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Nutr Clin Pract 2008; 23; 608
DOI: 10.1177/0884533608326060

Invited Review

Nutrition in Clinical Practice
Volume 23 Number 6
December 2008 608-620

10.1177/0884533608326060
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Nutrition Considerations in Traumatic Brain Injury

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Financial disclosure: none declared.

The provision of adequate nutrition support for patients with traumatic brain injury (TBI) has been a clinical challenge for decades. The primary and secondary injuries create unique metabolic derangements along with accompanying issues such as optimal timing and route of nutrition, appropriate fluid and electrolytes, drug administration, rehabilitation, and dysphagia. Enteral nutrition is clearly established as the preferential route of nutrition support for this population vs parenteral nutrition. There appears to be a consensus on early initiation of enteral nutrition, but less definitive are recommendations on advancement timing and formula components. Nutrition therapies should include exact fluid resuscitation goals specific for TBI and strict electrolyte monitoring to avoid extreme fluid, electrolyte, or glucose shifts that could be detrimental to the patient. While the critical care patient often tolerates small bowel feeding, the long-term rehabilitation patient should transition to and tolerate gastric feeding. Drug-nutrient and adverse drug reactions such as diarrhea should be routinely evaluated in patients receiving enteral nutrition. Monitoring for dysphagia is critical to avoid the costly negative aspects associated with aspiration and to capitalize on quality of life and appropriate oral nutrition. Emphasizing the priority of early nutrition support within a multi-disciplinary team may be the critical key for successful provision and tolerance of nutrition support in the TBI population. (*Nutr Clin Pract.* 2008;23:608-620)

Keywords: enteral nutrition; nutritional support; brain injuries; critical illness

Moderate to severe traumatic brain injury (TBI) results in a mortality rate of approximately 33%.[1] Nearly 1.4 million individuals per year suffer from TBI, leaving many of the survivors with significant deficits that often require extended medical and rehabilitation care.[2] Therapies that have been demonstrated to improve outcome after TBI are relatively limited. Interventions such as consistent avoidance of hypotension, maintenance of adequate cerebral perfusion, and prevention of stress-related mucosal damage and venous thromboembolism appear to prevent neurological and medical complications. Early and adequate nutrition support is challenging to provide in the TBI population, but it may improve the overall clinical course in TBI patients as well.[3]

TBI consists not only of the primary, or initial, injury, but also an insidious secondary injury cascade that occurs after the principal insult. Primary injury typically occurs due to direct injury to the brain. This type of injury can cause permanent brain damage due to direct tissue destruction. Common classifications of this type of injury range from concussion to contusion to diffuse axonal injury to intracranial bleeding such as an epidural hematoma, subdural hematoma, or intracerebral hemorrhage. Primary injury is difficult to treat due to the mechanism and rapidity of the injury. Much of the therapy for primary injury is targeted at treating intracranial hypertension, which occurs due to mass effect from hemorrhage or cerebrospinal fluid (CSF) outflow obstruction. Prompt surgical evacuation of hematomas and hemorrhages by means of craniotomy can often mitigate elevated intracranial pressures in the acute setting.

In contrast, secondary injury appears to be due to a natural inflammatory cascade that occurs subsequent to primary injury. Secondary injury is typified by brain cell swelling and apoptosis. These effects are mediated by deleterious neurotransmitters such as glutamate, reactive oxygen species, and inflammatory processes governed by complement and cellular immunity.[4] These harmful processes result in cerebral edema, brain cell metabolic dysfunction, and ultimately cell death due to energy failure. Therapies such as mannitol and hypertonic saline are often used to treat the resulting elevated intracranial pressure (ICP) by modulating the rheology and osmolarity of cerebral blood volume. Other medications such as neuromuscular blockers, sedatives such as propofol, and

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barbiturates such as thiopental or pentobarbital are used to suppress cerebral metabolism in an effort to abate the "energy stress" present in injured cells. Novel therapies such as calcium channel blockers, poly-ADP ribose polymerase inhibitors, and cyclosporine are currently being investigated for their potential to modulate secondary injury mechanisms.[4]

Metabolic Alterations After TBI

The brain's function as the regulator for metabolic activity leads to a complex milieu of metabolic alterations in TBI consisting of hormonal changes, aberrant cellular metabolism, and a vigorous cerebral and systemic inflammatory response in an effort to liberate substrate for injured cell metabolism. The degree of this hypermetabolic state is proportional to the severity of injury and motor dysfunction.[5] The end result of these alterations is systemic catabolism, which leads to hyperglycemia, protein wasting, and increased energy demand. Each of these factors occurs in such an overwhelming manner that they contribute to the morbidity of TBI. Effective nutrition support can play a major role in attenuating the catabolic response and avoiding the potentially harmful effects of prolonged hypermetabolism.

The injured brain stimulates the secretion of many hormones that affect metabolic function, including hypothalamic-pituitary axis products such as adrenocorticotrophin releasing hormone (ACTH), growth hormone, prolactin, vasopressin, and cortisol as a natural response to stress. Glucagon and catecholamines are also released in excess. Although catecholamines help to support blood pressure and cardiac output (and hence cerebral perfusion), catecholamines also increase basal metabolism, oxygen consumption, glycogenolysis, hyperglycemia, proteolysis, and muscle wasting. Increasing basal metabolism and cellular energy demand in the setting of TBI-induced metabolic dysfunction may shift cellular supply-demand coupling to conditions promoting energy failure. Hyperglycemia and intracellular lactate production are associated with the development of reactive oxygen species, particularly during the acute ischemic phase of TBI.[6,7] Proteolysis may result in cell-mediated immune dysfunction and muscle wasting. Exogenous substrates provided by enteral nutrition (EN) or parenteral nutrition (PN) may reduce the need for the liberation of endogenous substrate stores, and thus reduce these catabolic effects.

Acute phase reactants, electrolytes, and amino acids exhibit altered concentrations after TBI and may have an impact on secondary injury and TBI outcome (Table 1). Zinc is an important co-factor for substrate metabolism, immune function, and N-methyl-D-aspartate (NMDA) receptor function. In TBI, serum zinc concentrations are diminished due to liver sequestration and increased renal clearance. Supplementation of zinc appears to improve protein metabolism and neurologic outcome at 1 month after TBI.[8] Magnesium may also be neuroprotective due to activity at the NMDA receptor and modulation of cellular energy production and calcium influx.[9] Unfortunately, supplementation of magnesium in humans has yet to yield definitive benefits. Insulin-like growth factor binding protein-3 (IGFBP-3) is also decreased after TBI, which likely allows greater clearance (and thus less activity) of the growth hormone mediator, insulin-like growth factor-1 (IGF-1). Supplementation of exogenous IGF-1 in TBI patients appears to lower blood glucose and improve protein conservation.[10]

Table 1. Metabolic and Immune Alterations After Traumatic Brain Injury (TBI)[10,115,116]

Diminished Concentrations in TBI	Elevated Concentrations in TBI
Zinc	Interleukin-1 (IL-1)
Iron	Interleukin-6 (IL-6)
Albumin	Ceruloplasmin
Prealbumin	Alpha-1 acid glycoprotein
Transferrin	C-reactive protein
Insulin-like growth factor-1 (IGF-1)	
Insulin-like growth factor binding protein-3 (IGFBP-3)	

Reprinted from reference 35.

Alterations in the concentrations of amino acids may also affect the catecholamine stress response and affect which protein precursors are available for transport into the brain. Glutamine, which is typically associated with decreasing bacterial translocation, may increase glutamate synthesis in the brain. Glutamate interacts with the NMDA receptor to promote cell death by means of calcium influx.[4,11] The benefits and risks of L-arginine use is currently unclear, as nitric oxide concentrations may fluctuate depending on the phase of injury.[12] More information on the precise mechanism of action and clinical significance of electrolytes and amino acids such as magnesium and glutamine is needed to define their potential role in TBI therapy.

Enteral Nutrition Access

Patients who have sustained a brain injury may often have feeding intolerance.[13] Swallowing requires multiple neurologic inputs to perform correctly and damage to these circuits may occur as a result of TBI in as many as 61% of patients.[14] Patients with moderate to severe TBI may require mechanical ventilation, which abrogates the possibility of oral intake. Thus, many TBI patients require alternative means of feeding.

The advantages and disadvantages of parenteral and enteral nutrition are well defined. PN is often associated with an increased risk of infection, immunosuppression, hyperglycemia, hepatosteatosis, and diminished GL integrity and gut-associated lymphoid tissue (GALT).[15] EN stimulates blood flow to the highly metabolic GL mucosa. This effect may blunt perturbations in GI blood flow in situations of elevated intrathoracic pressure and during vasopressor infusions.[16,17] Caution is still warranted in patients receiving EN and high doses of vasopressors due to case reports of bowel necrosis, but it appears that provision of EN in patients on low to moderate doses of vasoconstrictors (particularly after adequate fluid resuscitation) is safer than initially thought. In addition, EN provides a more comprehensive mix of macro- and micronutrients, such as medium chain triglycerides and fiber producing short chain fatty acids.

Clinicians still debate the optimal location for administration of EN (in the stomach or small bowel). Although the use of percutaneous endoscopic gastrostomy (PEG) tubes has proven successful in establishing well-tolerated feeding access within 5 days of injury, feeding TBI patients in the stomach can be challenging, particularly in the acute phases of illness.[18,19] TBI patients often exhibit impaired gastric emptying due to vagus nerve damage, elevated levels of endogenous opioids and endorphins, or medications such as pentobarbital or narcotics.[20,21] Elevated ICP has been associated with feeding intolerance as well.[20] Nasally-inserted small bowel feeding access devices are generally safe and easily inserted at the bedside by a nurse. These tubes do not come without risk of misplacement into the lung and should be radiologically verified before initiating feedings. As many as 50% of nasoenteric tubes are eventually dislodged, typically due to patient agitation, discomfort, or inadequate sedation.[22] Adequate "anchoring" of the tube is essential. One method by which this may be accomplished is by bridling the tube.[21] Endoscopic feeding tube placement may also be perilous, particularly early after injury or in patients with ICP elevations.[23] Careful consideration of the patient and their clinical status is warranted before endoscopically placing a feeding device.

When enteral access cannot be achieved within 72 hours after TBI, many practitioners consider PN until enteral access can be obtained. While the typical TBI patient has a central venous catheter (CVC) placed upon admission for maintenance fluid, antibiotics, and other medications, administration of PN through a separate, designated CVC appears to be more prudent due to increased infections associated with PN use. The balance between the provision of early nutrition, in whatever form, and the preference to use EN when possible, is often difficult to optimize in neurologically ill patients and the time threshold for when to attempt PN early in illness is still under debate. Protocols and algorithms that specifically address the timing of establishing enteral access, tube placement confirmation, and initiation of nutrition support could assist clinicians and benefit the patient.[24,25]

When TBI patients require long-term EN, a more secured enteral access device, gastrostomy, is optimal and preferred by most long-term care facilities. Although TBI patients may not reliably tolerate gastric feedings in the early stages after injury, gastric feeding is better tolerated as the acute phase subsides.[26] The use of a PEG also eliminates the need for nasoenteric access. The prolonged use of nasal feeding access not only presents the continued risk of tube dislodgement and patient discomfort, but also increases the likelihood of sinusitis. The optimal timing for PEG placement has not yet been determined. However, it is advisable to wait until the patient's clinical status has stabilized, adequate bowel function and feeding tolerance has been demonstrated, and there is no active infection or acute intracranial processes.

Timing of Nutrition

Early EN (within 48 hours) is clearly an important goal for the initial nutrition support plan for a TBI patient. Early provision of nutrients forestalls the breakdown of protein and fat stores, blunts the innate inflammatory response, promotes immune competence, decreases intensive care unit (ICU) infections, limits the risk of bacterial translocation and may improve neurologic outcome at 3 months.[3,27] The benefits of early EN were first reported in the critically ill surgical, trauma, and burn patients.[28-30] Placement of enteral access in the first 24–48 hours after injury is needed to facilitate early feeding. Most TBI patients tolerate receiving at least 50% of their caloric needs by injury day 2.[31,32] Individuals that may exhibit intolerance in the first few days after injury are still likely to benefit from some EN, even if at a low rate (10-20 mL/hr). Clearly, the "trophic feeding" rate will not provide the optimal calorie and protein intake to meet the estimated energy expenditure, but it will stimulate GL blood flow, which appears to have clinical benefits despite not meeting nutrition goals.[16] Currently, the Brain Trauma Foundation promotes a level II recommendation that TBI patients attain full caloric replacement by day 7 after injury.[1,33]

Many of the early studies comparing PN and EN in TBI patients have revealed that PN may be better than EN. However, these studies used nasogastric feedings early in the course of TBI, which were not well tolerated. Therefore, many of the studies in effect compared early PN against delayed EN, hence the reported benefit with PN. More recent studies investigating nutrition in TBI have not focused on the preference of route, but rather the importance of timing, and support early EN. Feeding

Table 2. Common Equations for Estimating Basal Energy Expenditure

Harris and Benedict Equations (HBE)[a]:
Women: BMR = 655 + (4.35 × weight) + (4.7 × height) - (4.7 × age)
Men: BMR = 66 + (6.23 × weight) + (12.7 × height)- (6.8 × age)

Mifflin-St Jeor Equations[b]:
Male: BMR = (10 × weight) + (6.25 × height) – (5 × age) + 5
Female: BMR = (10 × weight) + (6.25 × height) – (5 × age) – 161

Ireton-Jones Equation for ventilated patients[c]:
EEE = 1925 – ([10 × age] + [5 × kg] + [281 × gender] + [292 × trauma] + [851 × burn])

Penn State Equation:
RMR (Kcal/d) = (HBE × 0.85) + (V_E × 33) + (T_M × 175) – 6433[d]

a. weight in pounds, height in inches, age in years; b. weight in kilograms, height in centimeters, age in years; c. gender: 0 for females, 1 for males; trauma: 1 for yes, 0 for no; burn: 1 for yes, 0 for no; d. V_E, minute ventilation; T_M, maximum body temperature(°C) in previous 24 hours
BMR, basal metabolic rate; EEE, estimated energy expenditure; RMR, resting metabolic rate.

to goal within 2–3 days has been associated with accelerated neurologic recovery as well as decreased incidence of death due to infection.[34] Given the risks of using PN and the relative efficacy of EN, every effort should be made to use EN early in the management of a TBI patient.[35]

Nutrition Assessment: Calories

Accurate assessment and estimation of caloric needs in TBI patients is a critical component in providing adequate nutrition support. Delayed or persistent, drastic underfeeding of TBI patients may result in negative outcomes such as impaired organ function, poor wound healing, and altered immunological status. Several different strategies for estimating caloric needs have been investigated, although few definitive answers have been found or agreed upon.[36] Indirect calorimetry remains the current "gold standard" for determining energy expenditure in TBI patients. However, the daily caloric requirements of brain-injured patients that have intermittent muscle contractions, sympathetic storming, or fever may not be accurately represented, even by indirect calorimetry.

Energy expenditure can also be predicted by using various calculations, such as the Harris-Benedict, Ireton-Jones, Penn State, weight-based calculations, and the current ADA-endorsed Mifflin-St Jeor equations (Table 2).[37,38] The Harris-Benedict equation (HBE) has been used for decades to estimate the basal energy expenditure (BEE) in the TBI population. However, use of unadjusted BEE does not appear to approach the elevated caloric need of TBI patients.[39] The estimated stress factors multiplied by the BEE were originally much higher than currently agreed upon. TBI patients exhibit 120%–250% of their BEE using the HBE. Sedatives, paralytics, and barbiturates can alter metabolism by 76%–120% of the estimated BEE. Providing 140% of calculated BEE will likely meet the needs of most TBI patients. More calories may be required if the patient has additional injuries/stress, especially long bone fractures or sepsis.

Currently, the ADA recommends the use of the Mifflin-St. Jeor equation to calculate BEE for critically ill patients. However, this method has not been well studied in the TBI population, which has clearly been shown to have unique caloric requirements compared with many other critically ill individuals. Regardless of which method is used, no single method of estimating energy expenditure is infallible and close monitoring of each individual patient is needed to prevent over or underfeeding. Prolonged or excessive overfeeding can be deleterious as well. Over-feeding can result in metabolic complications such as hyperglycemia, refeeding-like syndrome with electrolyte derangements, hepatic steatosis, pulmonary compromise with difficulty weaning from the ventilator, and even obesity in the long-term patient.

Nutrition Assessment: Protein

The hypercatabolism evident in TBI patients stimulated by inflammatory mediators and catecholamines often results in excessive protein breakdown. Protein catabolism appears to peak 8–14 days after injury and appears to be related to the severity of injury.[40] Urinary nitrogen elimination in TBI patients ranges from 0.2 to 0.28 g/kg/day.[41,42] Supplementation of excessive calories to abate protein loss does not appear to be effective.[43] Aggressive protein supplementation has not been demonstrated to consistently balance nitrogen excretion or maintain muscle mass after TBI.[22,33] Studies of other critically ill, catabolic patients have also shown the failure of high protein supplementation to reverse muscle catabolism.[44,45] The use of anabolic therapies such as growth hormone or IGF-1 is controversial due to studies showing increased mortality in critically ill patients receiving growth hormone.[46] However, IGF-1 is the only therapy that has resulted in a positive protein balance in TBI patients.[10] Regardless, current recommendations suggest protein provision ranging between 1.5 and 2 g/kg/day for acute TBI patients to account for the excess catabolism.[47]

Most TBI patients tolerate standard intact protein formulas. Very limited data exists regarding any benefits or detriment of specialty products with the TBI patient population. One study concluded that an enteral formula containing glutamine and probiotics decreased the infection rate and shortened the ICU stay of brain injury

patients.[48] The role of elemental and semi-elemental nutrition products is not well-defined in this population, though anecdotally, these products may be useful in patients with abdominal trauma, prolonged hypotension, or vasopressor therapy. Very high protein doses may cause azotemia in patients with renal insufficiency, so routine monitoring should be performed to ensure the safety and efficacy of this intervention. Adequate free water supplementation is necessary with these high-protein diets to prevent azotemia. Free water supplements should be supplied without glucose to avoid overfeeding and the complications seen with hyperglycemia in the TBI patient. Monitoring protein supplementation is difficult as albumin and prealbumin are both negative acute phase proteins and are more indicative of inflammation and not nutrition deprivation or recovery.[49-51] Protein doses should be adjusted during the course of TBI recovery.

Nutrition Assessment: Fluids and Electrolytes

Fluid therapy is an often overlooked component of care in TBI patients. Shortly after injury, TBI patients often require intravenous fluid resuscitation to maintain adequate mean arterial and cerebral perfusion pressures. Episodes of hypotension in this early period have proven to be deleterious.[52,53] Patients with elevated ICP may also receive osmotic diuretics, which also potentiate the need for intravenous fluid supplementation. However, excessive fluid volumes may decrease cerebral compliance and increase brain edema.[54] Extensive monitoring of blood pressure and volume status should be considered for patients with moderate to severe TBI. Readers are encouraged to refer to a recent excellent review of general fluid and electrolyte issues in TBI patients published in this journal.[55] Several contemporary, controversial topics related to fluid and electrolytes merit further discussion.

The optimal fluid for use in TBI fluid resuscitation is not well defined. Colloids and crystalloids both present advantages and disadvantages when used in this population. Albumin may be the prototype colloid for use in acute neurologic illness. In addition to being an effective plasma expander, albumin has also exhibited neuroprotective effects.[56] However, no clinical evidence exists that supports the use of albumin instead of crystalloid in TBI. To the contrary, a large randomized, double-blind study comparing 0.9% sodium chloride (normal saline) and 4% albumin for the fluid resuscitation of general intensive care unit patients (SAFE) revealed a possible increase in mortality in trauma patients receiving albumin (relative risk [RR] of death 1.36 [0.99–1.86]).[57] Subgroup analysis of the TBI population in this study (SAFE-TBI) revealed that patients with severe brain injury resuscitated with albumin had a significantly higher mortality (RR 1.88 [1.31–2.70]).[58] Other colloids such as hetastarch (at doses >1000 mL/24 hours) and dextran should also be used with caution due to bleeding risks.[59,60] There remains some doubt on the role of colloids as the primary resuscitative fluid in TBI due to the relative lack of data, increased cost compared with saline, and the specter of increased mortality.

Great care should be exercised when fluid resuscitating brain injured patients due to the risk of hemodilution (which may promote additional bleeding) and acute respiratory distress syndrome (ARDS). In a study comparing cerebral blood flow (CBF)-targeted and ICP-targeted management of TBI, subjects in the CBF-targeted group developed ARDS more often than those in the ICP-targeted group (15% vs 3.3%; $P = .007$).[61] The ARDS patients received more vasopressor agents for a longer duration than non-ARDS patients, as well as more intravenous fluids (4059 mL/day vs 2874 mL/day; $P = .0001$).[62] Unfortunately, the types of fluids used in this study were not reported, so the relationship of fluid type, hypervolemia, ARDS, and increased mortality in TBI is not completely defined. Although the current Brain Trauma Foundation Guidelines do not make a definitive statement on fluid choice for initial resuscitation of TBI, judicious use of normal saline appears to be the safest option at this point in time.[1]

Intravenous solutions containing dextrose should be avoided in the acute phases of TBI. Hyperglycemia after TBI is associated with worsened outcome.[63] The explanation for this phenomenon is multifactorial. First, patients with more severe TBI are likely to have a more vigorous stress response. As a result, elevated circulating catecholamines and cortisol cause hyperglycemia. Second, elevated glucose concentrations in insulin-independent tissues (such as neurons) may contribute to cellular toxicity and secondary injury.[6,64] Increased lactate production and brain tissue acidosis are also associated with hyperglycemia.[65] Finally, hyperglycemia also contributes to catabolism by enhancing proteolysis.[66]

Although the injurious effects of hyperglycemia are well-known in TBI, the effect of treatment of hyperglycemia in these patients is not well studied. It is unclear if the positive outcomes associated with maintenance of euglycemia with intravenous insulin in other critically ill patient populations can be extrapolated to TBI patients.[67-71] One common source of consternation for clinicians is the possibility of hypoglycemia in an already compromised brain. Recent reports of the association of hypoglycemia and worsened overall outcomes legitimize this concern.[72] To avoid complications associated with hyperglycemia and impaired glucose utilization, glucose administration rate should not exceed 3.5 g/kg/d.[73]

While euglycemia is likely to decrease infectious complications in the "long-term" critically ill patient (> 7

days in ICU) which applies to many TBI patients, the precise goal glucose range is not well defined. Several studies have used a goal range of 80–110 mg/dL, while others have been more liberal (up to approximately 150 mg/dL). In practice, either no guidance at all or excessively aggressive protocols are likely to lead to more hypoglycemia, which may be problematic. At this point, it may be reasonable to target glucoses in the 100–150 mg/dL range and use a simple, effective dose adjustment protocol to limit any excursions outside the range.

Medication Considerations

The initial intensive care management of TBI is of paramount importance. Patients with severe TBI will often require intubation for airway protection and mechanical ventilation to ensure adequate oxygenation and optimal serum carbon dioxide (CO_2) levels. Fluid resuscitation and use of vasopressor agents are often used to maintain the cerebral perfusion pressure (CPP) above 60 mm Hg. Patients with a Glasgow Coma Score < 8 and those with elevated ICP may need a ventriculostomy to facilitate CSF drainage and continuous measurement of ICP. Institution of supportive therapies such as acid suppressive therapy to prevent stress ulcerations, mechanical or pharmacologic venous thromboembolism prophylaxis, and pneumonia prevention measures (eg, head-of-bed elevation, oral care) are also commonplace.

Several medications used for the treatment of elevated ICP may affect nutrition support and electrolytes. Mannitol, an osmotic diuretic, is a first-line agent used to acutely lower ICP. Frequent use of mannitol requires close monitoring of serum osmolarity due to its potent diuretic action. Supplementation of additional fluids and electrolytes are often required to maintain homeostasis. Hypertonic saline (HTS) is another frequently used osmotherapy agent. Typical concentrations range from 3% to 23.4% sodium chloride. The osmotic effects of HTS are similar to mannitol, though HTS tends to be less of a diuretic. However, excesses in sodium and chloride can occur quickly with repeated dosing, so routine monitoring of acid-base status and the metabolic profile is necessary.

Propofol, a short-acting anesthetic and sedative, may be used to decrease cerebral metabolic activity. Propofol is solubilized in a soybean oil/egg phospholipid emulsion. This 10% lipid vehicle provides calories in the form of fat, primarily linoleic acid (1.1 kcal/mL).[74] The extra calories provided (as calculated from the propofol infusion rate) should be considered when recommending nutrition regimens to meet estimated needs. Combination of propofol and EN products containing ω-3 fatty acids like eicosopentanoic acid may erase the anti-inflammatory effects of the immunonutrients.

Metabolic suppression agents such as pentobarbital are used to induce a pharmacologic coma in an effort to decrease cerebral metabolism. Patients receiving pentobarbital for refractory elevated ICP may have a diminished energy requirement due to decreased cerebral and peripheral energy demands. Patients in a pentobarbital coma tend to require 76%–86% of the predicted energy expenditure.[75,76] Protein requirements may be less as well, as reflected by a 40% decrease in urinary nitrogen excretion.[76] The use of these potent sedating medications for the treatment of elevated ICP should be considered when estimating nutrition needs and developing a plan for the provision of nutrition support. Barbiturate coma and the use of narcotics, such as fentanyl or morphine, also decrease GL motility and gastric emptying, often leading to feeding intolerance. Routine use of bowel regimens with stool softeners and stimulants may delay or eliminate the development of a drug-induced ileus.

Drug-nutrient Interactions

Drug-nutrition interactions require consideration when planning to provide EN to patients with TBI. As the preference of EN over PN has progressed, so has the increased use of enteral formulations of medications. Many intravenous medications exhibit adequate bioavailability when administered enterally and may be converted to the enteral formulation as soon as bowel function is present and the patient is tolerant of nutrition.[77,78] Conversely, some antimicrobials are poorly absorbed when co-administered with EN solutions. Corticosteroids may cause insulin resistance that often leads to hyperglycemia. The use of corticosteroids is not recommended for the treatment of TBI.[53]

Phenytoin represents a classic drug-nutrition interaction within the TBI population. Phenytoin is an anticonvulsant often used for the prevention and treatment of posttraumatic epilepsy. Formulations commonly used in the TBI population include a phenytoin sodium salt injection and a phenytoin acid suspension. Regardless of the formulation, phenytoin is relatively well absorbed under normal conditions (>80%).[79] However, concomitant administration of the acid suspension with EN solutions may inhibit absorption.[80] Multiple mechanisms for this interaction have been proposed, including drug binding to the nasogastric (NG) tube, chelation with cations in the enteral product, or decreased pH in the NG tube and GL tract. Some practitioners have recommended that EN be held for 1–2 hours before and after each phenytoin dose to avoid concomitant administration, whereas others adjust the phenytoin suspension dose or use the injection solution enterally while administering simultaneously with EN.[81] Although multiple studies have been performed to address this controversy, none have completely simulated the intensive care environment and the range of conclusions derived from these studies has kept this issue unresolved. Enteral administration of the sodium

Table 3. Drug-Nutrition Interactions[117]

Drug-Nutrition Incompatibilities	Effects
Carbamazepine	Formation of orange rubbery precipitate when suspension combined with water/other medication diluents
Ciprofloxacin	Chelation when combined with enteral nutrition (EN)
Phenytoin	Diminished/delayed absorption when suspension combined with EN
Sucralfate	Tube obstruction
Drug Effects on Nutrients	**Effects**
Amphotericin B deoxycholate	Hypokalemia, hypomagnesemia
Bisacodyl	Hypocalcemia, decreased fat absorption
Carbamazepine	Hyponatremia
Cyclosporine	Hyperkalemia, hyperlipidemia, hypomagnesemia
Loop diuretics	Hypokalemia, hypomagnesemia, hypocalcemia, decreased zinc
Penicillin G	Hyperkalemia
Phenytoin	Decreased folate, vitamin D
Ticarcillin/Piperacillin	Hypernatremia

Reprinted from reference 35.

salt for injection or holding EN for 1 hour before and after each dose of the acid suspension (adequately shaken to ensure even particle distribution) both appear to be feasible and effective options for circumventing this interaction. Regardless of how phenytoin is provided in a TBI patient receiving EN, pharmacokinetic monitoring is essential for titrating the dose to a concentration that is likely to be therapeutic.

Other medications administered enterally in TBI patients may be incompatible with nutrition formulas, including carbamazepine and sucralfate (Table 3). When combined with water or diluents of other medications, carbamazepine suspension may form an orange rubbery precipitate.[82] Co-administration of carbamazepine and other medications should also be avoided if possible. Sucralfate, an agent now rarely used for the prevention of stress-related mucosal disease, coats gastroesophageal ulcers by forming a viscous, gel-like substance in the presence of acid. Acidic proteins in enteral formulas may interact with sucralfate and promote feeding tube obstruction.[83] A loss of feeding tube patency may be a significant complication in the care of a TBI patient, as placement of feeding access is not without risk.

Some enteral formula-medication incompatibilities do not cause tube obstruction but do lead to limited absorption. Ciprofloxacin bioavailability is decreased 44% by concomitant enteral feeding, likely due to chelation with polyvalent cations.[84] Low concentrations of ciprofloxacin may lead to infection treatment failure or superinfection with more resistant bacteria. Likewise, some medications may affect the concentrations of nutrients and electrolytes, either by supplementation (potassium and sodium salts of intravenous penicillins) or by affecting their absorption, metabolism, or elimination (Table 3). Chronic co-administration may result in nutrient or electrolyte abnormalities. As such, drug-nutrition compatibility and interaction in TBI patients should be analyzed each day to avoid preventable problems. Medications preferably should be in liquid formulation unless sorbitol and other excipients cause diarrhea. Otherwise, regular release tablets can be crushed to a fine powder and dissolved.

Facilitating Enteral Nutrition Tolerance

Clinical manifestations of feeding intolerance in TBI patients include diarrhea, marked abdominal distension, and aspiration pneumonitis.[85] Nasogastric feedings are no longer recommended for patients in the early phases of acute injury.[32,41,86] Although potential feeding difficulties are present in many TBI patients, safe, efficient, and adequate EN can be provided in the majority of these individuals.[87,88] Several strategies can be used to increase feeding tolerance in TBI patients.[20,21] First, elevating the head of the bed by 30 to 45 degrees is a well established practice and a grade I recommendation to decrease reflux of gastric contents into the pharynx and esophagus.[24] Second, feeding TBI patients in the small intestine allows for increased feeding tolerance and less reflux.[32]

Third, while many TBI patients are able to receive nearly adequate amounts of post-pyloric EN volume early in their illness, some patients may be relatively intolerant initially. In these patients, graduated increases in the EN rate should be attempted. The TBI patient can typically tolerate initiating EN at 20 mL/hr, and advancing to their specific goal by 10 to 20 mL/hr every 6–8 hours.

Continuous infusion of EN appears to be better tolerated early in neurologic illness, as patients receiving bolus feedings may have a higher rate of intolerance when compared with continuous feedings.[31] In addition, concentrated enteral formulas (≥ 1.5 kcal/mL) provide the caloric requirements with less volume, which in many cases will diminish the amount of reflux or intolerance.

Finally, to promote adequate peristalsis and tolerance, promotility agents such as metoclopramide or erythromycin may also be considered. Promotility agents are not without adverse effects, so these agents should be used for a short duration until the desired effect is obtained and maintained. TBI patients frequently require paralytic agents, narcotics, and other anticholinergic agents. These medications can contribute to poor GI motility. Abdominal distention and postoperative ileus can often inhibit the TBI patient from reaching their EN goal. Initiating aggressive bowel regimens with twice daily liquid stool softeners and rectal laxative stimulants upon initiation of EN may abate this complication.[89]

Diarrhea can be one of the most frustrating and common EN intolerance for nursing staff and other care-givers. Diarrhea is infrequent in the first few days of the acute TBI. Although *Clostridium difficile* infection should be ruled out if the patient has received a course of antibiotics, pseudomembranous colitis is not the most frequent cause of diarrhea in patients receiving EN.[90,91] The enteral formula itself was once thought to contribute to diarrhea but it is not likely the cause. Most EN formulas are lactose-free and are not exceedingly hypertonic to cause diarrhea.[92] TBI patients often receive electrolyte supplements, elixirs, and other medications that are extremely hypertonic compared with the EN. Many liquid medications are mixed or suspended in sorbitol diluents. A sorbitol dose of 8–10 g/day may result in cramping and abdominal bloating, higher doses of >10 g/day frequently contribute to diarrhea. If diarrhea is present, clinicians should minimize all enteral medications containing sorbitol. Hypoalbuminemia associated with the critically illness of TBI may contribute to diarrhea due to significant bowel edema and impaired absorption.[93,94]

The TBI patient with diarrhea should be evaluated and treated in a stepwise approach before using PN. Once infectious and medication-related factors have been eliminated as causes of diarrhea, changing to a fiber-fortified enteral formula may lessen diarrhea. A semi-elemental product may improve absorption and minimize diarrhea. If these initial therapies fail, the tube feeding rate can be decreased and anti-diarrheal agents can be added. In patients who have received antibiotics, the administration of probiotics may restore some balance to the indigenous gut flora, but data supporting this practice in adults are limited.[48]

Challenges in Providing Nutrition in Neurologically Ill Patients

Hypermetabolism that occurs as a result of TBI not only complicates the initial period of hospitalization and stabilization, but may also extend for weeks into the rehabilitation period.[34,95,96] Possible explanations for this continued increase in metabolism and protein loss may include a persistent inflammatory response and prolonged immobility due to injury. A similar phenomenon of extended periods of hypermetabolism has also been demonstrated for patients with severe burns.[97] Muscle tone may have an impact on the metabolic needs of TBI patients convalescing after the acute phase of illness. Spasticity, decorticate or decerebrate posturing, and periodic sympathetic discharges ("storming") are all associated with increased caloric needs. Inadequate nutrition support for TBI patients, even well past the initial injury, may result in malnutrition and muscle wasting. This cachexia increases rehabilitation length of stay, increases the difficulty in mobility and functional rehabilitation, and promotes the development of medical complications such as decubitus ulcers, pneumonia, urinary tract infections, and venous thromboembolism.[98]

Many TBI patients are not able to take in an adequate volume of fluids orally to meet their daily fluid needs due to impaired swallowing or altered consciousness. As the TBI patient transitions to a less intensive care setting, the calorically dense formula used in the ICU should be gradually converted to a more high-volume, isotonic enteral formula to provide a higher percentage of free water per volume. Individuals at this stage of illness are typically able to tolerate the higher enteral volume due to normalization of gastric motility. Patients who continue to require EN or oral diet supplementation with extra formula may not receive enough fluids to meet their typical daily requirement, even with more dilute enteral formulas. Additional supplementation of free water may be required to account for this shortfall. Serum sodium, blood urea nitrogen, serum creatinine, and physical signs of hypovolemia should be monitored to ensure adequate fluid balance. Hypernatremia, mental status alterations, and renal dysfunction are preventable sequelae if appropriate monitoring is performed.

A significant percentage of TBI patients admitted to long-term rehabilitation centers or sent home with skilled nursing support are markedly disabled and physically dependent upon others for care. Many of these individuals have cognitive and motor dysfunction, as well as difficulty in communication. Less than 33% of TBI patients in long-term rehabilitation facilities are able to eat independently.[99] TBI patients commonly have dysphagia after injury, resulting in approximately 37% of individuals admitted to rehabilitation centers requiring EN or PN

support. It is often essential to provide EN in this setting whenever possible, due in part to the aforementioned benefits of using the gut and also due to cost considerations. Of note, neither PN nor EN requires institutionalization. In fact, home PN saves 50% of the cost of the inpatient equivalent. Home EN is even more remarkable at 95% savings compared with the inpatient equivalent.[100] Overall, home EN is approximately 10% of the cost of home PN.

Oral Diets in the Neurologically Injured Patient

Due to impaired cognition and the physiological deficits affecting the mechanism for swallowing, the incidence of dysphagia after a TBI is reported to be as high as 61%.[101] Factors aside from neurologic injury, such as dental fractures, facial fractures and the need for prolonged cervical immobilization with a hard cervical collar may delay initiation of an oral diet. Most TBI patients regain their independence in oral feeding within the first 6 months after injury.[13] A significant correlation was found between the initiation of the first oral feedings in TBI patients and their ultimate outcome. This may also be related to a diminished severity of injury, overall greater recovery after injury, and avoidance of complications associated with EN and enteral access devices.

Although it is clear that oral feedings increase the quality of a patient's life compared with gastrostomy feedings, there are varying opinions on when it is safe to initiate oral feedings in the TBI patient population. The appropriate time for initial swallowing assessment varies among practitioners and is largely based on the patient's severity of illness, but is typically reported to be within 2–4 weeks of injury.[13,102] Patients should be evaluated for an oral diet even if there are no obvious signs or symptoms of dysphagia and if their cognitive function is adequate.[101] The role of a dedicated rehabilitation team is of paramount importance at this point, particularly including a speech pathologist who is trained to challenge the patient safely with varied food consistencies, strategies, and exercises to assess and train for safe oral feeding.[103] Speech pathologists are able to assess a patient's ability to swallow by performing clinical bedside, fluoroscopic, or endoscopic instrumental swallowing evaluations. Based on the results, modified food and liquid consistencies may be necessary for the patient's safety. The patient's swallowing ability should continue to be assessed and treated until the patient is able to tolerate the least restricted diet or functional recovery plateaus.[102]

Pediatric Considerations

The incidence of TBI doubles between the ages 5 and 14 years and accounts for 35% of all TBI.[104,105] The mechanisms of injury are similar to that of adults, consisting of the primary injury and the secondary injury cascade. One cause of TBI unique to the pediatric population is shaken baby syndrome, which is typified by the transfer of kinetic energy causing damage at the site of injury and at the opposite side of the brain (coup contrecoup injury). Children and teens are more likely to survive after TBI. This resiliency, coupled with advances in medical therapies and regional trauma care, result in a growing heterogeneous group with chronic, life-long disabilities, and significant financial and emotional burdens.[105,106]

Few studies are published that evaluate nutrition in pediatric patients after TBI. Two early studies described the metabolic alterations and requirements of pediatric severe TBI patients. The results were similar to what is evident in adults: from the acute phase response, hypoalbuminemia, increased metabolic requirements (up to 180%, by indirect calorimetry), negative nitrogen balance, and a tendency toward weight loss.[107,108] One randomized study compared an immunonutrition formula and conventional formula in pediatric patients with severe TBI.[109] Although gastric colonization and interleukin-8 were less in the immunonutrition group, there did not appear to be any significant clinical differences between the 2 formulas. Overall, there is little research on nutrition support and its influence on outcome of pediatric TBI. Extrapolation of data from the adult population, in addition to the limited data available in the pediatric population, suggests that nutrition support is an integral aspect of early and late pediatric TBI care.

Nutrition is especially important in pediatric TBI for cellular repair and growth during crucial developmental stages. Extremes in nutrition lead to similar problems as in adults, such as immune dysfunction in malnutrition and hepatic dysfunction in overfeeding. Although children typically are well-nourished before their injury, estimating pediatric caloric needs has been difficult. Overall, BEE equations to estimate the caloric needs in pediatric TBI patients do not appear to be accurate or precise compared with more individualized, objectively measured methods such as indirect calorimetry.[104] The current pediatric TBI guidelines recommend supplementation of 130%–160% of BEE in moderate to severe TBI.[110]

The issues of preferable route of nutrition and optimal timing of nutrition are ill-defined in the pediatric population. Instances of delaying the insertion of nasoduodenal feeding tubes to decrease the amount of instrumentation in a small child may be a disservice, as it typically delays adequate nutrition as well. The degree of hypermetabolism in pediatric TBI patients appears to be comparable (or even greater) to similarly injured adults. Coupled with the fact that most pediatric patients are still undergoing normal growth and development during this period, the urgency for initiating adequate nutrition is equal to or greater than the adult population.

Pediatric TBI patients also suffer from similar metabolic abnormalities as adults such as hyponatremia and

hyperglycemia. Elevated glucose levels have been found to be an independent predictor of death and poor neurologic outcome in children.[111] However, the efficacy of glucose control in critically ill pediatric patients, much less in the TBI population, is under debate. While there is evidence that hypermetabolism persists up to a year after injury, there is also evidence to suggest an increased prevalence of obesity in children with TBI.[112] Careful attention should be paid in the long-term care of the patient to ensure adequate nutrition provision without excess, which could lead to complications such as obesity. More quality evidence is needed in many areas of pediatric TBI to guide decision-making. At this point, it appears prudent to initiate nutrition (preferably EN) as soon as is feasible and to target up to 160% of the calculated BEE until indirect calorimetry can be performed.

Conclusion

Clearly, treating the TBI patient encompasses many aspects of care, but nutrition support appears to be incredibly important and often underappreciated. EN has been well established as the optimal route for providing nutrition. If the TBI patient experiences dysphagia or is unable to eat orally, the appropriate enteral access should be established promptly. Often these patients tolerate small bowel EN in the acute ICU settings but gastric feeds should be tolerated as recovery progresses. How quickly clinicians should move to PN in the case of enteral intolerance is not well defined and merits consideration of both the value of early feeding in this population and the risks of PN.

Administering a standard, intact, concentrated enteral formula delivers maximum nutrition with minimal volume and likely allows the patient to reach the goal rate more quickly. If intolerance to standard enteral formulas develops or if GI compromise is present, semi-elemental products may be an alternative before considering PN. Establishing specific institutional protocols may improve the success for initiating safe and effective nutrition support for the TBI patient.[113] These protocols should address the type and timing of feeding tube placement to diminish the delay in nutrition support. The routine practice of feeding tube maintenance, including monitoring residuals, flushing tubes, and drug administration, should be detailed to avoid tube occlusion. Standards to treat enteral intolerances and complications (such as occlusion, aspiration, reflux, and diarrhea) may reduce the practice of holding tube feeds, which leads to sub-optimal nourishment. Future studies are warranted to determine the precise benefits (or dangers) associated with each aspect of nutrition support, such as the optimal site for EN, type of formula, and supplemental therapy such as protein, vitamin, or mineral administration.

The TBI patient exhibits unique causes for stress, hypermetabolism, and hypercatabolism. Provision of adequate calories and protein is critical for recovery. Excessive calorie provision has not been proven to spare protein breakdown and is likely detrimental. A.S.P.E.N. and the Society of Critical Care Medicine have established consensus regarding the benefits of early EN initiated within 24–72 hours after injury.[114] The Brain Trauma Foundation recommends the TBI patient receive their goal nutrition support by at least day 7 of injury. Additional studies are needed to confirm the efficacy of early EN and to identify factors which hinder the provision of adequate nutrition to this compromised population.

Acknowledgement

We would like to thank Elizabeth Holt, MD, for her contributions to this paper.

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