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Protein Requirements of the Critically Ill Pediatric Patient

Jorge A. Coss-Bu, MD[1,2]; Jill Hamilton-Reeves, PhD, RD, CSO[3]; Jayshil J. Patel, MD[4]; Claudia R. Morris, MD[5]; and Ryan T. Hurt, MD, PhD[6]

Abstract

This article includes a review of protein needs in children during health and illness, as well as a detailed discussion of protein metabolism, including nitrogen balance during critical illness, and assessment and prescription/delivery of protein to critically ill children. The determination of protein requirements in children has been difficult and challenging. The protein needs in healthy children should be based on the amount needed to ensure adequate growth during infancy and childhood. Compared with adults, children require a continuous supply of nutrients to maintain growth. The protein requirement is expressed in average requirements and dietary reference intake, which represents values that cover the needs of 97.5% of the population. Critically ill children have an increased protein turnover due to an increase in whole-body protein synthesis and breakdown with protein degradation leading to loss of lean body mass (LBM) and development of growth failure, malnutrition, and worse clinical outcomes. The results of protein balance studies in critically ill children indicate higher protein needs, with infants and younger children requiring higher intakes per body weight compared with older children. Monitoring the side effects of increased protein intake should be performed. Recent studies found a survival benefit in critically ill children who received a higher percentage of prescribed energy and protein goal by the enteral route. Future randomized studies should evaluate the effect of protein dosing in different age groups on patient outcomes, including LBM, muscle structure and function, duration of mechanical ventilation, intensive care unit and hospital length of stay, and mortality. (*Nutr Clin Pract*. 2017;32(suppl 1):128S-141S)

Keywords

protein; child; nitrogen balance; critical illness; protein balance; intensive care; catabolism; pediatrics

Protein Needs During Growth

Protein turnover is the process of body proteins being continuously degraded and resynthesized. Proteins are folded, 3-dimensional macromolecules composed of amino acids that are in a constant change and are subject to degradation to free amino acids. Amino acids cannot be stored and must be incorporated into protein or be oxidized and lost as nitrogenous products such urea and ammonia.[1–4] Nitrogen constitutes 16% of the weight of a protein; therefore, a factor of 6.25 is used to convert nitrogen to protein. During critical illness, when the energy supply is insufficient to meet the metabolic demands, protein stores from tissues are used, undergo degradation, and are oxidized to produce energy. Nitrogen loss increases dietary amino acid needs to achieve adequate net accretion and maintenance of body protein. Therefore, the protein needs in children are based on the amounts needed to replenish amino acids lost during oxidation plus the amount needed to ensure adequate growth during infancy and childhood. Protein intake should be adjusted based on the conversion rate of dietary protein to body proteins or the biological value of protein after absorption.[5,6] In pediatric patients, 58% of dietary protein is used for growth from 0.5–13 years and 43% from 14–18 years.[5] Inadequate protein intake, or diets with low levels of specific amino acids, may lead to decreased protein synthesis while the needed amino acids are met through endogenous sources, leading to protein degradation.[5]

Determining dietary protein requirements in infants and children has been difficult, and the methods used are based on a

From the [1]Section of Critical Care, Department of Pediatrics, Baylor College of Medicine, Houston, Texas, USA; [2]Texas Children's Hospital, Houston, Texas, USA; [3]Department of Dietetics & Nutrition, University of Kansas Medical Center, Kansas City, Kansas, USA; [4]Division of Pulmonary & Critical Care Medicine, Medical College of Wisconsin, Milwaukee, Wisconsin, USA; [5]Department of Pediatrics, Emory-Children's Center for Cystic Fibrosis and Airways Disease Research, Emory University School of Medicine, Atlanta, Georgia, USA; and [6]Division of General Internal Medicine, Mayo Clinic, Rochester, Minnesota, USA.

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Corresponding Author:
Jorge A. Coss-Bu, MD, Section of Critical Care, Department of Pediatrics, Baylor College of Medicine, Intensive Care Service, Texas Children's Hospital, 6621 Fannin St, WT6-006, Houston, TX 77030, USA.
Email: jacossbu@texaschildrens.org

Table 1. Protein Requirements in Healthy Children in g/kg/d.

Age, y	Maintenance Requirement	Growth Requirement	Average Requirement	DRI
0.5	0.66	0.27	1.12	1.43
1	0.66	0.17	0.95	1.18
1.5	0.66	0.11	0.85	1.04
2	0.66	0.08	0.79	0.96
3	0.66	0.04	0.73	0.90
4–5	0.66	0.02	0.69	0.86
6–10	0.66	0.05	0.74	0.91
Girls				
11–15	0.66	0.03	0.71	0.88
16–18	0.66	0.01	0.67	0.83
Boys				
11–15	0.66	0.04	0.73	0.90
16–18	0.66	0.02	0.70	0.86

DRI, dietary reference intake. Adapted from Garlick PJ. Protein requirements of infants and children. Nestlé Nutrition workshop series. *Paediatr Program*. 2006;58:39-47. Copyright 2006 Nestec Ltd., Vevey/S. Karger AG, Basel.

biological response to the administration of the specific amino acid under study.[2,7] The methods for determining dietary protein requirements include nitrogen balance, individual plasma amino acid levels, direct amino acid oxidation and balance, and indicator amino acid oxidation and balance.[2,3,5–9] Plasma amino acid levels have not been useful because a plasma level is not a reflection of the whole metabolic pool for a specific amino acid. Results of nitrogen balance studies in infants and children have yielded mixed results. Direct oxidation and balance is limited to the few amino acids whose carboxyl group is released.[2,8,9] Based on these methodological flaws, indicator oxidation and balance is regarded as the optimal method to determine dietary indispensable amino acids.[2,8,10,11]

The expert consensus recommendation for pediatric protein requirements used the factorial approach because of the limited data on dietary amino acid requirements based on the indicator amino acid oxidation and not on nitrogen balance results.[2,11] The factorial approach is based on the assumption that the basal requirements of amino acids are the same at different life stages and requirements in infants and children are higher than those in adults because of growth.[5,9] The protein requirement for an individual is the minimum intake of dietary protein that will cover the needs to ensure adequate age-appropriate growth rate in the absence of energy deficit from inadequate caloric intake or excess of physical activity. Protein requirements for children are expressed as the average requirement and dietary reference intake (DRI). Protein requirements represent the amount that will cover the needs of 50% of the population. The DRI is the amount that covers the needs of at least 97.5% of the population, which leaves a small proportion of the population (2.5%) with inadequate protein intakes.[2] The protein requirements at different ages are listed in Table 1.

Compared with adults, pediatric patients require a continuous supply of nutrients to maintain growth and in periods of rapid growth have better utilization of dietary protein and amino acids released from endogenous protein breakdown.[5,11–14] Whole-body protein turnover and muscle breakdown are highest in the neonatal period when tissues are maturing and the growth rates are highest.[6,14,15] In infants and children, an influx of amino acids to the tissues from the diet rapidly stimulates protein synthesis and accretion of skeletal muscle mass occurs, translating into growth.[13,16–18] In healthy neonates, muscle protein degradation is not affected by anabolic stimulation of insulin and amino acids, but the degradation slows down as the infant matures.[19–21]

Alterations in Protein and Amino Acids During Critical Illness

Catabolism of body protein due to starvation, immobility, stress, and inflammation has been described in the critically ill pediatric patient.[22–26] Pediatric intensive care unit (PICU) patients are a vulnerable population with a high risk of developing low or depleted protein reserves, and chronic illness with associated malnutrition will increase morbidity and mortality.[27,28] Mechanical ventilation, organ transplantation, exogenous steroids, sedatives, immunosuppression, organ dysfunction, and life support modalities (continuous renal replacement therapy and extracorporeal support) have been associated with protein catabolism and a negative nitrogen balance.[27,29,30] The nutrition needs of critically ill children should include sufficient protein to avoid negative nitrogen balance and to maintain the lean body mass (LBM) and growth, achieve a positive protein balance, and thus minimize the chronic state of protein deficiency.[29–32]

Postsurgical state, sepsis and inflammation induce endogenous protein breakdown. Skeletal muscle mass release amino acids in the systemic circulation to supply the substrate for whole-body protein metabolism.[33–35] This response is mediated by stress hormones, neural mediators, and cytokines and is not attenuated by additional exogenous protein intake. Circulating plasma amino acids are cleared from the system for oxidation, gluconeogenesis, fuel, and substrate for immune cells and enterocytes. In addition, these circulating amino acids provide the liver with substrate to synthesize acute-phase reactants. If the overall energy supply is suboptimal, amino acids may be oxidized to produce energy,[33–35] leading to lower plasma amino acid concentrations in patients with critical illness.[35,36] In critical illness, whole-body protein synthesis is increased and if dietary protein is not provided in adequate amounts, the splanchnic bed does not receive amino acids from absorbed protein. This may result in decreased synthesis of proteins such as serum albumin and prealbumin and lead to intestinal epithelial breakdown.[26,37]

Critically ill children have an increased protein turnover due to an increase in whole-body protein synthesis and breakdown.[25,38,39] During inflammatory conditions, there is a decrease in protein synthesis at the skeletal muscle level and an increase in protein degradation to shuttle amino acids and nitrogen to the tissues.[38,40] Protein degradation can be greater than muscle protein synthesis and create a negative protein balance. A sustained imbalance between muscle protein synthesis and protein degradation leads to loss of LBM and, if severe enough, to subsequent development of growth failure in children.[41,42]

The cellular protein mass is maintained by a balance between protein synthesis and degradation. Protein synthesis occurs by activation of the mammalian target of rapamycin (mTOR) signaling pathway that stimulates translation of messenger RNA (mRNA) into protein.[43,44] Sepsis and inflammation impair the effectiveness of translation of mRNA into protein at the muscle level, while activating the synthesis pathway at the liver.[43–45]

Protein Catabolism and Role of Insulin

In contrast to starvation, critical illness may induce a loss of LBM unresponsive to exogenous nutrition support.[41] Even when amino acids are provided during injury and sepsis, insulin resistance, cortisol, cytokines, inflammatory mediators, and alterations in growth hormone may limit the physiological response to protein intake due to decreased anabolic response to hormones and nutrients at the skeletal muscle level.[44,46]

Insulin is essential for skeletal muscle protein deposition by inhibiting muscle protein degradation, stimulating protein synthesis, and improving energy homeostasis.[47] Several studies have found that insulin stimulates skeletal muscle protein synthesis and inhibits muscle protein degradation during critical illness[48,49] but has failed to attenuate whole-body proteolysis when provided at higher than physiological concentrations,[50,51] due to systemic inflammation and circulating cytokines (ie, tumor necrosis factor–α).[52,53] The beneficial effects of insulin on whole-body protein metabolism are present only with adequate availability of amino acids,[25,50,53,54] related to glucose and energy homeostasis,[42,55] and are associated with stimulation of translation signaling pathways with a resultant increase in protein synthesis,[56] modulation of protein degradation,[42,50] and intrinsic anti-inflammatory effects.[57]

Role of Amino Acids in the Anabolic Response

Seventy-five percent of the body's nitrogen requirement is supplied by 5 amino acids: leucine, isoleucine, valine, threonine, and lysine.[58] Amino acids are anabolic and can stimulate muscle protein synthesis during basal conditions of insulin secretion.[50] During period of stress, the amino acids alanine, glutamine, glutamate, and aspartate become gluconeogenic substrates. Glutamine serves as a fuel for enterocytes and is a major component in muscle protein, shuttling about one-third of all nitrogen.[59] Arginine is a precursor of nitric oxide and modulates protein anabolism.[60,61] In neonates, citrulline is a precursor for arginine synthesis at the intestinal level, while in adults, citrulline released from the small intestine is converted to arginine in the kidney.[59,60] Leucine has a primary anabolic effect in skeletal muscle and has been used to stimulate nitrogen retention.[62,63] Parenteral administration of branched-chain amino acids (leucine, isoleucine, and valine) have been used in the critically ill patient with improvement in nutrition status and outcome.[33] To date, the American Society for Parenteral and Enteral Nutrition (ASPEN) does not recommend the use of specific amino acid therapies in critically ill children due to a lack of proven efficacy.[64] More studies are needed to understand the use of amino acids for specific therapeutic targets to modulate pediatric critical illness physiology.[38]

Assessment of Body Composition and Protein Turnover During Critical Illness

Critical illness is a condition in which protein requirements, utilization, and balance are changing rapidly in proportion to the acute physiologic state.[52,53] Clinical examination, weight for height, body mass index (BMI), and weight velocity can help to identify risk factors for cachexia, limited muscle mass, the presence of edema, obesity, and stunted growth.[65] The traditional methods that assess body protein stores do not reflect the changing protein and amino acids needs of the critically ill child. Fat deposition may determine weight gain in chronically ill children in response to nutrition support without restitution of LBM. Skinfold thickness to measure body composition is inaccurate in children with severe neurologic impairment.[66,67] Children have rapid fat accumulation during the first year of life.[16] Excess body fat may hide low or depleted LBM.[68–70] In addition, BMI does not distinguish between alterations in LBM and body fat in pediatric patients with chronic conditions.[66] A multicenter cohort study reported BMI and outcomes in 1622 mechanically ventilated children; underweight and obesity were associated with a higher risk of hospital-acquired infections and a lower likelihood of hospital discharge. In addition, underweight children had a higher risk of mortality and fewer ventilator-free days.[71]

Body Composition

Estimations of body composition to measure body protein reserves have shown that decreases in LBM may exist despite preserved BMI.[70] In contrast to adults, children (including neonates and infants) have high rates of protein turnover and skeletal muscle growth, which is the most important component and contributor to weight gain and body mass during periods of rapid growth.[19,72–74] In addition, expansion of the fat mass compartment also occurs rapidly during infancy, thus obscuring the evaluation of LBM.[16,68,69] Estimations of LBM and body fat determination in critically ill children with prolonged PICU stays can provide valuable information for patient assessment.[75] Body composition measurements have been used to evaluate protein reserves and assess the response to nutrition interventions in critically ill patients.[75] Muscle and LBM have been shown to correlate with disease severity, respiratory endurance, inflammation, and clinical outcomes during pediatric and adult illness.[70,75–77]

Body composition techniques, such as dual-energy x-ray absorptiometry (DXA), computed tomography, and magnetic resonance imaging, provide information related to tissue density or volume of the protein compartments but lack practicality or validation in the intensive care unit (ICU).[65,67,78] Air displacement plethysmography,[79] bioelectrical impedance analysis (BIA),[80] and the use of tracer dilution with stable isotopes[68] may allow measurement of body composition in critically ill children, but careful consideration should be given when using these modalities with the presence of major fluid shifts. These methods need further refinement and validation in the ICU setting.

Proteins, Amino Acids, and Other Markers

Visceral proteins, including serum albumin, prealbumin, and retinol-binding protein, are synthetized by the liver in response to amino acid influx into the circulation, and their serum levels have been used to evaluate nutrition status.[26] Given that 35%–45% of body mass resides in muscles, circulating levels of visceral proteins do not reflect losses or gains in total body protein. This is highlighted with protein wasting occurring despite adequate visceral protein concentrations.[6,65] The presence of capillary leak from third-space fluid shifts associated with postsurgical state or malnutrition limits the interpretation of plasma concentration of serum visceral proteins, and thus plasma proteins with a shorter half-life, such as prealbumin and retinol-binding protein, are better indicators of acute changes in response to dietary protein intake than proteins with a longer half-life such as serum albumin.[6,22,23,26]

C-reactive protein, an acute-phase reactant, helps to evaluate the liver shift of the synthesis of acute-phase reactants in preference of visceral proteins in response to nutrition support.[22,37] Anabolism and catabolism are driven by the systemic inflammatory response and not just by the availability of macronutrients from the diet.[29,41,81] Low prealbumin levels, despite adequate protein intake, may occur in the presence of elevated plasma C-reactive protein because of the shift in production of visceral proteins by the liver.[82] In normal conditions, serum urea nitrogen decreases during starvation and increases during dehydration, renal insufficiency, presence of excessive dietary protein, and presence of blood in the gastrointestinal (GI) tract. However, in the ICU patient, circulating serum urea nitrogen can decline in the presence of decreased muscle mass or be increased with high protein utilization and acute kidney injury.

Plasma amino acid concentrations are lower in patients with critical illness and are difficult to interpret due to varying degrees of injury response; prior existing nutrition, metabolic, and hemodynamic status; and the distinctiveness of the nutrition intervention.[33,35] 3-Methylhistidine (3-MH) is an important component of the myofibrils that is liberated when the muscle structure is damaged, and it has been linked to muscle degradation in humans.[83,84] 3-MH released from muscle is excreted unchanged in the urine, allowing serums levels to be used as an indirect measure of skeletal muscle breakdown.[85] Similarly, full-length (42-kDa) α-actin is released when the muscle structure is degraded and has been linked with muscle damage during injury.[86,87] Some investigators have used the cleaved fraction of α-actin (14 kDa) as an accurate tool to assess muscle protein degradation in humans.[87,88]

Nitrogen Balance

A significant negative nitrogen balance has been reported in critically ill children with hypercatabolic conditions like injury, trauma, postsurgical condition, or severe sepsis.[25,89–100] To accurately estimate the protein status, nitrogen balance is calculated as nitrogen intake minus nitrogen losses from urine, stool, skin, and other fluids, including dialysate and thoracic or abdominal drainage.[100–105] Positive protein balance has been used as an indicator of anabolism and is considered a surrogate for maintenance of LBM, but it does not imply protein or amino acid utilization or the degree of protein reserves. Nitrogen utilization is affected by energy deficits, and protein can be oxidized for energy in catabolic conditions.[42,102,103] In addition, adequate amounts of energy are required to effectively use the supplemented protein. During critical illness in children, variable increases in nitrogen intake have improved nitrogen balance in the first week after admission to the PICU.[90,98,106,107] In the presence of adequate intake of protein and energy during critical illness, protein synthesis rates are increased without affecting protein breakdown, leading to improved protein balance. Therefore, the improvement in protein balance as a result of higher protein synthesis[25,94] occurs despite resulting ongoing losses of body protein; however, achieving protein balance may not prevent loss of skeletal muscle mass.[108,109]

Nitrogen balance has significant limitations in assessing protein metabolism in the ICU setting. The rapidly changing physiology during the acute phase does not allow for an accurate steady-state estimation of nitrogen intake, resulting in inaccurate nitrogen balance calculations.[11] Careful evaluation should be given to studies reporting nitrogen balance calculations based on urinary urea measurements, because excretion of urea is highly variable in critical illness. In contrast, the measurement of total urinary nitrogen is superior in this population of patients, resulting in an accurate nitrogen balance estimation.[101–103] Because of methodological differences among clinical studies in critically ill children reporting nitrogen balance, comparisons are difficult with regard to nutrition interventions and clinical outcomes.*

*References 89–92, 94–97, 99, 100, 104, 106, 107, 110–112.

Tracer Methods

Isotope techniques trace interorgan and systemic movement of the labeled amino acid, their metabolic fate, and the degree of incorporation into tissue protein or fluids.[113] Tracer methods can be used to determine whole-body protein balance and synthesis of specific proteins in healthy and ill neonates, children, and adolescents. The indicator amino acid oxidation model has been applied to measure the metabolic availability of amino acid from the diet to determine protein needs. This technique is based on the concept that when an indispensable amino acid is deficient, all other amino acids, including the indicator, will be oxidized. With increasing intake of the limiting amino acid, oxidation of the indicator amino acid will decrease, reflecting increasing incorporation into protein. Once the requirement is met for the limiting amino acid, there will be no further change in the oxidation of the indicator amino acid, establishing the breaking point indicating the mean or estimated average requirement of the tested amino acid.[1]

Tracer methods have significant limitations in assessing protein metabolism in the ICU setting.[114] While these methods are very accurate to measure protein kinetics, they require specialized equipment and expertise to conduct the studies. Several authors have reported the use of stable isotopes to assess protein metabolism and needs in critically ill children.[15,25,26,40,54,115,116]

Prescription of Protein in the Critically Ill Child

The prescription of optimal nutrition support therapy during critical illness requires an individualized assessment of the risks and benefits associated with the timing, route, and quantity of nutrient intake.[117] Malnutrition in critically ill children has been reported with a prevalence ranging from 24%–70%[29,118–123] with suboptimal nutrition support being prevalent in many PICUs. Therefore, assessment of the nutrition status on admission to the PICU is a very important initial step to provide optimal nutrition support. Adequate protein provision during critical illness is essential to provide enough substrate for metabolic purposes and tissue repair and should be based upon an understanding of protein metabolism, as most recommendations are based on expert opinion. Protein requirements in critically ill children recommended by ASPEN are higher than protein recommendations for healthy children by the World Health Organization (WHO).[5,11] Estimated protein requirements by ASPEN for injured children of various age groups are as follows: 0–2 years, 2–3 g/kg/d; 2–13 years, 1.5–2 g/kg/d; and 13–18 years, 1.5 g/kg/d; this higher protein provision is intended to meet the higher needs in critical illness.[64]

Just providing adequate protein intake to maintain nitrogen balance may not prevent whole-body catabolism and loss of skeletal muscle mass.[108,109] Early administration of protein and energy enriched formula in critically ill infants and children has been shown to promote protein balance by increasing protein synthesis without adverse effects. Provision of enteral protein above recommended intakes has been well tolerated without excess amino acid oxidation and urea formation.[15,98,124]

Enteral nutrient delivery is the preferred method to provide protein to replenish the amino acid pool during critical illness.[125] The type of protein—amino acids, semi-digested, and whole protein—in the enteral formulation given to critically ill children may affect tolerance, absorption, and utilization. Proteins, such as whey, are rapidly digested and absorbed and quickly induce an anabolic drive; on the other hand, protein as casein has a longer enteric transit time, allowing a less robust but more sustained delivery to the amino acid pool.[126,127] Continuous enteral tube feeding with small volume is frequently used in the ICU setting due to better tolerance, but continuous enteral delivery lacks the pulsating effect that a rapid rise in amino acid level provides with a greater stimulus on skeletal muscle protein synthesis when intermittent bolus feeding is used.[21] Protein-energy enriched formulas have been used in critically ill infants during the first week after admission to the PICU and compared with standard formula. These formulas were well tolerated and have improved protein balance and biochemical parameters.[15,90,98,116]

Parenteral protein administration is recommended in the critically ill child when the GI tract is not ready to tolerate dietary protein. Different specialized amino acid formulations, such as branched-chain, sulfur, or essential amino acids, may be indicated for infants to meet specific essential amino acids requirements.[128] Currently, we lack evidence-based recommendations to design an ideal, target-oriented parenteral amino acid composition for the critically ill child.

The caloric proportions for the nutrition prescription commonly used (50%–60% of calories from carbohydrates, 25%–35% from protein, and 10%–25% from fat) should be adjusted based on the nutrition needs of each pediatric patient. Several authors have recommended that calories provided by protein be included in the estimations of nutrition requirements and in the calculation of the calories to nitrogen ratio.[129,130] In critical illness, the recommended calorie-to-nitrogen ratio has been suggested around 130–150 kcal/g of nitrogen (1 g of protein = 6.25 g of nitrogen). For critically ill children, protein underfeeding is more pronounced than caloric underfeeding.[28,120–122,131] Currently, patients in the PICU receive <50% of estimated caloric and protein requirements in the first 10 days of ICU care.[28,121,131,132] Protein underfeeding during critical illness contributes to increased catabolism and decreased LBM in the already malnourished patient, a situation that is exacerbated in small infants and children.[28,131,133,134] Metabolic utilization rate of macronutrients, dynamic changes in protein requirements, variation in nutrition practice, and protein cumulative deficits should be considered when providing protein support during critical illness.[114]

Clinical Studies

Multiple studies in infants, children, and adolescents have reported protein prescription practices and protein balance results in different clinical conditions, including neonates on extracorporeal life support,[54,115] surgical infants,[135–138] postsurgical repair of congenital heart disease,[92,97,116,139–141] children with acute kidney injury on continuous renal replacement therapy or hemodialysis,[100,104,105,120] and critically ill children admitted to the PICU (Table 2).[26,28,97,110,124,131,142]

The goals of nutrition support during the acute phase of critical illness are to provide adequate substrate intake to mitigate the effects of the catabolic response and preserve LBM. To achieve these goals, it is necessary to supply adequate energy and protein, but the question of how much protein and energy are needed to achieve balance in various age groups remains unclear. A systematic review by Bechard et al[143] analyzed protein balance results in children <18 years of age and receiving mechanical ventilation. A total of 9 studies with 347 patients were included in this review, 5 of which were randomized controlled trials comparing different levels of protein intakes. The study found that a minimum intake of 57 kcal/kg/d and 1.5 g/kg/d of protein was required to achieve a positive protein balance.

Based on results from the studies listed in Table 2, the following observations can be made. Infants and children 0–2 years of age who received EN[15,90,95,98,107,116] had negative protein balance when protein intake was <1 g/kg/d, protein balance was positive in children who received protein intakes of ~3 g/kg/d, and the protein balance was even more positive when protein intake was ~5 g/kg/d. For children with protein intakes of ≥3 g/kg/d, the serum urea nitrogen values reported were twice as high as the values reported for children with intakes <2 g/kg/d.[98,116,144] Children aged 2–13 years who received EN[106,145] had positive protein balance with protein intakes of at least 2 g/kg/d, while the children who received PN[94,100,111] had negative protein balance with protein intakes of ~2 g/kg/d. The study by Verbruggen et al[25] found that children 13–18 years of age who received PN had a positive protein balance with protein intake of ~3 g/kg/d. Three conclusions can be made from these findings: (1) there is an association between age and protein intake, 2) higher protein intakes per body weight are necessary in infants and young children to achieve a positive protein balance compared with older children and adolescents, and (3) protein intake given via the enteral route appears to be more efficient in achieving a positive protein balance than similar protein intakes by the parenteral route. It is important to mention important limitations from these studies. The first is that 3 studies measured total urinary nitrogen (TUN), 7 studies measured urea urinary nitrogen (UUN), and 1 used the combustion method. The other 3 studies measured protein balance based on whole-body kinetics of 3 different amino acids. The second limitation is the correction factor used to account for skin and stool losses. These differences in method could have introduced an error in the protein balance calculation, therefore limiting the interpretation of the results.

Cited reasons for inadequate protein intake in the critically ill child are fluid restriction, low prescription practices, no use of feeding algorithms, and acute kidney injury (AKI). Underprescription of protein intake is common in critically ill children with AKI. A retrospective study of 195 children from the Prospective Pediatric Continuous Renal Replacement Therapy Registry[105] reported an average protein prescription of 1.3 ± 1.5 g/kg/d at initiation of continuous renal replacement therapy (CRRT). A subsequent study of 15 children with renal failure by Zappitelli et al[100] found that CRRT nitrogen losses corresponded to 20% of intake, indicating that prescription doses should account for losses during CRRT. A recent study by Kyle et al[146] of 520 children admitted to the PICU found no association of a higher protein intake (≥80% of recommended) and a delay in renal recovery, suggesting no harmful effect of adequate protein intake in this population. A Cochrane review found insufficient evidence for or against the need for nutrition support in children during the first week of critical illness, mainly because the appropriate studies had not been performed.[147] Faced with a paucity of evidence,[148,149] the assumption for the latter is commonplace in PICUs across the United States and internationally. Delays in EN initiation are common in PICUs, as are multiple long interruptions that further defer achievement of goal nutrition.[28,117,131,150] An international prospective cohort study of 500 patients, aged 1 month to 18 years and on mechanical ventilation for greater than 48 hours in 31 PICUs in academic hospitals,[28] reported an average prescribed protein intake of 1.7 ± 0.7 g/kg/d and an actual average protein intake of 61% ± 94% (enteral and parenteral routes) and 43% ± 44% (enteral route) of prescribed, respectively. EN was used in 67% of children and was initiated within 48 hours in most patients. However, EN was subsequently interrupted on average for at least 2 days in 71% of the patients. A higher percentage of goal energy intake via the EN route was significantly associated with lower 60-day mortality. Mortality was also higher in children who received PN, while patients admitted to a unit that used a feeding protocol had a lower prevalence of acquired infections, and mortality was independently associated with the amount of energy or protein intake.

The impact of protein intake on clinical outcomes in critically ill children remains unclear, in view of the challenges of delivering adequate protein at the bedside. A recent prospective, multicenter study by Mehta et al[131] (n = 1245 critically ill children, aged 1 month to 18 years, who required mechanical ventilation for ≥48 hours) examined the association between protein intake and mortality. Average energy and protein of 69 ± 28 kcal/kg/d and 1.9 ± 0.7 g/kg/d, respectively, were prescribed. The mean delivery of enteral energy and protein was 36% ± 35% and 37% ± 28%, respectively. In relation to mean enteral protein intake <20%, intake ≥60% of the prescribed goal was associated with an odds ratio of 0.14 (95% confidence interval [CI], 0.04–0.52; P = .003) for

Table 2. Studies Examining the Role of Macronutrient Intake on Protein Balance.[a]

Author/Study Design	Participants/Population	Energy Intake, kcal/kg/d	Protein Intake, g/kg/d	Protein Balance, g/kg/d	Comments
Nitrogen balance method					
Jotterand Chaparro et al, 2016,[107] prospective observational study	N = 74; mean age 21 months (95% CI, 4–35) MV for at least 72 hours 69 patients receiving EN	48 (46–51)	1.2 (1.2–1.3)	–0.05 (–0.05 to –0.03) TUN was measured Balance corrected for fecal and skin losses	Protein and energy balance reached with 1.5 g/kg/d and 58 kcal/kg/d
Botran et al, 2011,[90] RCT	N = 41; median age 7 months (IQR, 3–13); 21 patients to STF, 20 to HPF; MV for at least 72 hours on EN	68 (56–72) STF day 5 77 (66–93) HPF day 5	1.5 (1.3–2.1) STF 3.1 (2.6–3.4) HPF	–0.4 (–1.1 to –0.1) STF 0.5 (–0.6 to 0.80) HPF UUN was measured and converted to TUN	NB was (+) for HPF group and (–) for STF group on day 5 Higher SUN in HPF group
van Waardenburg et al, 2009,[98] RCT	N = 20; age 2.7 ± 2.2 (mean ± SD) months; HPF (n = 8); 3.0 ± 2.7 STF (n = 10) Patients with RSV on MV and EN	82 ± 18 STF day 5 112 ± 58 HPF day 5	1.5 ± 0.4 STF 2.8 ± 1.3 HPF	0.12 ± 1.0 STF 0.29 ± 1.8 HPF UUN was measured and converted to TUN	Higher energy and protein intake promotes a (+) NB Higher SUN in HPF group
Zappitelli et al, 2009,[100] prospective observational study	N = 15, age 7.7 ± 6.7 (mean ± SD) years; critically ill children receiving PN and CVVHD	42.4 (29.8–65) IQR Day 2	2.09 (1.0–2.6) IQR Day 2	–0.22 (–0.4 to –0.2) IQR Day 2 Nitrogen measured by combustion method	Children on CVVHD had (–) NB on day 2, likely due to low caloric and protein intake
Briassoulis et al, 2006,[106] RCT	N = 40; age 127 ± 51 (mean ± SD) months for HPF (n = 20), 112 ± 95 for STF (n = 20); MV with TBI on EN	62 mean STF day 5 57 mean HPF day 5	2.2 mean STF 2.5 mean HPF	0.15 ± 0.38 STF 0.25 ± 0.63 HPF UUN was measured and converted to TUN	NB was (+) on day 5 in 70% of pts. in HPF group vs. 31% in STF group
Briassoulis et al, 2005,[91] RCT	N = 50; age 116 ± 48 (mean ± SD) months for HPF (n = 25), 93 ± 47 for STF (n = 25), MV for 5 days and receiving EN	–0.9 ± 1.4 STF –6 ± 21 HPF Intake difference from days 1–5	–0.06 ± 0.71 STF –0.30 ± 28 HPF Intake difference from days 1–5	–0.06 ± 0.28 STF day 5 0.07 ± 0.49 HPF day 5 UUN was measured and converted to TUN	No differences in NB on day 5 between the 2 groups
Briassoulis et al, 2002,[145] noncontrolled trial	N = 71, median age 54 (IQR, 24–120) months; MV for 5 days and receiving EN on day 1 PICU	22 ± 9.3 day 1 66 ± 23 day 5	0.69 ± 0.25 day 1 1.9 ± 0.59 day 5	–0.26 ± 0.17 day 1 0.03 ± 0.17 day 5 UUN was measured and converted to TUN	94.4% of patients reached nutrition goals Early EN improves NB in the first 5 days
Coss-Bu et al, 2001,[94] cross-sectional observational study	N = 33; age 5.5 ± 5.3 (mean ± SD) years; patients on MV and receiving PN; energy needs by IC	59.7 ± 33	2.1 ± 1	–0.89 ± 0.17 TUN was measured Balance corrected for fecal and skin losses	Patients with a (+) NB had positive energy balance and protein intake of 2.8 g/kg/d
Joosten et al, 1999,[95] cross-sectional observational study	N = 36; median age 10 (IQR, 2–25) months; patients on MV and receiving PN or EN	62 ± 29 (SD)	1.6 ± 1.2	0.10 ± 1.1 UUN was measured and converted to TUN	Protein and energy balance reached with 2.2 g/kg/d and 78 kcal/kg/d

(continued)

Table 2. (continued)

Author/Study Design	Participants/Population	Energy Intake, kcal/kg/d	Protein Intake, g/kg/d	Protein Balance, g/kg/d	Comments
Coss-Bu et al, 1998,[111] cross-sectional observational study	N = 19; age 8 ± 6 (mean ± SD) years; patients on MV and receiving PN; energy needs by IC	49 ± 22	1.7 ± 0.78	–0.12 ± 0.15 TUN was measured Balance corrected for fecal and skin losses	REE higher 48% than BMR; NB correlated with energy and protein intake and age
Chaloupecky et al, 1997,[92] RCT	N = 37, age 6 ± 3 (mean ± SD) months for PN (n = 19), 8 ± 3 for IVF (n = 18), surgical infants for CHD	33 ± 9 PN day 1 25 ± 15 IVF day 1	0.8 ± 0.10	–0.11 ± 0.08 PN –0.24 ± 0.08 IVF UUN was measured and converted to TUN	Single-center study PN can improve NB on day 1, after surgery in infants with CHD
Stable isotope method					
Geukers et al, 2015,[116] RCT	N = 28; median age 9 (IQR, 3–15) months; postsurgical infants for CHD on EN, day 1	85 (79–92) STF 84 (70–87) HPF	2.0 (1.8–2.1) 4.7 (4.3–5.0)	0.78 (–0.65 to 2.0) 1.73 (–2.35 to 5.6) Based on whole-body valine kinetics	Underpowered study; possibly the surplus protein was oxidized Higher SUN in HPF
Verbruggen et al, 2011,[25] randomized, crossover trial	N = 9; age 15 ± 1.2 (mean ± SD) years; patients had diagnosis of sepsis or septic shock on PN (SAA vs HAA)	32.7 ± 10 SAA PN 37.8 ± 10 HAA PN	1.5 ± 0.2 2.8 ± 0.4	–0.4 ± 1.0 0.3 ± 1.0 Based on whole-body leucine kinetics	Single-center study Protein intake of 3 g/kg/d was needed to reach balance
de Betue et al, 2011,[15] RCT	N = 18; age 2.7 ± 1.4 (mean ± SD) months (n = 8) for HPF, 2.9 ± 1.8 months for STF (n = 10) Patients with RSV on MV and EN	84 ± 15 STF day 5 119 ± 25 HPF day 5	1.7 ± 0.2 3.1 ± 0.3	0.02 ± 0.6 0.73 ± 0.5 Based on whole-body phenylalanine kinetics	Single-center study Higher protein and energy intakes promote anabolism

BMR, basal metabolic rate; CHD, congenital heart disease; CVVHD, continuous veno-veno hemodialysis; EN, enteral nutrition; HAA, high amino acid content; HPF, high-protein formula; IC, indirect calorimetry; IVF, intravenous fluids with dextrose; IQR, interquartile range; MV, mechanical ventilation; NB, nitrogen balance; PICU, pediatric intensive care unit; PN, parenteral nutrition; RCT, randomized controlled trial; REE, resting energy expenditure; RSV, respiratory syncytial virus; SAA, standard amino acid content; STF, standard formula; SUN, serum urea nitrogen; TBI, traumatic brain injury; TUN, total urinary nitrogen; UUN, urea urinary nitrogen.
[a]Values are mean ± SD, median (IQR), or otherwise indicated.

60-day mortality. Early initiation, postpyloric route, shorter interruptions, larger PICU size, and a dedicated dietitian in the PICU were associated with higher enteral protein delivery. A significant dose response for this association was documented, and the effect on mortality was independent of energy intake and most striking in patients with a higher severity of illness. These data suggest that the influence of enteral protein delivery may have a greater impact on important clinical outcomes than overall calories delivered, which is an observation that warrants further study. In addition, this study highlights the importance of implementing strategies at the bedside to increase delivery of enteral protein in critically ill children.

In conclusion, the determination of dietary protein requirements in infants and children is difficult and challenging. The protein needs in healthy children should be based on the amounts needed to ensure adequate growth during infancy and childhood, and children require a continuous supply of nutrients for growth. The protein requirements are expressed as an average requirement and dietary reference intake, the last one representing values that will cover the needs of 97.5% of the population. Critically ill children have an increased protein turnover due to an increase in whole-body protein synthesis and breakdown with protein degradation leading to loss of LBM and subsequent development of growth failure, malnutrition, and negative outcomes. The results of protein balance studies in critically ill children indicate higher protein needs, but close monitoring of the side effects of increasing protein intakes, particularly increased uremia and acidosis, should be done frequently. Recent studies found a survival benefit in critically ill children who received a higher percentage of prescribed dietary energy and protein goal by the enteral route. Future randomized controlled studies should evaluate the effect of protein dose on important patient outcomes, including LBM, muscle structure and function, duration of mechanical ventilation, ICU and hospital length of stay, and mortality in different age groups.

Statement of Authorship

J. A. Coss-Bu, J. Hamilton-Reeves, J. J. Patel, C. R. Morris, and R. T. Hurt contributed to conception/design of the manuscript; contributed to acquisition, analysis, or interpretation of the data; drafted the manuscript; critically revised the manuscript; agree to be fully accountable for ensuring the integrity and accuracy of the work; and read and approved the final manuscript.

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Discussion

Ryan T. Hurt: Have they looked at specific amino acids such as leucine or other BCAAs in the pediatric ICU population like we have in adults?

Jorge A. Coss-Bu: I am not aware of any trial evaluating a specific amino acid composition. I have been a true believer of branched-chain amino acids for the past 20 years. When I did my nitrogen balance studies on pediatric patients receiving PN, I recalculated the percentage of branched-chain amino acids that were delivered to evaluate whether it had any effect. Unfortunately, I was not able to detect a difference from these studies. This raises the question, do we need to conduct a trial with leucine in critically ill infants and children?

Ryan T. Hurt: Given the large number of studies that have looked at adult obesity in the ICU, has anybody looked at obesity in the pediatric ICU population?

Jorge A. Coss-Bu: Two groups, one from Boston and the other from Milwaukee, have published database studies looking at outcomes in obese pediatric ICU patients. From these studies, we have learned that BMI is an important factor in terms of outcomes, including length of stay, infections, and mortality.

Jill Hamilton-Reeves: As you were evaluating the literature, did you find any studies that measure body composition in a validated robust way?

Jorge A. Coss-Bu: There are studies looking at body composition. I have been using and researching body composition in pediatrics over the past 5 years. The problem with ICU patients is the variability in fluid status, making the interpretation of results difficult unless you have baseline measurements. There are a number of imagining modalities such as CT scans and bioelectrical impedance. Bioelectrical spectroscopy may assist with some of the limitations of BIA and fluid shifts in the ICU. There are some studies looking at body composition after discharge from the ICU. We published a study on body composition in cystic fibrosis patients after lung transplant. We evaluated body composition after lung transplant, and we were able to see changes in body composition over time. There are other studies looking at body composition but in patients outside the ICU.

Jill Hamilton-Reeves: My mentor is a pediatric nutritionist interested in the internal validity of these imaging modalities. Air displacement plethysmography or Bod Pod is a good alternative to bioelectrical impedance.

Jorge A. Coss-Bu: The limitation of air displacement plethysmography is that it is not practical for measurements in the ICU. I am interested in evaluating the child who comes very sick and is intubated on high ventilator settings. Bod Pod is great once the patient is stable and out of the ICU. I think it has been used extensively in the neonatal and premature population because body composition changes are evaluated after discharge from the nursery, but yes, those two techniques are available and we need an internal validity to really understand what am I measuring and how do I interpret the numbers.

Peter J. M. Weijs: We actually have been doing bioelectrical impedance measurements in acutely ill adults, not for monitoring but for assessment in the first day of ICU stay. We have demonstrated that those individuals with lower muscle mass may have higher mortality. We have been doing bioelectrical impedance measurements in the pediatric wards as well. Because we didn't have actual healthy control data, we measured the BIA in 2000 healthy schoolchildren. We are developing fat-free mass gross charts because we find that pediatricians are judging malnutrition in children based on weight and height growth charts. We actually see that some of the obese children have very low fat-free mass.

Jorge A. Coss-Bu: We recently published a review article on bioelectrical impedance in children. The problem is we do not have enough validated data in both different ages and ethnic groups. To use nonvalidated equations versus direct measurements to calculate fat-free mass and lean body mass, I think would be the wrong approach. Some researchers have suggested that we should use phase angle, which has been actually found to correlate with outcomes in adults. When you measure phase angle, we end up with low phase angle and impedance index. Those two variables have been shown adequate correlation with clinical outcomes, and both are independent of body composition.

Claudia R. Morris: The issue of enteral protein delivery in pediatric critical illness and trauma really is a modifiable risk factor that we have to address. The time for randomized controlled trials is here. With this in mind, mortality seems to be the outcome everyone is interested in for adults, and fortunately our kids in the ICU are not dying. This is not an ideal outcome for kids, and we need better outcomes, specifically long-term functional outcomes in pediatric ICU patients. These can include things like quality of life, time to rehabilitation, time to normal play, and back to school. One comment I have is about feeding protocols and nutrition guidelines. We have fantastic nutrition ICU guidelines for both adults and children, but ICUs across the country are just not using them. We need a paradigm shift that is going to require a culture change. For example, we have only one nutritionist in the pediatric critical care ICU, the only level 1 trauma center in Georgia. She is really dedicated, but less than 50% of our patients actually get nutrition evaluations. Feeding is often delayed and in many cases does not start until 4 or 5 days after they have been in the ICU. Part of this is how hospitals are getting reimbursed for nutritionists. There are data to show that if you institute these guidelines with a nutritionist, you can improve outcomes, which is ultimately going to save the hospital money.

Jorge A. Coss-Bu: I agree with you and think it is important that we convince our administrators that we need more support from dietitians on a daily basis. We have only 1 full-time equivalent dietitian for a 30-bed pediatric ICU and 1 dietitian for a 36-bed step-down unit. Since we are now going to be coding malnutrition and can potentially show a benefit in terms of outcomes, this may lend support to more resources. We can develop all the nutrition guidelines we want, but if we don't have the nutritionists to implement them, these recommendations will not be effective.

Jayshil J. Patel: The theme that I think we can kind of take home from this weekend is that protein is important, but an emerging theme is the value of exercise in combination with optimal protein delivery. What are you finding when you couple exercise particularly in the pediatric ICU?

Jorge A. Coss-Bu: This is a very challenging topic because most of the time, half of our children admitted to the ICU are less than 2 years of age. When we have these little guys intubated and restrained with sedation, there is always a fear that the child will self-extubate. One of the metrics that we follow in our ICU is self-extubations, and there is an intrinsic fear from the whole system to prevent self-extubations. There are different options for older kids, which would be more aggressive intervention and early mobilization. I think we have more challenges than our adult colleagues, particularly with the infants and younger children. I think we need to start being more systematic in our approach to mobilization and exercise in the pediatric ICU.