

# Chapter 16. Glucose and nutrition

## I. RECOMMENDATIONS

Strength of the Recommendation: Weak.

Quality of Evidence: Moderate, from one moderate-quality class II study.

### A. Level 1

There are insufficient data to support a level I recommendation for this topic.

### B. Level II

The evidence does not support the use of an immune-modulating diet for the treatment of severe traumatic brain injury (TBI) to improve outcome.

### C. Level III

In the absence of outcome data, the specific approach to glycemic control in the management of infants and children with severe TBI should be left to the treating physician.

## II. EVIDENCE TABLE (see Table 1)

## III. OVERVIEW

Providing nutritional support to children after TBI is a decision with wide-ranging implications. Similar to adults, traumatically injured children require energy for wound healing, repair, alterations in normal organ function, and other pathologic processes initiated by the injury. However, children have greater nutritional needs for normal growth and development. The decision to administer nutritional support, including the timing, the quantity, the manner, and the composition of such support, may have profound effects on short- and long-term outcome, and results from studies in adults may not be applicable to infants and children.

## IV. PROCESS

For this update, MEDLINE was searched from 1996 through 2010 (Appendix B for search strategy), and results were supplemented with literature recommended by peers or identified from reference lists. Of the 104 potentially relevant studies, one was added to the existing table and used as evidence for this topic.

## V. SCIENTIFIC FOUNDATION

One class II randomized controlled trial met the inclusion criteria for this topic and provides evidence to support the recommendation (1). A study by Briassoulis et al (1) prospectively studied the effect of an immune-enhancing formula on various outcomes after TBI in a cohort of 40 children in a single center. Subjects with severe TBI (Glasgow Coma Scale [GCS] score  $\leq 8$ ) without renal or gastrointestinal disease were eligible. Enteral nutrition was initiated within 12 hrs of TBI. Children were randomized within a block design to either a specialized formula (Stresson, including supplemental glutamine, arginine, antioxidants, and omega-3 fatty acids) or a more standard formula (Tentrini) through a nasogastric tube. For each 100 mL, the specialized formulation contained greater amounts of protein (7.5 g vs. 3.3 g), fat (13.2 g vs. 11.1 g), glutamine (1.3 g vs. 0 g), arginine (0.89 g vs. 0 g), docosahexaenoic acid (0.028 g vs. 0 g), eicosapentaenoic acid (0.072 g vs. 0 g), selenium (14.1 mg vs. 4.9 mg), copper (338  $\mu\text{g}$  vs. 0  $\mu\text{g}$ ), vitamin E (12.5 mg vs. 1.3 mg), carotenoids (0.38 mg vs. 0.15 mg), and carnitine (7.5 mg vs. 3 mg). Furthermore, the experimental formula demonstrated an increased osmolality (420 mOsm/L vs. 245 mOsm/L) compared with the standard preparation. Administration of feedings was targeted based on predicted energy expenditure (PEE) that included compensatory increases for various injury factors. The amount of nutritional support from each formula was escalated over the first 5 days after TBI based on PEE (0.5%, 100%, 125%, 150%, and 150%, respectively). In both groups, feeding intolerance was treated with gastric-emptying

agents and diarrhea was treated with temporary discontinuation of feedings. Failure of a regimen was defined as inability to follow the prescription outlined here. Nitrogen balance, serum nutritional indices, and cytokines were determined in each group as the primary outcome parameters. The mean age of enrolled children was 120 months with a majority being male (71.4%). There were five deaths (12.5%). There were no significant differences in outcomes between the two feeding groups for survival (enhanced vs. standard: 80% vs. 95%), length of stay (16.7 vs. 12.2 days), or length of mechanical ventilation (11 vs. 8 days). Nitrogen balance was achieved in a greater percentage of children receiving the enhanced formula by day 5 (69.2% vs. 30.8%), but zinc, copper, retinol-binding protein, and transthyretin were not different between the groups throughout the study period. The only cytokine measured that was independently associated with the enhanced diet was interleukin-8. Levels were lower in the immune enhanced vs. standard treatment group.

## VI. INFORMATION FROM OTHER SOURCES

### A. Indications From the Adult Guidelines

Based on three class II and 11 class III studies (2), a recommendation to obtain full caloric replacement by 7 days postinjury was made in the adult guidelines. Overall, studies included within this guideline addressed the manner of feeding, the quantity of calories administered/expended, hyperglycemia, and mineral supplementation.

In comparing the manner in which nutrition is administered, a class II study by Rapp et al (3) randomized 38 subjects to total parenteral nutrition (TPN) or enteral nutrition (EN) and found that the TPN group had decreased mortality (zero vs. eight subjects,  $p < .001$ ). They also found that the TPN group achieved higher caloric intake and reached full nutritional replacement by 7 days postinjury (compared with 14 days postinjury for EN

Table 1. Evidence table

Reference	Study Description	Data Class, Quality, and Reasons	Results and Conclusion
New study Briassoulis et al, 2006 (1)	Design: randomized controlled trial N = 40 GCS: mean 6.2 (SEM 0.5) Age: mean 127 month $\pm$ 7.9 for immune-modulating group; 112 months $\pm$ 14.5 for standard group Protocol: children randomized to immune-enhancing diet containing supplementation with glutamine, arginine, and antioxidants vs. a regular formula from 12 hrs after admission Purpose: determine if an immune-enhanced diet would alter mortality Outcomes: hospital mortality, length of stay, nutritional indices, and cytokine concentrations	Class II Moderate quality: attrition not reported; unclear if intention-to-treat analysis conducted; otherwise met all criteria	Immune-enhancing vs. regular formula Survival: 80% vs. 95% Length of stay: 16.7 vs. 12.2 days Length of mechanical ventilation: 11 vs. 8 days <i>P</i> values not reported; no significant differences between groups Fewer positive gastric cultures in immune-enhancing group ( <i>p</i> < .02), but infections did not differ The group fed an immune-modulating diet; was more likely to have positive nitrogen balance at 5 days (69% vs. 31%, <i>p</i> < .05)

GCS, Glasgow Coma Scale; SEM, standard error of mean.

group). Class III studies provided complementary information regarding this issue. Specifically, a study by Hadley et al (4) demonstrated that subjects randomized to TPN had higher mean daily nitrogen intakes and losses, resulting ultimately in no difference in nitrogen balance between the intervention groups. A study by Young et al (5) randomized 51 subjects with severe to moderate TBI (GCS 4–10) to TPN or EN and found the TPN group had increased protein intake, improved nitrogen balance, and improved outcome at 3 months postinjury. Finally, a study by Borzotta et al (6) found that TPN and EN were equally effective when prescribed based on measured energy expenditure (MEE). They found that MEE remained between 135% and 146% of predicted for the first 4 wks postinjury and neither feeding regimen was associated with differences in infection rates or hospital costs.

In comparing various EN strategies, a class II study by Taylor et al (7) demonstrated that an accelerated EN regimen to meet goals within the first week postinjury in mechanically ventilated TBI victims was associated with improved outcome at 3 months (yet no difference at 6 months). Furthermore, fewer infections were also observed in the accelerated EN group. Other class III studies demonstrated that 1) percutaneously placed feeding tubes could safely administer calories after TBI (8, 9); 2) continuously fed subjects demonstrated less feeding intolerance and reached caloric goals more quickly (10); and 3) nasojejunal feedings

permitted increased delivery of calories (11). A study by Clifton et al (12) recommended that a nomogram be used to estimate energy requirements to guide caloric intake, whereas other recent studies suggest that published formulas poorly predict the energy requirements of adults (13) or children (14).

Regarding supplementation of feedings, a class II study showed a nonsignificant trend (*p* = .09) toward decreased mortality in subjects randomized to receive 12 mg elemental zinc in parenteral nutrition for 15 days followed by 22 mg oral zinc for an additional 15 days (15). Improvements in nutritional markers (albumin, prealbumin, and retinol-binding protein) were observed in this treatment group compared with the standard subjects. Finally, two class III studies demonstrated that hyperglycemia early after TBI was associated with poor outcome (16, 17), although this effect may reflect a stress response after injury rather than a nutritional effect.

In summary, the adult guidelines (2) suggest that starved patients with TBI lose sufficient nitrogen to reduce weight by 15% per week and support administration of 100% to 140% replacement of resting energy expenditure with 15% to 20% nitrogen calories, which may reduce nitrogen loss. The data support full feeding at least by the end of the first week. It has not been established that any method of feeding is better than another or that early feeding before 7 days improves outcome. Based on the level of nitrogen-wasting documented in patients with

TBI and the nitrogen-sparing effect of feeding, it is a level II recommendation that full nutritional replacement be instituted by day 7 postinjury for adult patients.

## B. Information Not Included as Evidence

A number of studies have been reported on this topic that failed to meet inclusion criteria because they did not compare specific nutritional regimens. There have been several studies addressing the effect of TBI on metabolism with a focus on the amount of consumed calories in the immediate post-TBI time period. This information is thought to be an important precursor to studies that would target the amount of calories required after TBI and the possible effect of different nutritional support strategies on overall outcome. Evidence suggests that underfed critically ill, nontrauma pediatric patients have increased mortality, infections, and poor wound healing (14). However, overfeeding is associated with increased carbon dioxide production and respiratory complications. Caloric needs can be measured using indirect calorimetry (MEE) or estimated by various mathematical formulae (PEE). Because many factors after TBI can affect caloric expenditure (including sedation, neuromuscular blockade, hemodynamic support, seizures, temperature, other injuries, and others), MEE currently represents the most accurate method for determining energy requirements (18).

Two studies have reported MEE after severe TBI in children. Phillips et al (19) studied the effect of TBI on energy expenditure (measured by indirect calorimetry), nitrogen excretion, and serum markers of nutritional adequacy in children with GCS 3–8. This observational study followed 12 children (aged 2–17 yrs) for the first 2 wks after TBI. There was one case of penetrating TBI, whereas all others had closed TBI. Multiple other injuries are described, yet the “major injury” was to the brain. Six children developed intracranial hypertension that was treated with hyperventilation, neuromuscular blockade ( $n = 4$ ), cerebrospinal fluid diversion, mannitol, or barbiturates ( $n = 4$ ). Phenytoin was administered only when seizures were observed. All children received antibiotics and antipyretics (aspirin/acetaminophen). Nutrition was administered enterally starting 3–12 days after injury ( $n = 5$ ) or parenterally starting 2–6 days after injury ( $n = 7$ ). MEE was performed on nine children, 1–14 days after TBI. The mean MEE was 130% of PEE derived from the Harris/Benedict formula, and the lowest MEE/PEE was 94%.

Diarrhea ( $n = 5$ ) and gastric residuals ( $n = 2$ ) were noted as limitations to enteral feeding regimen. Mean nitrogen excretion was 307 mg/kg/day for adolescents and 160 mg/kg/day for younger children, and nitrogen balance remained negative throughout the 2-wk period. Mean serum albumin decreased during the 2-wk study period (2.9 g/dL to 2.4 g/dL), whereas mean serum protein increased (5.4–6.0 g/dL) with both being below laboratory normals for the first week after TBI. Other nutritional markers (retinol binding protein and prealbumin) were slightly increased in week 2 compared with week 1. Weight loss was prominent, ranging 2–26 pounds among all subjects. This represents 9% loss of body weight for adolescents and 4% loss of body weight for children. The possible effects of neuromuscular blockade, sedation, temperature, and seizures were not addressed.

In another study, Moore et al (20) measured MEE within the first 48 hrs after TBI in 20 subjects with severe TBI, including seven children. Entry into this study was limited to patients with an Injury Severity Score for head injury greater than all other organ systems. All subjects underwent pulmonary artery catheterization for cardiac output monitoring, 17 received intracranial pressure

monitoring, and two received corticosteroids. Within the pediatric group (age, 3–16 yrs), oxygen consumption was 180% of predicted and energy expenditure was 173% of predicted. None of the values were <100% of predicted. The average respiratory quotient was 0.68, indicating consumption of lipids as a predominant fuel. The mean rectal temperature at the time of the metabolic testing was 38.2°C. Nutritional support started within 48 hrs after TBI, but information regarding the administration of enteral or parenteral nutrition, neuromuscular blockade, and barbiturates was not reported.

Two additional manuscripts, comprising some of the same patient population, were reported regarding MEE measurements (21, 22). Eighteen children after severe TBI (GCS <8) were studied and all received standard therapies including sedation and paralysis during the study period. Nasogastric feedings were begun on day 2 and MEE was determined serially for the first several days after TBI using the Douglas bag method. A total of 107 MEE measurements were obtained, with 1) 82% within the normal reference ranges for resting children (85% to 115% PEE); 2) 4% at >115% PEE; and 3) 14% at <85% PEE. Logistic regression demonstrated a significant association between MEE and rectal temperature with an increase of 1°C corresponding to an increase in MEE by 7.4%. Furthermore, MEE was significantly associated with plasma epinephrine, triiodothyronine, and glucagon concentrations.

Although the precise mechanism underlying the association between hyperglycemia and outcome is still unclear, the possibility exists that it may be related in part to nutrient delivery. Two studies regarding hyperglycemia and TBI included admission glucose concentrations among children with TBI. A study by Michaud et al (23) retrospectively studied 54 children (age, <16 yrs) with severe TBI (GCS  $\leq 8$ ) treated in a single center. Children who died in the emergency department, those with gunshot wounds to the head, and those who had fatal outcomes from multiple or extracranial injuries ( $n = 8$ ) were excluded. Children who received dextrose-containing solutions at another institution before serum glucose testing were separately analyzed. Discharge Glasgow Outcome Scale (GOS) scores were recorded. In the 16 children who died or remained in a vegetative state, mean admission glucose concentration was 288 mg/dL compared with 194 mg/dL for

those with more favorable outcome ( $p = .01$ ). Increases in blood glucose were also associated with hypotension, acidosis, abnormal pupillary responses, lower GCS, and cerebral edema on initial computed tomography scan.

A study by Cochran et al (24) was of 170 children with both moderate and severe TBI (Abbreviated Injury Score of the head at admission  $\geq 3$ ) who had admission serum glucose concentration measured. GOS scores were obtained at hospital discharge and mortality rate was 9.4%. Children who died had greater mean serum admission glucose concentration (267 mg/dL) compared with those with severe (GOS = 3; 249 mg/dL), moderate (GOS = 4; 168 mg/dL), or mild disability (GOS = 1; 128 mg/dL).

A study by Chiaretti et al (25) retrospectively analyzed 122 children after severe TBI (GCS  $\leq 8$ ) for various factors that might be associated with an adverse neurologic outcome. Inclusive in these factors was hyperglycemia, defined as blood glucose concentration >150 mg/dL. Glucose measurements were obtained at hospital admission and at least twice daily during the admission. Other factors considered in the analysis were hypoxia ( $\text{PaO}_2 < 60$  mm Hg or  $\text{Sao}_2 < 90\%$  for at least 15 mins or apnea/cyanosis noted on examination), hypotension (arterial pressure less than the fifth percent for age for at least 15 mins), radiologic findings (cerebral hemorrhages, cerebral edema, and other findings as interpreted by an independent radiologist), hematologic, coagulation, metabolic and seizures. Outcomes were assessed by GOS scores at 6 months after TBI and dichotomized into favorable (GOS 4–5) and unfavorable (GOS 1–3). Of the children enrolled, the mean age was 122 months, 74 had isolated head injury, whereas 48 had multiple trauma. There were 47 children with a poor outcome (38.5%) at 6 months. All children had admission glucose concentrations obtained and initial GCS and blood glucose were highly correlated ( $p = .001$ ). Mean admission serum glucose varied by outcomes that included some overlap between the groups (GOS 4–5, 221 mg/dL  $\pm 70$ ; GOS 3–4, 261 mg/dL  $\pm 102$ ; GOS 1–2, 290 mg/dL  $\pm 88$ ). Hyperglycemia after TBI was associated with poor outcome based on bivariate analysis, which remained significant in multivariate analysis adjusting for GCS, type of trauma (isolated vs. multi-trauma), hypoxia, hypotension, disseminated intravascular coagulation, and

early posttraumatic seizures. Administration of glucose, insulin, and other nutritional support was not reported.

## VII. SUMMARY

Although multiple studies examined the timing, quantity, manner, and composition of nutritional support for patients with TBI, only one met the inclusion criteria for this topic. That class II randomized controlled trial showed no difference in outcomes for children provided an immune-enhancing diet vs. regular formula. There is insufficient evidence to recommend the use of glycemic control after severe pediatric TBI to improve outcome despite evidence indicating that posttraumatic hyperglycemia is associated with poor outcome.

## VIII. KEY ISSUES FOR FUTURE INVESTIGATION

- Prospective trials of nutritional support, either enteral or parenteral, to determine the superiority of various potential strategies.
- Measurement of caloric expenditure and other nutritional indices in larger studies to gain a broader understanding of the role of nutrition after TBI so that novel strategies, including the possible targeting of caloric expenditure, can be tested.
- Prospective trials of glycemic control with protocolized administration of nutrition and insulin.
- More complete reporting of nutritional strategies used in large, randomized controlled trials of other therapies in TBI that would increase our understanding of the effect of nutrition on important outcomes.
- Fundamental observational studies of the effect of TBI on nutritional markers (including standard indices and metabolomics) for the design of rational clinical trials.

## REFERENCES

1. Briassoulis G, Filippou O, Kanariou M, et al: 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* 2006; 7:56–62
2. Bratton SL, Chestnut RM, Ghajar J, et al: Guidelines for the management of severe traumatic brain injury. XII. Nutrition. *J Neurotrauma* 2007; 24(Suppl 1):S77–S82
3. Rapp RP, Young B, Twyman D, et al: The favorable effect of early parenteral feeding on survival in head-injured patients. *J Neurosurg* 1983; 58:906–912
4. Hadley MN, Graham TW, Harrington T, et al: Nutritional support and neurotrauma: A critical review of early nutrition in forty-five acute head injury patients. *Neurosurgery* 1986; 19:367–373
5. Young B, Ott L, Haack D, et al: Effect of total parenteral nutrition upon intracranial pressure in severe head injury. *J Neurosurg* 1987; 67:76–80
6. Borzotta AP, Pennings J, Papisadero B, et al: Enteral versus parenteral nutrition after severe closed head injury. *J Trauma* 1994; 37: 459–468
7. Taylor SJ, Fettes SB, Jewkes C, et al: Prospective, randomized, controlled trial to determine the effect of early enhanced enteral nutrition on clinical outcome in mechanically ventilated patients suffering head injury. *Crit Care Med* 1999; 27:2525–2531
8. Kirby DF, Clifton GL, Turner H, et al: Early enteral nutrition after brain injury by percutaneous endoscopic gastrojejunostomy. *JPEN J Parenter Enteral Nutr* 1991; 15: 298–302
9. Klodell CT, Carroll M, Carrillo EH, et al: Routine intragastric feeding following traumatic brain injury is safe and well tolerated. *Am J Surg* 2000; 179:168–171
10. Rhoney DH, Parker D Jr, Formea CM, et al: Tolerability of bolus versus continuous gastric feeding in brain-injured patients. *Neurol Res* 2002; 24:613–620
11. Graham TW, Zadrozny DB, Harrington T: The benefits of early jejunal hyperalimentation in the head-injured patient. *Neurosurgery* 1989; 25:729–735
12. Clifton GL, Robertson CS, Choi SC: Assessment of nutritional requirements of head-injured patients. *J Neurosurg* 1986; 64: 895–901
13. Walker RN, Heuberger RA: Predictive equations for energy needs for the critically ill. *Respir Care* 2009; 54:509–521
14. Skillman HE, Wischmeyer PE: Nutrition therapy in critically ill infants and children. *JPEN J Parenter Enteral Nutr* 2008; 32: 520–534
15. Young B, Ott L, Kasarskis E, et al: Zinc supplementation is associated with improved neurologic recovery rate and visceral protein levels of patients with severe closed head injury. *J Neurotrauma* 1996; 13:25–34
16. Lam AM, Winn HR, Cullen BF, et al: Hyperglycemia and neurological outcome in patients with head injury. *J Neurosurg* 1991; 75:545–551
17. Young B, Ott L, Dempsey R, et al: Relationship between admission hyperglycemia and neurologic outcome of severely brain-injured patients. *Ann Surg* 1989; 210:466–472; discussion 472–473
18. Levine JA: Measurement of energy expenditure. *Public Health Nutr* 2005; 8:1123–1132
19. Phillips R, Ott L, Young B, et al: Nutritional support and measured energy expenditure of the child and adolescent with head injury. *J Neurosurg* 1987; 67:846–851
20. Moore R, Najarian MP, Konvolinka CW: Measured energy expenditure in severe head trauma. *J Trauma* 1989; 29:1633–1636
21. Matthews DS, Aynsley-Green A, Matthews JN, et al: The effect of severe head injury on whole body energy expenditure and its possible hormonal mediators in children. *Pediatr Res* 1995; 37:409–417
22. Matthews DS, Bullock RE, Matthews JN, et al: Temperature response to severe head injury and the effect on body energy expenditure and cerebral oxygen consumption. *Arch Dis Child* 1995; 72:507–515
23. Michaud LJ, Rivara FP, Longstreth WT Jr, et al: Elevated initial blood glucose levels and poor outcome following severe brain injuries in children. *J Trauma* 1991; 31:1356–1362
24. Cochran A, Scaife ER, Hansen KW, et al: Hyperglycemia and outcomes from pediatric traumatic brain injury. *J Trauma* 2003; 55: 1035–1038
25. Chiaretti A, Piastra M, Pulitano S, et al: Prognostic factors and outcome of children with severe head injury: An 8-year experience. *Childs Nerv Syst* 2002; 18:129–136