



Nutrition in the Neurocritical Care Unit: a New Frontier

Tachira Tavarez^{1, *}

Kelly Roehl²

Lauren Koffman¹

Address

¹Department of Neurologic Sciences, Rush University Medical Center, 1725 West Harrison Street Professional Office Building, Suite 1106, Chicago, IL, USA

Email: Tachira_Tavarez@rush.edu

²Department of Food and Nutrition, Rush University Medical Center, Chicago, IL, USA

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This article is part of the Topical Collection on *Critical Care Neurology*

Keywords Nutrition support · Neurocritical care · Microbiome · Immunonutrition · Cerebral metabolism · Ketogenic diet

Abstract

Purpose of Review This review presents the most current recommendations for providing nutrition to the neurocritical care population. This includes updates on initiation of feeding, immunonutrition, and metabolic substrates including ketogenic diet, cerebral microdialysis (CMD) monitoring, and the microbiome.

Recent Findings Little evidence exists to support differences in feeding practices among the neurocritical care population. New areas of interest with limited data include use of immunonutrition, pre/probiotics for microbiome manipulation, ketogenic diet, and use of CMD catheters for substrate utilization monitoring.

Summary Acute neurologic injury incites a cascade of adrenergic and neuroendocrine events resulting in a pro-inflammatory and hypercatabolic state, which is associated with an increase in morbidity and mortality. Nutritional support provides substrates to mitigate the damaging effects of hypermetabolism. Despite this practice, studies on feeding delivery outcomes remain inconsistent. Guidelines suggest use of early enteral nutrition using standard polymeric formulas. Population heterogeneity, variability in interventions, complexities of the metabolic and inflammatory responses, and paucity of nutrition research in patients requiring neurocritical care have led to controversies in the field. It is imperative that more pragmatic and reproducible research be conducted to better understand underlying pathophysiology and develop interventions that may improve outcomes.

Introduction

Critical illness, including acute neurologic injury, is associated with a hypercatabolic state with significant increases in stress hormones and pro-inflammatory cytokines, which is associated with increased morbidity and mortality [1, 2]. To mitigate the detrimental metabolic response, nutrition support is provided to offer an exogenous fuel source, preserve lean body mass, and prevent malnutrition. Despite this knowledge, critically ill patients are a heterogeneous group with varying comorbidities, genetic makeup, disease severity, nutrition risk, and microbiome [3, 4••], leading to inconsistent feeding outcome data [5]. Researchers generally agree that early enteral feeding improves outcomes, though there is debate regarding dose adequacy and advancement goals [6–8]. Research to support use of

specialized feeding practices or specific micronutrients to improve outcomes among the general critical care and neurocritical care populations remain limited, though several promising theories warrant further investigation [6, 9]. One must also consider the complexities of inflammation and cellular metabolism and their role in delivery of nutrition to critically ill patients.

This review is divided into two main sections: the first focuses on nutritional assessment and the second on nutritional therapies. Within these sections, we describe current nutritional guideline recommendations, cerebral microdialysis as a complementary nutritional monitoring tool, immunomodulating diets, and microbiome changes in critically ill patients.

Diagnostic Evaluation

Nutrition Assessment among Critically Ill Patients, Including Neurocritical Care Patients

Malnutrition is more common among neurologically injured patients, likely due to delay in feeding and/or interruptions in nutritional delivery due to hospital transfers, severity of illness, increased metabolic demands, higher incidence of oropharyngeal dysphagia, cognitive dysfunction, reduced level of alertness, and perception deficits [10, 11]. To identify the risk for developing complications associated with inadequate nutritional intake, the American Society for Enteral and Parenteral Nutrition (A.S.P.E.N.) and Society of Critical Care Medicine (SCCM) recommend that a validated screening tool be utilized to determine nutritional risk within 24 to 48 h of admission to an intensive care unit (ICU) [6]. When risk is identified, a comprehensive nutrition assessment should be completed as soon as possible to identify those most likely to benefit from early nutrition intervention when oral intake is anticipated to be insufficient [6]. Several consensus recommendations have been developed for the assessment and diagnosis of malnutrition, which include evaluation of comorbidities, changes in nutritional intake, ability to meet needs (i.e., gastrointestinal (GI) function and risk of dysphagia or aspiration), and changes in body composition (fat and muscle wasting, and presence of edema) [12, 13].

In patients that are unable to provide nutritional history, biochemical markers may offer a better understanding of metabolic state and potential inadequacy of intake prior to admission. Use of serum proteins, such as albumin and prealbumin, are not recommended for use in evaluating nutritional intake due to correlation with inflammatory response as negative acute phase respondents [6]. Other serum and urinary biomarkers such as electrolytes and ketones may guide understanding of metabolic response and fuel utilization. Ketones (acetone, acetoacetate, and beta-hydroxybutyrate) are produced through fatty acid oxidation during periods of starvation. This ketonuria should not be mistaken for ketonuria with glucosuria due to poor glycemic control. In

the absence of glucosuria, ketonuria may indicate inadequate nutritional intake [14]. Positive urinary ketones may suggest reduced intake over several days or longer prior to admission and may be used as an indicator of nutritional adequacy prior to admission, as well as risk for refeeding syndrome.

Metabolic Demands and Substrate Utilization in Neurocritical Care

Neurologic injury triggers a hypercatabolic state, primarily mediated by glucocorticoids, catecholamines, and glucagon [15]. Resting energy expenditure (REE) has been found to be as high as 200% of usual needs in two-thirds of patients during the first 2 to 4 weeks following brain trauma [1, 10, 16]. Energy requirements of patients with stroke vary widely depending on stroke type [17]. Elevated REE in patients with higher grade aneurysmal subarachnoid hemorrhage (SAH) has been associated with higher incidence of vasospasm [18–20]. Additionally, metabolic demands may vary throughout the ICU course as various therapies common in neurocritical care influence metabolic demands including the use of barbiturates, sedation, normothermia, and hypothermia [15, 21].

Indirect calorimetry (IC) is the gold standard and recommended method to determine energy requirements in the critically ill population [6]. IC uses the amount of oxygen and carbon dioxide consumed to provide a measurement of REE, which is then extrapolated over a 24 h time period. IC is advantageous because it is non-invasive while providing real-time information of energy requirements in circumstances when equations for predicting REE are unreliable [21]. For example, sedating medications and paralytics make predicting REE with IC unreliable. Use of IC may be limited by the need for high positive pressure and oxygen settings among those requiring mechanical ventilation, also in patient who require use of non-invasive mechanical ventilation, continuous renal replacement therapy, extracorporeal membrane oxygen exchange (ECMO), and chest tubes with poor seals [21]. Unfortunately, IC is costly, labor intensive, and requires specially trained clinicians to perform and interpret the measurement. For these reasons, it is rarely used in clinical practice, but if done, should be repeated routinely as conditions change to ensure that the measurement accurately reflects the patient's current metabolic state to prevent under or overfeeding.

In addition to an increase in REE, metabolic processes such as glycogenolysis and gluconeogenesis result in concomitant hyperglycemia and increased skeletal protein catabolism [15]. This elevated protein catabolism in the setting of inadequate nutritional intake or delivery may result in a negative nitrogen balance, reflecting the loss of total body protein [16]. Traumatic brain injury (TBI) patients have shown altered energy metabolism for weeks after injury with elevated nitrogen excretion [22••], which likely contributes to malnutrition. This catabolic derangement is associated with an increase odd of 30- and 90-day mortality and 40% increased odds of 365-day post-discharge mortality, compared to those without malnutrition [23••]. Furthermore, malnutrition with negative nitrogen balances and altered C-reactive protein (CRP) and transthyretin (TTR) ratios have been associated with significantly more hospital-acquired infections and worse neurologic outcomes in this population [24•]. Greater than 40% of patients with ischemic stroke (IS) have been found to have a negative nitrogen balance [25], suggesting catabolism and malnutrition.

Malnutrition has been observed in 16% of patients with IS upon admission, increasing to 26% 1 week following stroke occurrence [26]. Factors associated with increased risk for having or developing malnutrition after IS include cognitive deficits, upper extremity paresis, impaired self-feeding ability, apraxia, depression, prior stroke, diabetes, dysphagia, and need for enteral nutrition [27].

No individual tool can provide a complete picture of a patient's nutritional needs. Multiple monitoring strategies with frequent evaluations, along with participation of an integrated nutritional team allow for a complete assessment of the patient's nutritional needs.

Metabolic Substrates: a Role for Cerebral Microdialysis Monitoring

A healthy human brain, while only 2–3% of the total body weight, consumes 20% of the total oxygen and 25% of total glucose available to the body. Glucose is the preferred fuel source when available, and the brain is unable to store or produce glucose, and as an adaptive response can metabolize other substrates may be metabolized for ATP production. These substrates include ketone bodies, lactate, glycerol, and amino acids [22••]; and may be preferential substrates during cerebral energetic crisis to minimize potential deleterious effects associated with hyperglycemia and aggressive insulin therapy leading to hypoglycemia [23••].

Cerebral microdialysis (CMD) is an invasive parenchymal monitor that provides insight into the nuances of cerebral metabolism, and allows for the study of real-time substance concentrations within brain tissue and can be implemented as a tool for multimodal monitoring [15].

Limitations often discussed in using CMD are whether or not data from these catheters reflect a regional versus global picture, or if any interventions equally effect normal brain tissue [17]. Despite limitations, CMD research has allowed for the understanding that there are pathologic patterns, such as high CMD lactate-to-pyruvate ratio (LPR) and low CMD glucose, which are associated with increased mortality [15]. Only a few studies describe the effects of nutritional interventions on these markers. CMD has been used to evaluate brain substrate availability in SAH [17] and TBI populations [18–20]. Kofler et al. reported that in patients with aneurysmal SAH, serum glucose was associated with CMD glucose concentration, and that providing enteral nutrition increases CMD glucose including in the setting of neuroglucopenia [17]. Availability of alternative brain fuel sources has also been described among the TBI population. Researchers reported that TBI patients administered sodium lactic acid experienced an increase CMD pyruvate, an indication of substrate utilization, and an increase availability of brain glucose [24•]. This suggests a potential advantage of using hypertonic lactate as opposed to hypertonic sodium chloride, not only because of the potential metabolic advantages but also to avoid hyperchloremic acidosis [24•]. Additionally, Bernini and colleagues used CMD to study ketone metabolism in TBI patients and found that although cerebral ketone body levels were not associated with cerebral glucose, they were associated with cerebral glutamate, lactate, and pyruvate. These findings suggest that in the setting of metabolic crisis, the brain produces ketone bodies to serve as an alternate source of energy [20]. This is consistent with known astrocyte

production of ketone bodies from fatty acid oxidation or catabolism of amino acids [25].

Unfortunately, no studies directly establish how CMD guided nutritional interventions impact outcomes such as morbidity and mortality. Given what we understand about cerebral metabolism and the use of alternative substrates in the setting of acute injury, there is potential in using nutritional interventions such as the ketogenic diet. And in the case of super-refractory status epilepticus, use of a ketogenic diet has been shown to be safe and efficacious [26].

Treatments

Nutrition Initiation, Advancement, and Monitoring

For those at high nutritional risk that are unable to meet needs orally, early enteral nutrition (EN) should be initiated within 24–48 h of admission, and advanced as quickly as tolerated toward goal of >80% of estimated or measured energy and protein requirements over the next 7 days [6]. Early EN supports the functional integrity of the endothelial cells and junctions within the gut, the associated gut-associated lymphoid tissue (GALT), and the downstream mucosal-associated lymphoid tissue (MALT). Inadequate nutritional delivery during the acute inflammatory state may result in bacterial translocation, increase risk for systemic infection and inflammation, and likelihood of multiple organ dysfunction. All of these factors contribute to increasing risk of morbidity and mortality [6]. For patients with adequate baseline nutritional status on admission, guidelines suggest that supplemental parenteral nutrition (PN) be considered after 7–10 days of inadequate intake via oral or enteral route (<60% of requirements), but has not been shown to improve outcomes and may be detrimental if initiated prior to this time period [6]. However, PN is recommended in those with high risk or severe malnutrition on initial assessment as soon as possible following ICU admission when oral or enteral routes are not feasible.

Much of the literature encouraging use of nutrition support among critically ill patients is under the assumption that increased delivery improves outcomes, such as reduced infection rates and LOS, when early goal feeds are achieved. However, the majority of these results are from observational studies or clinical trials with small sample sizes [27, 28]. Multiple large prospective randomized controlled trials (RCTs) have failed to demonstrate these benefits and suggest increased mortality with higher energy delivery [7, 8, 29–37]. Disruption of autophagy and subsequent alterations in mitochondrial function have been suggested as potential mechanisms by which exogenous nutrient delivery may worsen outcomes [7, 8]. Significant debate exists within the nutrition support community with regard to how much and how quickly to advance calorie delivery critically ill patients, thus care must be taken to optimize nutrient delivery and to prevent overfeeding. For these reasons, use of repeated measures IC or simplistic predictive equations are recommended when determining needs and feeding goals [6].

Evaluation of gastric residual volumes (GRVs) remains a controversial topic. The most current guidelines recommend against using GRVs due to lack of correlation with incidence of pneumonia, regurgitation, or aspiration [6]. A RCT conducted by Reigneir and colleagues in 2013 found that not checking GRVs did not lead to increased incidence of ventilator associated pneumonia in

critically ill patients requiring mechanical ventilation [6, 38]. Patients receiving vasopressor therapy with symptoms of gastrointestinal feeding intolerance (abdominal distension, increased nasogastric tube output, hypoactive bowel sounds, decreased motility or passage of stool, metabolic acidosis, and/or base deficit) should be monitored for early signs of ischemic bowel, holding EN until condition stabilizes or improves [6].

Ongoing monitoring and evaluation of energy, protein, fluid, and electrolyte requirements, and adequacy of intake in relation to needs should be conducted throughout the ICU and hospital stay. These processes prevent overfeeding and potential for increased mortality, as well as chronic underfeeding and development of malnutrition. This can be achieved by early involvement by the nutrition support team to implement and continue to monitor tolerance and appropriateness of nutrition interventions.

Ketogenic Therapy Among Neurocritical Care Populations

Ketogenic diets (KDs) alter human metabolism with parallel synergistic effects, including alterations in energy metabolism (decrease in glycolysis, increase in fatty acid oxidation with ketone production) and alterations in neurotransmitter production, release and uptake [39–41]. A review of TBI animal models suggests KDs reduce cerebral edema, apoptosis, improves cerebral metabolism, and behavioral outcomes in rodents [42]. KDs and their modified forms have been found to reduce seizure frequency by approximately 50% in both pediatric and adult populations regardless of seizure type [43–45], efficacy similar to that of medications. A recent systematic review on use of KDs among adult patients with status epilepticus (SE) demonstrated safety and efficacy as adjuvant therapy in SE treatment [46], although should be interpreted with caution due to small sample sizes. Ketogenic diet has been shown to be a feasible and safe therapy for super-refractory status epilepticus (SRSE) [26]. Of the 14 patients that completed treatment, SRSE was resolved in 11 patients in a median of 5 days. Given the overall safety of administering KDs and their multiple therapeutic targets, they are a promising adjunct therapy for multiple acute neurologic pathologies.

Immunonutrition

Diets high in processed carbohydrates and fats and low in fiber and micronutrients contribute to a pro-inflammatory state that underlies the development of many chronic diseases [47–49]. Comparatively, diets rich in minimally processed, nutrient-dense foods are associated with long-term health [47–49]. The mechanisms involved are multifactorial and beyond the scope of this review, though are the basis for the theory that nutrients can modulate the immune and inflammatory response [50], often referred to as “immunonutrition.” Potential mechanisms for immune-modulating effects include delivery of specific amino acids as preferred fuel sources for enterocytes, omega-3 (*n*-3)-rich polyunsaturated fatty acids (PUFAs) to manipulate eicosanoid production and downstream anti-inflammatory cytokine response [50, 51], as well as reducing oxidative stress through delivery of specific vitamins, minerals, and phytochemicals involved in human antioxidant systems [50] (Table 1).

Immunonutrition attempts to modulate the immune response by altering nutrients involved in the inflammatory process, and has been studied in various

Table 1. Proposed mechanisms of immune-modulating nutrients

Nutrient	Proposed mechanism of immune modulation
Amino acids	
Glutamine	Primary fuel source for enterocytes, lymphocytes, macrophages; conditionally essential during metabolic stress
Arginine	Conditionally essential amino acid during metabolic stress; required for normal T- and B lymphocyte and macrophage function
Fatty acids	
Eicosapentaenoic acid (EPA) and Docosahexaenoic acid (DHA)	Less pro-inflammatory cytokine response with potential to reduce impact of the eicosanoids, prostaglandins, leukotrienes, and thromboxanes produced omega-6 fatty acids
Antioxidants	
Vitamin C, vitamin E, beta-carotene, selenium, and zinc	Antioxidant effect reducing oxidative stress at cellular level by enhancing superoxide dismutase, glutathione peroxidase

[51]

critically ill populations, including those in neurocritical care. Nutrients involved in immunonutrition research include various macronutrients such as amino acids glutamine and arginine, and *n*-3 fatty acids and micronutrients such as vitamin C, zinc, and selenium (Table 1). Given the complexity of the pathophysiologic pathways leading to secondary injury, various micronutrients have been suggested for their potential to impart a therapeutic effect on outcomes associated with critically ill patients. The primary targets of immunonutrition therapy include the mucosal barrier, cellular immune defenses, and both local and systemic inflammatory responses [50].

Micronutrients have been shown to have a variety of mechanisms and overall low toxicity, making them an attractive candidate for supplemental therapies in patients with neurologic injury [52]. While beyond the scope of this review, researchers have previously summarized outcomes associated with micronutrient delivery among the neurologically impaired population (Table 2). Use of immune-enhancing enteral products has not shown to improve outcomes compared to standard formulas, and are not recommended for routine use among the general ICU populations [6]. Despite lack of outcomes related to morbidity or mortality, consensus guidelines site low-grade evidence for use of either arginine-containing immune-modulating formulations or EPA/DHA supplementation with standard EN in those with TBI [6], suggesting use may be beneficial. These recommendations are based on results from one study [58].

Use of glutamate and probiotics were simultaneously studied in a small RCT in patients with brain injuries [58]. Researchers reported fewer infections, fewer mechanical ventilation days, and shorter ICU LOS among those receiving a glutamine and probiotic enriched formula ($n = 5$) compared to those in an isocaloric, isonitrogenous control ($n = 5$). While this warrants further investigation, the study was limited by small sample size and inadequate power to detect these differences for the reported outcomes. Another limitation was that the intervention contained both immune-modulating nutrients and probiotics,

Table 2. Review of therapeutic targets of nutrients and diet interventions in neurocritical care populations

Micronutrient	Patient population	Findings
Vitamin C and E [53]	Traumatic brain injury	- Vitamin E was associated with improved mortality and GCS scores at discharge - High-dose vitamin C was associated with stabilization of perilesional edema
Vitamin D [54]	Ischemic stroke	- Associated with increased survival at 6 months and a trend toward improved functional outcome at 6 months
Vitamin D and progesterone [55]	Acute spinal cord injury	- Associated with significant improvement in motor and sensory American <i>Spinal Injury Association</i> impairment scale (AIS) scores
Magnesium [56]	Subarachnoid hemorrhage	- Significant decrease in occurrence of vasospasm, delayed cerebral ischemia, and secondary infarction in the intervention group
Ketogenic diet [26, 57]	Acute spinal cord injury, SRSE	- Significant improvement on motor and sensory scores in AIS and improvement in inflammatory markers - Safe and efficacious in the resolution of SRSE

making it difficult to determine if the beneficial mechanism was related to immunonutrition or changes in the microbiome. Another RCT aimed to evaluate the effect of an immunonutrition enteral formula containing arginine, glutamine, and omega-3 fatty acids on serum biomarkers (IL-6, glutathione, CRP, albumin, and total protein) among patients with TBI [59]. Although those receiving the immune-enhancing formula were found to have a concurrent reduction in serum IL-6 and rise in glutathione compared to control, morbidity, and mortality outcomes were not reported.

Fatty acids, specifically n-3 PUFAs including DHA and EPA, have shown promising results in preclinical studies [52], though translation to clinical research is limited. Theoretic benefits include a reduction in inflammatory and oxidative responses, antithrombotic effects, and improved maintenance of tissue micro perfusion [50, 52]. The effect of daily administration of n-3 supplementation (via EPA, mixed EPA/DHA, and EN containing EPA/DHA) during the vasospasm window following SAH has been found to have significantly fewer occurrences of vasospasm [60, 61], infarcts [61], and more favorable outcomes [60]. However, these studies are limited by lack of consistency in supplementation dose and type, thus it is unclear whether participants received the intended doses as many did not achieve target volume feedings containing the immune-modulating nutrients.

Outcomes of immunonutrition research in the neurocritical care population is similar to that of the general ICU population and is limited by heterogeneity, dose response, outcome measures, as well as inadequate sample size. Additionally, use of certain nutrients (n-3 and arginine) has been demonstrated to potentially increase risk for harm [6]. Common criticisms include heterogeneity of populations, underreporting with regard to actual nutrient delivery compared to goal doses, unclear demonstration of changes in biomarkers and clinical outcomes, as well as differences in other nutrition-related outcomes (i.e., macronutrient delivery). These factors make it difficult to interpret whether beneficial effects are due to nutritional intake as a whole or due to delivery of

immune-enhancing components [51]. Additional research is needed with larger sample sizes, reporting of delivery and biomarkers, and assessment of clinical outcomes before routine use among the neurocritical care population can be recommended.

The Microbiome and the Gut-Brain Axis—Implications Relating to Nutrition, Inflammation, and Critical Illness

The microbiome describes the species and genetic profile of the microorganisms living in and on the human body, with the largest number residing within the gut. The microbiome influences the development of many diseases, including those of the enteric nervous system (ENS) and central nervous system (CNS) through modulation of the “gut-brain axis [62].” Examples of these include motility disorders, behavioral disorders, neurodegenerative disease, cerebrovascular injury, and neuroimmune-mediated disorders [62]. Potential influences of the microbiome include, but are not limited to: alterations in hypothalamic-pituitary-adrenal axis [63], vagal nerve stimulation [64, 65], SCFA activation of microglial cells [66], changes in permeability of the blood brain barrier [67], modulation of host biosynthesis pathways, and production/modulation of neuroendocrine hormones such as gamma-amino butyric acid (GABA) and serotonin [62].

Two large phylogenic types dominate the commensal bacteria of a healthy gut: *Firmicutes* and *Bacteroidetes* [68]. Under healthy conditions these microbiota play crucial roles in maintaining host (human) metabolism, production of short-chain fatty acids (SCFAs), micronutrient production, immunocompetence, gut integrity, and colonization resistance [3]. Disruption of microbiome homeostasis—described as dysbiosis or pathobiome—is characterized as a shift to low within group (alpha) diversity and high between group (beta) diversity with decreases in the beneficial species of *Firmicutes* and *Bacteroidetes*, including those that produce SCFAs, and rises in *Proteobacteria* [3, 4••]. This shift may be equally or more important than the host’s genetics in development of many chronic diseases mediated by chronic inflammation, including inflammatory bowel disease, obesity, diabetes, and cardiovascular disease [47–49].

Dietary patterns associated with low intake of processed foods and high intake of prebiotic fibers (i.e., fructooligosaccharides and inulin naturally found in non-starchy vegetables) offer a fermentable fuel source to support growth of commensal microbes capable of producing SCFAs, such as *Bifidobacteria* and *Lactobacillus* [35]. Pro-inflammatory diets low in fiber, and high in fat, protein, and sugar have been found to reduce SCFA production, shifting to a pro-inflammatory microbiome profile [69]. Pro-inflammatory bacteria may exacerbate endotoxemia and inflammation by increasing transport of lipopolysaccharides (LPSs), structures present on the outer membrane of gram-negative bacteria that exert immunogenic effects. One of those effects is activation of toll-like receptor (TLR)-4, a receptor that upregulates transcription of pro-inflammatory cytokines [70].

It has been hypothesized that the gut is the “motor” of multiple organ dysfunction syndrome in critical illness due to complex interactions between the gut epithelium and immune system, [71–73, 74•]. Critical illness alone has been found to induce profound shifts toward a pathogenic microbiome within hours of admission to the ICU [75, 76], which is exacerbated by medications

that significantly impact the microbiome including antibiotics, opioids, and proton pump inhibitors [77–79]. Commensal microbiota help to metabolize medications, nutrients, and hormones, modulate immune responses, and maintain mucosal barrier homeostasis [48]. Therefore a disruption during critical illness may increase risk for invasion of pathogenic bacteria, including bacterial translocation [70]. The dysbiosis worsens and shifts toward more pathogenic microbiota with longer ICU duration [80–83]. This has also been demonstrated in neurocritical care populations, including animal and human models of TBI and spinal cord injury [84–86]. It has been suggested that serial changes in the ratios of beneficial species of *Firmicutes/Bacteroidetes* can potentially predict patient outcomes [80].

Patients in the neurocritical care unit are at high risk for developing nutrition-related complications, including malnutrition and worse clinical outcomes. Identification of nutrition risk through appropriate assessment to identify pre-existing malnutrition should occur as soon as possible following ICU admission to determine when and which type of nutrition intervention may offer the most benefit.

Critical Care Interventions Impacting the Microbiome

While a pathogenic microbiome has been described among critically ill patients, there is very little evidence to demonstrate that nutrition administration during critical illness impacts the microbiome of critically ill patients. The available literature focuses on modulation of the microbiome through administration of pre- and probiotics to improve GI alterations (i.e. diarrhea); however, variability in fiber composition and bacterial species have yielded mixed results. Consensus guidelines suggest use of a probiotic soluble fiber for diarrhea treatment over use of mixed-fiber formulas, citing fermentation and production of SCFAs [6].

Withholding enteral nutrition in the setting of critical illness is associated with alterations in microbiome composition and impaired epithelial barrier function with subsequent bacterial translocation and sepsis [87–89]. The effect of EN and pre- and probiotic supplementation, as well as SCFAs delivery among neurologically injured patients has been described.

One group of researchers examined the differences in energy delivery, complications, and biochemical markers (including CRP) among a heterogeneous group of neurocritical care patients randomized to receive standard enteral formula versus enteral formula-containing probiotics [90]. No significant differences were found in achievement of target energy delivery or inflammatory outcomes between groups, though those receiving EN with probiotics were found to require less insulin and have lower rates of diarrhea. In another study conducted among patients with severe TBI receiving EN, with and without probiotic supplementation, serum inflammatory markers (IL-6, IL-10, TNF-alpha, and CRP) were reported to decrease more significantly among patients receiving a probiotic containing *Bifidobacterium*, *Lactobacillus*, and *Enterococcus faecalis* [91].

Bypassing the delivery of probiotics capable of producing SCFAs, one group administered SCFAs in a post-stroke recovery mouse model, demonstrating improved recovery of motor function, as well as in vivo, finding changes in synapse density and microglial activation dependent on T cell recruitment in

infarcted brain cells [92]. This suggests that microbiota-derived SCFA may modulate post-stroke recovery through systemic and immunologic effects [92].

Perhaps the inability to demonstrate significant microbiome or inflammatory modulation among critically ill patients is related to pre-admission dysbiosis associated with a pro-inflammatory diet and microbiome. Manufacturers of nutrition support products have incorporated specific nutrients and compounds to enhance the immune response and microbiome. However, standard polymeric enteral formulas do not resemble whole-food diets, and typically lack the beneficial phytochemicals that have been found to impact long-term health through various inflammatory pathways, including the gut microbiota and gut integrity [93]. It is possible that whole-food-based nutrition therapy may offer beneficial outcomes on morbidity and mortality among critically ill populations. However, safety and efficacy to modulate the immune response should first be evaluated among the general healthy population given concerns for infection risk with blenderized, whole-food feedings without safe food-handling practices [94].

Conclusion

There is likely a synergistic effect between diet quality, gut microbiome, and inflammatory response mechanisms. Much attention has been paid to the impact of macronutrient and micronutrient composition, the processing on digestibility and fermentability of nutrients, the presence of phytochemicals or lack thereof, and fasting on the human microbiome and inflammatory responses. The ability to modulate these effects is a crucial factor in improving human health long-term health, as well as those with critical illness and neurologic injury. Despite current research revealing the potential therapeutic benefits of different aspects of nutrition therapy, the exact mechanisms of nutrition are not fully understood likely due to the complex interactions and evolving food diversity and microbiota species. More pragmatic, randomized control trials are necessary to provide high levels of evidence for future recommendations, especially within the neurocritical care population.

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Papers of particular interest, published recently, have been highlighted as:

- Of importance
- Of major importance

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