



Nutritional Support for Pediatric Severe Traumatic Brain Injury

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In critically ill children with severe traumatic brain injury (sTBI), nutrition may help facilitate optimal recovery. There is ongoing research regarding nutritional practices in the pediatric intensive care unit (PICU). These are focused on identifying a patient's most appropriate energy goal, the mode and timing of nutrient delivery that results in improved outcomes, as well as balancing these goals against inherent risks associated with nutrition therapy. Within the PICU population, children with sTBI experience complex physiologic derangements in the acute post-injury period that may alter metabolic demand, leading to nutritional needs that may differ from those in other critically ill patients. Currently, there are relatively few studies examining nutrition practices in PICU patients, and even fewer studies that focus on pediatric sTBI patients. Available data suggest that contemporary neurocritical care practices may largely blunt the expected hypermetabolic state after sTBI, and that early enteral nutrition may be associated with lower morbidity and mortality. In concordance with these data, the most recent guidelines for the management of pediatric sTBI released by the Brain Trauma Foundation recommend initiation of enteral nutrition within 72 h to improve outcome (Level 3 evidence). In this review, we will summarize available literature on nutrition therapy for children with sTBI and identify gaps for future research.

Keywords: nutrition, traumatic brain injury, pediatric intensive care unit, neurocritical care, enteral nutrition

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INTRODUCTION

Nutritional support is an important component of the comprehensive care for critically ill children. Evidence shows that appropriate delivery of energy and macronutrients maximizes the potential for positive outcomes in the pediatric intensive care unit (PICU), while over- or underfeeding may place patients at risk for increased morbidity and mortality (1–9). Guidelines from the Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (ASPEN) suggest using indirect calorimetry (IC) to determine an appropriate caloric goal, initiating enteral nutrition (EN) within 24–48 h of PICU admission, and reaching two-thirds of the caloric goal by 7 days (10, 11).

However, questions remain about the optimal prescription of nutrition for children that have suffered a severe traumatic brain injury (sTBI). Prescribing nutrition therapy that is targeted for this population is important because inadequate nutrition results in loss of lean body mass and reduced functional capacity, both of which are uniquely important for recovery from sTBI (12, 13). Additionally, the pathophysiology underlying secondary injury cascades could be modulated through nutritional targets (14).

Here we will present available data regarding nutrition for pediatric patients in the acute period after sTBI, the potential impact of nutrition on patient outcome, and identify gaps for future research.

ENERGY EXPENDITURE AFTER TBI

In the PICU, nutrition support should be individualized to each patient's unique needs because both overfeeding and underfeeding are associated with deleterious effects (15, 16). However, estimating energy and protein requirements is a complex task. In healthy children, nutritional needs vary greatly depending on age, growth velocity, body composition, current nutritional status, and level of physical activity (17). When children become critically ill, the number of variables grows to include fever, sepsis, sedative/neuromuscular blockade, pharmacotherapy, and duration and stage of critical illness (18). Predictive equations are frequently used to estimate energy expenditure and guide prescription of nutrition in critically ill children, but they may over- or underestimate the true metabolic demand (18). The gold standard for measuring resting energy expenditure is indirect calorimetry.

Several studies have applied this technique to sTBI patients to determine their energy expenditure in the acute post-injury period. Original data from several decades ago suggested that sTBI induced a state of hypermetabolism with energy expenditure up to 170% of expected (19, 20). However, these studies were performed before contemporary neurocritical care practices were firmly established, and it has been shown that neuroprotective strategies such as temperature control (21), sedation (22), neuromuscular blockade (23), and burst suppression (24) result in decreased energy expenditure in sTBI patients. In support of this notion, recent studies of energy expenditure after sTBI do not show the same degree of hypermetabolism, with some studies even showing hypometabolism during the acute post-injury period (25, 26). In a prospective observational study by Mtaweh et al. (27), 13 pediatric patients in their first week after sTBI had intermittent measurements of energy expenditure (MEE) by indirect calorimetry. All patients were intubated and sedated with opiates, nearly all were receiving neuromuscular blockade, and none were febrile or seizing during testing. MEE was then compared to predicted resting energy expenditure (pREE) as calculated by two commonly used predictive equations: the Harris-Benedict equation and the Schofield equation. The result was an average MEE/pREE ratio of $70.2 \pm 3.8\%$ and $69 \pm 4.5\%$ expected, respectively.

These data support the notion that contemporary neurocritical care practices may be acting to blunt any expected hypermetabolism. This results in a hypometabolic state during the first week post-injury. Because of this difficulty in predicting energy expenditure after sTBI, indirect calorimetry remains the gold standard for determining caloric need and should be used whenever feasible.

MODE OF NUTRITION DELIVERY

In addition to determining total energy requirement, clinicians must decide the safest and most appropriate mode of nutrient delivery. EN is increasingly considered as the preferred mode of delivery. Compared to parental nutrition (PN), EN may decrease the risk of metabolic derangements, hepatobiliary dysfunction, and infection. EN is also considerably less costly compared to PN

(28, 29). In a multicenter, randomized controlled trial of 1,440 critically ill pediatric patients, Fizez et al. showed that delaying the initiation of PN until the 8th day of hospitalization was superior to initiation of PN within 24 h of admission. Patients with delayed initiation of PN had lower rates of new infections, shorter durations of mechanical ventilatory support, and shorter durations of PICU stay (30). A similar result was seen in a large international study of nutrient delivery in mechanically ventilated children by Mehta et al. The study found that intake of a higher percentage of the prescribed dietary energy goal enterally is associated with improved 60-day survival, while mortality is higher in patients who received any amount of PN compared to those that received none (5).

With regard to studies specifically examining TBI patients, a small, randomized control trial of adult patients with moderate TBI by Meirelles et al. showed no difference in mortality, length of ICU stay, and days of mechanical ventilation based on mode of energy delivery (31). However, the authors did report significantly higher serum glucose in the PN group compared to the EN group (102.4 vs. 133.3 mg/dL). To our knowledge, there are no studies evaluating mode of nutrient delivery in pediatric sTBI.

TIMING OF SUPPORT

Delays in nutrition initiation and frequent interruptions to feeding commonly result in largely insufficient macronutrient delivery in PICU patients (5). Numerous studies have shown benefit for patients who receive early EN and for those who achieve adequate energy and protein delivery within 7–10 days (3, 5, 6, 8, 32). Although there is evidence that early EN is feasible and safe in the PICU (33–35), sTBI patients experience many barriers to reaching EN goals, including but not limited to need for vasoactives, high doses of sedatives, and fasting for procedures (36).

In a large adult retrospective cohort study with sTBI patients by Härtl et al. there was significantly higher two-week mortality among patients who were not fed within 5–7 days after TBI. This result represented a 2- and 4-fold increased likelihood of death respectively compared to those who were fed within 5 days of injury (37). In addition, every 10-kcal/kg decrease in caloric intake over the first 5 days was associated with a 30–40% increase in mortality rates.

Similar data have been reported for pediatric TBI patients. In a retrospective analysis of 109 children aged 8–19 years with sTBI, starting nutritional support within 72 h of admission and achieving goal caloric intake by day 7 was correlated with shorter ICU length of stay and improved clinical outcome at discharge (38). Similarly, Meinert et al. showed that patients who had nutritional support initiated within 72 h post-injury had lower mortality and improved functional outcome (favorable GOS-E Peds at 6 months and 12 months) when compared to those who received no nutritional support over the first 7 days post-injury (39). And most recently, a retrospective multicenter study of pediatric TBI patients of all severities showed that initiation of EN later than 48 h after admission was correlated with worse functional status at ICU discharge (change in POPC and change

TABLE 1 | Nutrition for pediatric severe traumatic brain injury.

Reference	Study design	Population			Study aim	Results/conclusions
		N	Inclusion criteria*	Exclusion criteria*		
Balakrishnan et al. (40)	Retrospective	Total N = 416 (N with GCS < 9 = 107)	-Age 0 to 18 -Head injury associated ICD9 diagnosis code	-Head abbreviated ISS of <2 -Died <48h from admission	To compare patients who received enteral nutrition early (≤ 48 h) and late (> 48 h)	-Lower GCS and higher ISS were associated with delayed initiation of enteral nutrition -Delayed enteral nutrition was associated with worse functional status (POPC/PCPC) at PICU discharge ($p = 0.02$), but not mortality or increased length of stay
Meinert et al. (39)	Secondary analysis of RCT	N = 90	-Age 0 to 18 -Post-resuscitation GCS < 9	-Normal head CT -GCS = 3 with unreactive pupils -Hypotension for >10 min -Hypoxia for >30 min -Penetrating injury	To understand the relationship between the timing of initiation of nutritional support in children with severe traumatic brain injury (TBI) and outcomes	Initiation of nutritional support before 72 hours after TBI was associated with decreased mortality ($p = 0.01$) and favorable outcome (GOS-E Peds) at 6 months ($p = 0.03$) and 12 months ($p = 0.04$)
Mtaweh et al. (27)	Prospective observational study	N = 13	Same as Meinert et al. (39) -Weight > 10 kg -Mechanically ventilated	Same as Meinert et al. (39)	To evaluate energy expenditure in a cohort of children with sTBI	-MEE/pREE averaged $70.2 \pm 3.8\%$, suggesting that contemporary neurocritical care practices may blunt a hypermetabolic response -Mean MEE/pREE in the favorable outcome group was $76.4 \pm 6\%$ vs. $64.7 \pm 4.7\%$ in the unfavorable outcome group ($p = 0.13$)
Malakouti et al. (68)	Retrospective	sTBI N = 101 control N = 92	-Age 0 to 15 -GCS < 9	-Admitted to PICU for <7 days	To examine nutritional support in severe pediatric traumatic brain injury patients (cases) and non-traumatic brain injury patients (controls) at a single center	-Nutrition was started 53 ± 20 hrs (range 12–162) after PICU admission -Patients whose intake met nutritional goals on PICU day 7 had earlier initiation of nutrition support than patients who never met the goals; both $p < 0.001$ -Average caloric and protein intakes for PICU days 0-7 were less for the TBI group ($52\% \pm 16\%$ caloric goal and $42\% \pm 18\%$ protein goal) than for the non-traumatic brain injury group ($65\% \pm 11\%$ of caloric goal and $51\% \pm 20\%$ of protein goal); both $p < 0.01$
Taha et al. (38)	Retrospective	N = 109	-Age 8 to 18 -GCS < 9	-Multisystem trauma	To examine the timing of nutritional supplement initiation and the timing of achieving full caloric intake in pediatric sTBI	-Starting nutritional support within 72 h of admission and achieving goal caloric intake by day 7 was correlated with shorter ICU length of stay ($p < 0.01$) and improved clinical outcome (modified PCPC) at discharge ($p < 0.05$)
Briassoulis et al. (41)	RCT	N = 40 (n = 20 for immune-enhancing diet, n = 20 for standard enteral diet)	-GCS < 9 -Age 0 to 18 6 -Enteral feeds starting within 12h of admission	-Renal or gastrointestinal disease	To analyze the effect of an immune enhancing (IE) diet on infection and metabolic indices in children with sTBI	-Interleukin-8 levels were lower in the IE group compared with the regular formula group by day 5 ($p < 0.04$) -Less gastric cultures were positive in the IE group compared with the regular formula group (26.7 vs. 71.4% ; $p < 0.02$) -Nosocomial infections (15 vs. 25%), length of stay (16.7 vs. 12.2 days), length of mechanical ventilation (11 vs. 8 days), and survival (80 vs. 95%) did not differ between groups
Havalad et al. (26)	Retrospective	N = 30	-GCS < 9 -Mechanically ventilated	-Required inotropes or pentobarbital	To determine if pREE varies significantly from MEE in a population of head-injured children	-More than half of the estimates of REE differed from measured REE by >10% and there was no correlation between severity of illness and measured REE to explain these inaccuracies, which suggests that nutrition should be prescribed to children with sTBI based on REE to avoid consequences of overfeeding or malnutrition

*Selected criteria relevant for understanding sample characteristics. TBI, traumatic brain injury; sTBI, severe TBI; ISS, illness severity score; GCS, glasgow coma scale; MEE, measured energy expenditure; pREE, predicted resting energy expenditure.

in PCPC) (40). Of note, this correlation did not hold when patients were stratified by TBI severity.

SITE OF ENTERAL NUTRITION DELIVERY

Feeding intolerance, though hard to define, is common in critically ill children. PICU patients that are unable to tolerate gastric feeding may receive EN that is delivered to the small bowel via naso-duodenal or naso-jejunal feeding tube. A randomized controlled trial of pediatric patients receiving mechanical ventilation showed that the percentage of daily caloric goal achieved was less in patients receiving gastric EN vs. small-bowel EN ($30 \pm 23\%$ vs. $47 \pm 22\%$) (42). There was no significant difference in signs or symptoms of feeding intolerance such as abdominal distension, vomiting, or diarrhea between groups.

sTBI patients may be more susceptible to feeding intolerance due to altered gastric motility, prolonged immobilization, and medication-related ileus (43). Due to this concern, one study in adult patients examined the tolerability of bolus vs. continuous gastric feeds and found that the patients receiving continuous feeds achieved their nutritional goals faster and had less frequent feeding intolerance (44). There are currently no pediatric studies comparing sites of EN delivery in sTBI patients.

IMMUNONUTRITION

Given the complex interplay of the intestines with the immune system, there is emerging interest in the effect of diet beyond its strictly nutritional value (45). The acute period after sTBI is characterized by neuroinflammation that paradoxically perpetuates secondary injury while also promoting repair (46). Due to their roles in cellular metabolism and the inflammatory cascade, substances such as amino acids, electrolytes, and antioxidants have been proposed as dietary supplements that could aid in modulating this delicate balance (47). In a randomized controlled trial with pediatric sTBI patients, patients who were given an immune-enhancing diet supplemented with glutamine, arginine, antioxidants, and omega-3 fatty acids showed no difference in outcomes when compared to patients who were on a regular formula regimen (41).

Based on emerging knowledge about the gut-brain axis, it has been hypothesized that alterations in gut microbiota could influence post-traumatic neuroinflammation (48). A recent study of children with sTBI by Rogers et al. characterized the temporal and spatial alterations in the microbiome during their initial ICU admission (49). Compared to healthy controls, sTBI patients quickly developed dysbiosis. They showed depletion of beneficial bacterial species and enrichment of pathogenic bacterial species over time. Additional studies are needed to determine how these changes impact clinical outcomes.

GLYCEMIC CONTROL

Hyperglycemia is a commonly observed response to the stress of critical illness, which is mediated by alterations in glucose metabolism that are caused by increases in pro-inflammatory and

counter-regulatory hormones, such as cortisol and epinephrine (50). This stress hyperglycemia (SH) represents a common secondary insult to the brain after sTBI (51), and has been associated with increased morbidity and mortality in adult and pediatric patients (52–56). Studies examining the effect of tight glycemic control in PICU patients have yielded inconsistent results, with most studies showing no benefit or concern for harm from severe hypoglycemia (57–59).

In a large international RCT in adults with TBI, patients receiving intensive glucose control (target range 80–110 mg/dL) and patients receiving conventional glucose control (target of less than 180 mg/dL) had similar long-term outcomes (60). However, intensive glucose control resulted in more frequent episodes of moderate to severe hypoglycemia, suggesting possible harm. In addition, several small studies in adult sTBI patients have used cerebral microdialysis to demonstrate tight glycemic control is associated with critical reduction in glucose and elevation of lactate/pyruvate ratio in the brain (61, 62). This increase in markers of cellular distress suggests that tight glycemic control results in damaged brain tissue being unable to access the glucose that is necessary for cellular repair and survival (62). There have been no studies evaluating glucose control in pediatric sTBI patients.

DISCUSSION

Adequate nutrition is essential for all critically ill children because malnutrition contributes to immune dysfunction and infections (63), weakness (64), and delayed healing and recovery (65). However, delivering nutrition to patients with sTBI is not a straightforward task. Nutrition therapies for sTBI patients must take into account hydration and electrolyte goals to prevent fluid shifts that could worsen cerebral edema (66). In addition, sTBI is accompanied by unique physiologic derangements. Damage to axons in the autonomic nervous system can lead to delayed gastric emptying and intestinal hypomotility (43). These symptoms are compounded by the use of sedatives and barbiturates (67), which lead to feeding intolerance and the subsequent withholding of enteral nutrition.

Despite these factors, few studies have attempted to identify nutritional interventions that could improve outcome for this patient population (Table 1). In general, high-quality nutrition studies are scarce and studies that focus on sTBI are even more uncommon. Most studies to date have been limited by small sample size, retrospective or observational design, and inconsistent inclusion or exclusion criteria. This leads to reduced statistical power, poor generalizability, and difficulty in assessing correlation vs. causation.

In 2019, the Brain Trauma Foundation released updated guidelines for the management of pediatric sTBI, which include a section on nutrition (69). Based on available evidence the authors were able to make two primary recommendations: (1) early initiation of EN (within 72 h of injury) to decrease mortality and improve outcomes, and (2) immune-modulating diet is not recommended to improve outcomes. These recommendations are largely consistent with established guidelines for all critically

ill pediatric patients. The currently available data are insufficient to warrant making further statements about nutritional goals that are unique to sTBI patients; providers should continue to prescribe nutritional support according to the previously mentioned SCCM/ASPEN guidelines.

Further studies are needed to elucidate nutritional recommendations for sTBI patients. It is important that future studies are designed in a manner that generates high-quality data. These studies should optimally be large, prospective trials, and should seek to identify unique nutrition targets for pediatric sTBI patients. This includes identifying an appropriate caloric goal and identifying a threshold for the initiation of targeted glucose control. Additional studies should also seek answers to questions about the timing, mode, and composition of macronutrient delivery and their effect on outcome.

Beyond the strictly caloric value of a sTBI patient's diet, nutritional supplementation may present an opportunity to mediate the effects of brain injury on a cellular level (14, 47, 66). Future clinical and pre-clinical studies should examine how supplementation of certain electrolytes, vitamins, minerals, or amino acids could interact with cellular processes to mediate the inflammatory cascade and restore normal metabolic activities.

Another important consideration when designing future studies is the choice of outcome measure. Although mortality is a traditional primary outcome, functional status is equally

important and may be more pertinent in pediatric research (70). Future studies should examine how nutrition combined with early mobilization and rehabilitation impacts deconditioning, muscle wasting, and change in overall functional status. Completion of high-quality studies that answer these questions will maximize the potential for positive outcomes in survivors of sTBI.

Of note, the Approaches and Decisions for Acute Pediatric TBI (ADAPT) Trial recently completed enrollment of 1,000 pediatric patients with sTBI. This trial was designed to use comparative effectiveness to examine the acute medical management of infants, children, and adolescents with severe TBI. Several of the a priori hypotheses put forward by the ADAPT investigators addressed nutrition questions, including many of those raised in this article. We anticipate new data will emerge from ADAPT and from other innovative trial designs, and we look forward to additional studies that will allow for more robust recommendations in the future.

AUTHOR CONTRIBUTIONS

EE, MS, MB, and KW contributed to the writing and editing of this manuscript. All authors contributed to the article and approved the submitted version.

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