number of children generally seen at these centers, their audit revealed that approximately 557 children per year with severe TBI are cared for at these centers. With respect to their goals for medical therapies routinely employed at these centers, there was some unanimity for the results of various thresholds for cerebrohemodynamics. All centers report that they use an ICP threshold of 20 mm Hg for the majority of subjects. Eight of the centers (25%) report that they use slightly lower ICP thresholds for the youngest children (10 mm Hg at one site, 15 mm Hg at four centers, and 18 mm Hg at three centers). For cerebral perfusion pressure (CPP), one site does not target CPP thresholds, whereas all others report use of a minimum CPP threshold. Three centers (9.4%) use a single CPP threshold (one site at 70 mm Hg, the other two at 60 mm Hg) for all subjects admitted with severe TBI. Nine centers report two different thresholds for subjects based on age, whereas the others report at least three different age-related thresholds. The lowest CPP threshold from any site was 35 mm Hg, whereas the highest was 75 mm Hg.

For intracranial hypertension therapies, CSF diversion was stratified into continuous drainage, intermittent drainage, or no drainage and a wide variety of strategies were identified (Table 3). For hyperosmolar therapies, one center does not use hypertonic saline while three do not use mannitol. The concentrations of hypertonic saline solutions used within centers are also striking, with one center reporting use of six different concentrations of such agents. In addition, three centers use the highest commercially available saline concentration of 23.4% saline. In four centers, only bolus doses of hypertonic saline solutions are used, whereas others use both boluses and continuous infusions. For hypoxia/ischemia prevention and detection, none of the centers report intentionally using hyperventilation during periods of normal ICP. Ten centers (31.3%) monitor partial pressure of interstitial brain oxygen (P_{bO_2}) with threshold values ranging from 20 to 35 mm Hg. For metabolic support, the distributions regarding timing of nutritional support and glucose administration are seen in Figures 1 and 2, respectively. For nutritional support, the most common time to start nutritional support was 48 hours after TBI, but the distribution varied widely. Within centers, there was significant variability in this goal as well (as indicated by the bars on the figure), starting from within the first 24 hours to starting from 48 to 96 hours after TBI. As for choices of nutritional support, 20 centers routinely use enteral feedings, eight parenteral prescriptions, and four use a combination of both. For glucose, the distribution of timing of administration is also variable, but earlier than for the start of nutritional support (Fig. 2). Interestingly, one site provides glucose only when the patient becomes hypoglycemic, one site administers glucose on an “age-dependent” basis, and one site begins glucose administration when ICP is less than 20 mm Hg. Nineteen centers (59.4%) use insulin regularly to control hyperglycemia, of which 10 use a locally derived

standard protocol for its administration. Thirteen centers do not use insulin regularly to control hyperglycemia after TBI.

DISCUSSION

We report that the medical goals, as derived from the self-described usual practices at centers that care for hundreds of children with severe TBI each year, vary greatly between institutions within our international consortium. This variability appears to be most prominent in areas where the literature is the least conclusive, including CSF diversion, metabolic goals, and Pb_{O_2} monitoring. For topics with more evidence—hyperosmolar therapy and perhaps hyperventilation—there was a more unified approach to the medical goals. One comparable survey of these medical goals was performed by Segal et al (12) more than a decade ago. In this U.K. survey, they found that all centers practiced hyperventilation and mannitol use, whereas a subset of centers used furosemide, corticosteroids, fluid restriction, barbiturates, and hypothermia. Although the specific therapies in question were different than ours, this likely reflects the changes in TBI practice as new evidence has emerged over the past decade. Intriguingly, the ICP and CPP goals adopted by these institutions were quite similar to the ones that we observed. More recently, a survey of 194 U.S. clinicians found that approximately 60% of recommendations made within the contemporary guidelines (13) were part of their clinical goals. These results were similar to ours in that age-dependent ICP and CPP goals were reported and approximately 36% of respondents did not use CSF diversion. However, the use of hyperosmolar therapies was significantly less than in our survey (57% for mannitol and 68% for hypertonic saline). Other efforts to understand medical decision making in pediatric TBI have used data collected from either databases or retrospective registries, generally concentrating on decisions for placement of ICP monitors (14, 15) or prospective studies discerning variations in practices between centers (16). Our survey is unique in outlining the variables that a large number of international institutions use as a part of their usual practice in children with severe TBI in three specific categories— intracranial hypertension therapies, hypoxia/ ischemia detection and prevention, and metabolic support—that have significant implications for outcomes and clinical trials.

Intracranial Hypertension Therapies

The decision regarding CSF diversion is quite unique, in that a clinician *must* decide whether or not to drain CSF in all cases. This binary question arises because ICP monitoring technology necessarily involves an externalized ventricular drain (which drains CSF) or a strain-gauge monitor within the parenchymal space (which cannot drain CSF). Currently, no studies are of sufficient quality to demonstrate the superiority of any CSF diversion strategy. The best evidence supporting CSF diversion is derived from a series of 23 children with *refractory* ICP—of which 20 children achieved control of intracranial hypertension with CSF diversion (17). Conversely, the evidence for the use of hyperosmolar therapies for intracranial hypertension is among the strongest for any topic within the guidelines. Based on two small RCTs (18, 19), the utility of hypertonic saline solutions to lower ICPs generated a level II recommendation that hypertonic saline “should” be considered. Although similar studies have not shown beneficial effects of mannitol, it has been used for

decades for treatment of intracranial hypertension (20). Our findings reflect these differences in level of evidence. There was wide disparity in CSF diversion goals between the various centers—and even within clinicians within centers themselves. This is quite consistent with the lack of conclusive evidence of the effectiveness of CSF drainage within the literature—as proponents may argue for its therapeutic potential and others may be concerned with complications of device placement. On the other hand, our study demonstrated wide adoption of hyperosmolar therapies, with only a few centers opting to not use either mannitol or hypertonic saline solutions. The variability we observed in this aspect of TBI care was focused more on the wide variety of concentrations of hypertonic saline solutions which was surprising.

Hypoxia/Ischemia Prevention and Detection

Hyperventilation—which lowers ICP by lowering cerebral blood flow and thereby cerebral blood volume in regions with intact C_{O_2} reactivity—has been among the more controversial topics in pediatric neurotrauma care. Although a common practice in older studies, Skippen et al (21) demonstrated a significant decrease of cerebral blood flow with incremental decreases in Pa_{CO_2} , and other studies suggested that hypocarbia may be associated with unfavorable outcome (22). In our survey, centers reported that they did not intentionally use hyperventilation during periods of normal ICP, but it is likely to be a goal that the centers strive to achieve. In the Hyp-HIT study, more than 40% of subjects in the study were severely hyperventilated to Pa_{CO_2} less than 30 mm Hg (9). For Pb_{O_2} monitoring of cerebral hypoxia, a number of reports have been published describing the utility of this system in children investigations have emerged in the past several years. Figaji et al (23, 24) have published several series describing the integration of Pb_{O_2} into the neuromonitoring milieu of children with severe TBI, and it appears that a threshold of Pb_{O_2} may be possible to determine in a large series. Our survey reflects the adoption of this technique by several centers, but the penetration of use for this technology is still limited—likely reflecting the relatively small amount of information currently available.

Metabolic Support

Although believed to be extremely important for wound healing, growth, and providing energy for physiologic/pathological processes, evidence for providing metabolic support for children with severe TBI is still rudimentary. Within the guidelines, only a single RCT of 40 children who were fed an immune-enhanced diet was sufficiently rigorous to be included, and this study demonstrated that this diet was not associated with any meaningful outcomes (25). In adult TBI victims, the timing of nutritional support appears to play a role in outcomes (26). Specifically, in an audit of 797 adult TBI victims from New York State, those patients who did not get fed until the fifth or seventh day after trauma had a 2.4-fold and four-fold increase in mortality, respectively. Data from our survey suggest that the pediatric neurotrauma community is cognizant of this association, as most centers have the goal of starting nutritional support within the first several days after TBI. As for glucose, the data are similarly nebulous. Although several series have found that hyperglycemia is associated with adverse outcome in both the acute and more delayed time periods after TBI (27–29), there is little evidence to guide the clinician on when glucose administration should start and how hyperglycemia should be managed. This is reflected by the data from our

survey, where the range of time for starting glucose administration and insulin usage is quite wide across centers.

Limitations and Implications

There are several limitations to this study. First, this survey was performed in a relatively small number of centers in the United States, United Kingdom, and Europe and the results may not reflect the pediatric neurotrauma community as a whole. However, the purpose of this survey was to determine the variations that currently exist in a number of important treatments that are standardly applied for children, and the centers within this study treat more than 500 such children each year. Second, the respondents stated that the answers they gave were reflective of the overall care of children at their center. Obviously, actual practices at centers might deviate significantly from the stated goals—either because patient care dictates that a given goal could not be achieved or based on variability of care provided by clinicians at the centers. Lastly, this survey cannot address which goals are associated with the best outcomes for patients—an obvious goal for any future study. We believe that a prospective, observational, and cohort study with sufficient statistical power and detailed data collection could inform the pediatric neurotrauma community on the relative effects of these strategies on patient outcomes.

In conclusion, clinicians reported marked differences in medical goals for children with severe TBI across our international consortium. We believe that our data have significant implications. First, we speculate that there are superior strategies to achieve the medical goals outlined within our survey and believe that a study such as the one outlined above may yield important advances for the field. Second, given our data, it is conceivable that the widespread variability in clinical goals across institutions would yield marked variations in patient outcomes at the various centers. This may explain, in part, the failure of multicentered RCTs—as the effect of variability in medical therapies outlined in our survey may lead to variations in outcomes that obscure observable treatment effects of experimental interventions. We believe that future studies that determine the superiority of the various medical therapies outlined within our survey would be a significant advance for the pediatric neurotrauma field.

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APPENDIX 1. THE MULTIPLE MEDICAL THERAPIES FOR PEDIATRIC TRAUMATIC BRAIN INJURY WORKGROUP (LISTED ALPHABETICALLY BY CENTER)

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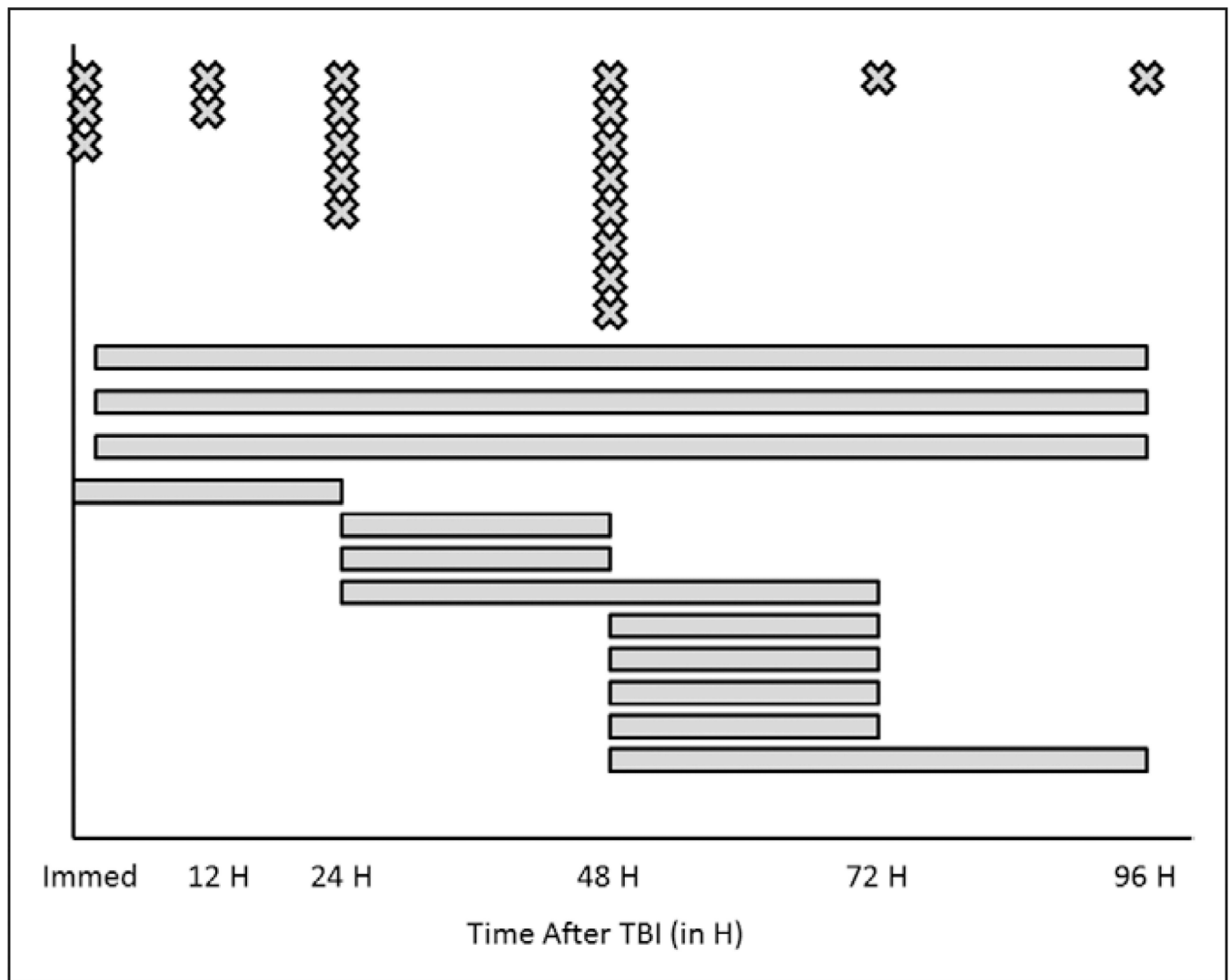


Figure 1.

Summary of the goals for starting of nutritional support from an international pediatric neurotrauma consortium consisting of 32 centers from the United States and Europe. Centers were asked, “When do you start nutritional support to patients?” and were able to respond in freeform text. Centers responded with discrete time points (“X” in the figure) or by describing a range of time periods where nutritional support was intended to be started (“line” in the figure). All times are expressed as time after traumatic brain injury (TBI).

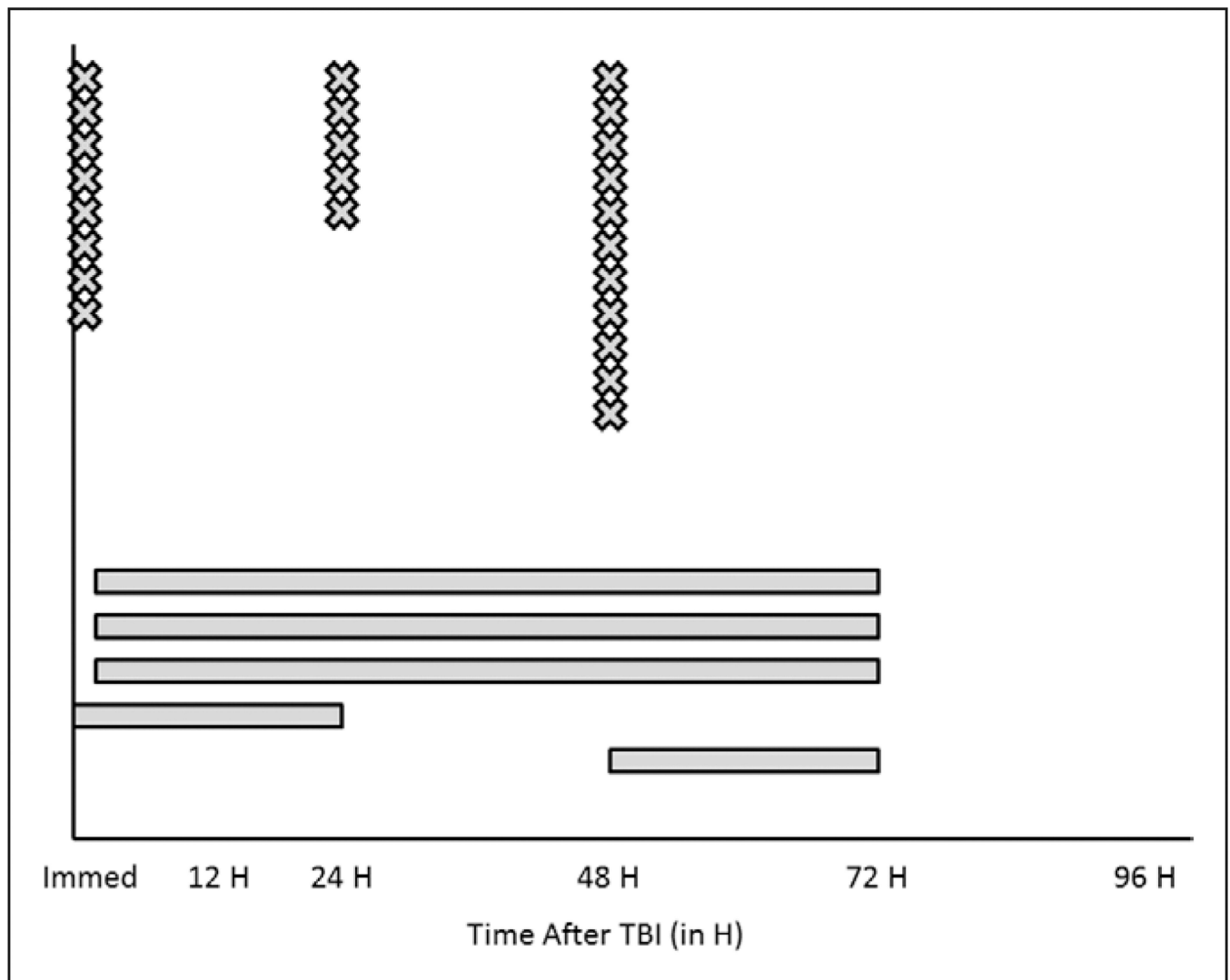


Figure 2.

Summary of the goals for starting of glucose from an international pediatric neurotrauma consortium consisting of 32 centers from the United States and Europe. Centers were asked, “When do you start to administer glucose to patients?” and were able to respond in freeform text. Centers responded with discrete time points (“X” in the figure) or by describing a range of time periods where nutritional support was intended to be started (“line” in the figure). Three centers responded with goals that were not time-based (when intracranial pressure < 20, when hypoglycemic, based on the age of patient) and are excluded from this figure. All times are expressed as time after traumatic brain injury (TBI).

Table 1

Summary of Evidence and Recommendations Generated From the 2012 Pediatric Traumatic Brain Injury Guidelines (26)

Topic	Level of Evidence	Recommendation
Indications for ICP monitoring	Level III	"Use of ICP monitoring may be considered..."
Threshold for treatment of intracranial hypertension	Level III	"Treatment of ICP may be considered at a threshold of 20 mm Hg"
Cerebral perfusion pressure thresholds	Level III	"A minimum CPP of 40 mm Hg may be considered... A CPP threshold of 40–50 mm Hg may be considered..."
Advanced neuromonitoring	Level III	"If brain oxygenation monitoring is used, maintenance of Pb_{O_2} 10 mm Hg may be considered"
Neuroimaging	Level III	"In the absence of neurological deterioration...routine repeat CT scan...may not be indicated..."
Hyperosmolar therapy	Level II Level III	"Hypertonic saline should be considered...for intracranial hypertension...effective doses... range between 6.5 and 10 mL/kg" "Hypertonic saline may be considered...effective doses as a continuous infusion of 3% saline range between 0.1 and 1.0 mL/kg/hr administered on a sliding scale..."
Temperature control	Level II Level III	"Moderate hypothermia...for only 24 hr duration should be avoided...moderate hypothermia starting within 8 hr after injury and lasting for 48 hr duration should be considered to reduce ICP...rewarming at a rate of 0.5°C/hr should be avoided" "Moderate hypothermia...for 48 hr duration may be considered."
Cerebrospinal fluid drainage	Level III	"Cerebrospinal fluid drainage through an externalized ventricular drain...may be considered...The addition of a lumbar drain may be considered..."
Barbiturates	Level III	"High-dose barbiturate therapy may be considered in hemodynamically stable patients with refractory intracranial hypertension...continuous arterial blood pressure monitoring and cardiovascular support to maintain adequate CPP are required"
Decompressive craniectomy for the treatment of intracranial hypertension	Level III	"Decompressive craniectomy with duraplasty...may be considered for pediatric patients...showing early signs of neurological deterioration or herniation or are developing intracranial hypertension refractory to medical management..."
Hyperventilation	Level III	"Avoidance of prophylactic severe hyperventilation to a Pa_{CO_2} < 30 mm Hg may be considered within the first 48 hr...If hyperventilation is used...advanced neuromonitoring for evaluation of cerebral ischemia may be considered"
Corticosteroids	Level II	"The use of corticosteroids is not recommended to improve outcome or lower ICP..."
Glucose and nutrition	Level II Level III	"The evidence does not support the use of an immune-modulating diet...to improve outcome" "...glycemic control...should be left to the treating physician"
Antiseizure prophylaxis	Level III	"Prophylactic treatment with phenytoin may be considered to reduce the prevalence of early posttraumatic seizures..."

ICP = intracranial pressure (levels of evidence based on current traumatic brain injury guidelines with levels I–III ["must be considered," "should be considered," and "may be considered," respectively]), CPP = cerebral perfusion pressure (mean arterial blood pressure minus mean ICP), Pb_{O_2} = partial pressure of interstitial brain oxygen.

Table 2**Survey Questions**

General	
	Audit of eligible patients over the past 3 yr
	What is the ICP threshold routinely used in your institution?
	Is the ICP threshold age-related? If so, how?
	What is the CPP threshold routinely used in your institution?
	Is the CPP threshold age-related? If so, how?
Intracranial hypertension therapies	
CSF diversion	Do you use CSF diversion (via an externalized ventricular drain) in children with severe TBI?
	If you use CSF diversion, do you drain CSF continuously or intermittently?
	If you drain CSF intermittently, do you have a goal amount of CSF to drain or a goal ICP that you will drain CSF to achieve?
Hyperosmolar therapies	Do you use mannitol, hypertonic saline solutions, or both during intracranial hypertension crises?
	If you use hypertonic saline solutions, what concentration(s) do you use?
	If you use hypertonic saline solutions, do you use it as a bolus administration or as a continuous infusion or both?
Hypoxia/ischemia detection	
Hyperventilation	Do you intentionally use hyperventilation during periods of normal ICP?
Pb _{o2} monitoring	Do you use Pb _{o2} monitoring in all children? If only a portion, approximately what percentage?
	If you use Pb _{o2} monitoring, what is your Pb _{o2} target?
Metabolic support	
Nutritional support	When do you start nutritional support to patients?
	Do you use enteral nutrition, parenteral nutrition, or both?
Glucose	When do you start to administer glucose to patients?
	Do you use insulin to control blood glucose? If so, do you use it by a defined protocol or by the bedside clinician's judgment?

ICP = intracranial pressure, CPP = cerebral perfusion pressure (mean arterial blood pressure minus mean ICP), CSF = cerebrospinal fluid, Pb_{o2} = partial pressure of interstitial brain oxygen.

Table 3**Summary of Cerebrospinal Fluid Diversion Strategies and Hyperosmolar Therapies**

CSF Diversion Strategies	<i>n</i> of 32 (% [95% CI])
Never use CSF diversion	11 (34.4% [18.6–53.2])
Intermittent CSF diversion only	0 (0% [0–10.9])
Continuous CSF diversion only	11 (34.4% [18.6–53.2])
Combinations	
No CSF diversion + continuous CSF diversion	2 (6.3% [0.8–20.8])
No CSF diversion + intermittent CSF diversion	2 (6.3% [0.8–20.8])
Intermittent CSF diversion + continuous CSF diversion	6 (18.8% [7.2–36.4])
Hyperosmolar therapy strategies	
Never use mannitol	3 (9.4% [2.0–25.0])
Never use hypertonic saline solutions	1 (3.1% [0.1–16.2])
Concentrations of hypertonic saline solutions	
Only use one concentration	22 (68.8% [50–83.9])
3% only	18
2.7% only	2
6.4% only	1
7.4% only	1
Use more than one concentration	10 (31.3% [16.1–50.0])

CSF = cerebrospinal fluid.